NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 313

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MIREX

(1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta[*cd*]pentalene)

(CAS NO. 2385-85-5)

IN F344/N RATS

(FEED STUDIES)

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

NOTE TO THE READER

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a comprehensive audit before being presented for public review. This Technical Report has been reviewed and approved by the NTP Board of Scientific Counselors' Peer Review Panel in public session; the interpretations described herein represent the official scientific position of the NTP.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MIREX

(1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta[*cd*]pentalene)

(CAS NO. 2385-85-5)

IN F344/N RATS

(FEED STUDIES)

James Huff, Ph.D., Study Scientist

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

February 1990

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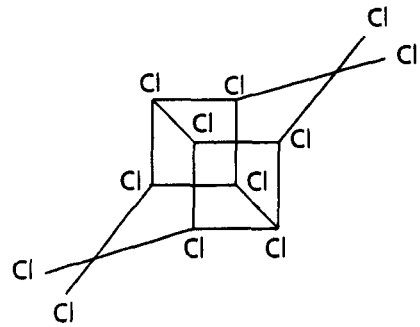

Mirex

Synonyms and trade names: 1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta[*cd*]pentalene; Hexachloropentadiene dimer; dodecachloropentacyclodecane; perchloropentacyclodecane; hexachlorocyclopentadiene dimer; Dechlorane®; Ferriamicide®

CAS NO. 2385-85-5

$C_{10}Cl_{12}$ Molecular weight 545.6

ABSTRACT

Mirex (95% pure), formerly used as a systemic insecticide and as a fire retardant, was studied for toxicologic and carcinogenic effects by administering diets containing 0, 0.1, 1.0, 10, 25, or 50 ppm mirex to groups of 52 F344/N rats of each sex for 104 weeks. Doses selected for the 2-year studies were based primarily on the effects on body weights and survival of rats in a 26-week study. During the first 6 months of the 2-year study, because of good survival and the absence of observable toxic effects in female rats, additional groups (termed second study) of 52 F344/N female rats were started at higher dietary concentrations of 0, 50, and 100 ppm mirex. Based on feed consumption data, the estimated average intake per day was 0, 0.007, 0.075, 0.75, 1.95, and 3.85 mg mirex/kg body weight for male rats and female rats in the first study, and 0, 3.9, and 7.7 mg/kg for female rats in the additional study.

Body Weights, Feed Consumption, and Survival in Two-Year Studies: Mean body weights of male rats that received 25 or 50 ppm mirex were 5%-18% lower than those of the controls throughout most of the study; mean body weights of female rats that received 50 or 100 ppm mirex were 4%-18% lower than those of the controls after week 40; mean body weights of groups receiving 0.1, 1.0, or 10 ppm were similar to those of controls. Feed consumption by dosed male rats was 83%-91% that by controls, and that by dosed female rats was 86%-99% that by controls. The top dietary exposure groups of rats received the equivalent of 3.85 mg mirex/kg body weight, whereas the 100-ppm group of female rats (second study) averaged 7.7 mg/kg. At the end of the study, survival of male rats that received 25 or 50 ppm mirex was lower than that of controls, whereas survival of all dosed groups of female rats was similar to that of controls (male: control, 44/52; 0.1 ppm, 37/52; 1 ppm, 36/52; 10 ppm, 37/52; 25 ppm, 19/52; 50 ppm, 15/52; female--first study: 38/52; 38/52; 35/52; 35/52; 41/52; 35/52; female--second study: control, 44/52; 50 ppm, 44/52; 100 ppm, 39/52).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: The most notable compound-related effects were observed in the liver of male and female rats. Fatty metamorphosis, cytomegaly, angiectasis (males only), and necrosis of the liver were observed at increased incidences in dosed rats. The incidences of neoplastic nodules of the liver were dose related, and in the 10-, 25-, and 50-ppm groups of males and the 50- and 100-ppm groups of females (second study), they were markedly greater than those in controls (52/group--male: control, 3; 0.1 ppm, 5; 1 ppm, 5; 10 ppm, 14; 25 ppm,

15; 50 ppm, 26; female (second study): control, 2; 50 ppm, 23; 100 ppm, 30). In the first study in female rats, the incidences of neoplastic nodules were not significantly different between control and dosed groups (10; 5; 4; 5; 9; 7). The 10 neoplastic nodules of the liver seen in the control group (19%) was significantly greater than the mean incidence observed historically (57/2,015; 2.8%). The incidences of hepatocellular carcinomas in control and dosed groups were relatively low and were not significantly different between groups.

The incidences of pheochromocytomas of the adrenal gland occurred with a positive trend in male rats (8/51; 7/52; 13/52; 11/52; 18/51; 19/51); the incidences in the 25- and 50-ppm male rats were greater than that in controls; malignant pheochromocytomas were observed in 2 controls and in 2 mirex-exposed male rats. The incidence of pheochromocytomas in 50-ppm female rats in the first study was marginally greater than that in controls (control, 1/51; 50 ppm, 6/52); this borderline increase was not observed in the second female rat study and thus is not considered to be due to the dietary administration of mirex.

Nephropathy occurred at similar incidences in control and mirex-exposed groups of male and female rats; however, the severity of this nonneoplastic lesion was judged to be slightly greater in the groups given 25, 50, or 100 ppm mirex (male: severe vs. moderate in controls; female: moderate to severe vs. moderate). Hyperplasia of the transitional epithelium of the kidney pelvis was observed in dosed male rats (0/51; 2/51; 2/52; 5/52; 14/51; 9/52). Transitional cell papillomas of the renal pelvis in male rats occurred with a positive trend ($P<0.02$) (0/51; 0/51; 0/52; 1/51; 3/52). The highest incidence previously observed in untreated male F344/N rats in NTP studies is 1/48, and the mean historical incidence is 5/1,968 (0.3%).

In both the first and second studies in female rats, the incidence of mononuclear cell leukemia showed dose-related increases (first study: 8/52; 8/52; 11/52; 14/52; 18/52; 18/52; second study: 6/52; 9/52; 14/52). When the data from both studies are combined, the incidences are significantly increased in the 10-, 25-, 50-, and 100-ppm groups. The mean historical incidence is 19% (375/2,021).

For the thyroid gland, there was a positive trend for follicular cell neoplasms in male rats (0/51; 1/50; 0/47; 1/47; 0/35; 4/49) and a negative trend for C-cell neoplasms in male rats (8/51; 6/50; 4/47; 7/47; 3/35; 0/49) and in female rats in the first study (12/50; 13/50; 7/48; 9/47; 6/48; 2/46). Neither observation is considered to be associated with the dietary administration of mirex.

Genetic Toxicology: Mirex was not mutagenic in the *Salmonella typhimurium*-microsome assay when tested in a preincubation protocol in the presence or absence of exogenous metabolic activation in strains TA98, TA100, TA1535, or TA1537. Mirex did not induce either sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of S9.

Conclusions: Under the conditions of these 2-year feed studies of mirex, there is *clear evidence of carcinogenic activity** for male and female F344/N rats, as primarily indicated by marked increased incidences of benign neoplastic nodules of the liver, as well as by increased incidences of pheochromocytomas of the adrenal gland and transitional cell papillomas of the kidney in males and by increased incidences of mononuclear cell leukemia in females.

Nonneoplastic effects induced by mirex administration include cytomegaly, fatty metamorphosis, angiectasis (males only), and cellular necrosis in the liver.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF MIREX

Male F344/N Rats	Female F344/N Rats
Dietary concentrations 0, 0.1, 1, 10, 25, or 50 ppm mirex	0, 0.1, 1, 10, 25, or 50 ppm mirex (first study) and 0, 50, or 100 ppm (second study)
Body weights in the 2-year study Exposed lower than controls	Exposed lower than controls
Survival rates in the 2-year study 44/52; 37/52; 36/52; 37/52; 19/52; 15/52	38/52; 38/52; 35/52; 35/52; 41/52; 35/52 (first study); 44/52; 44/52; 39/52 (second study)
Nonneoplastic effects Fatty metamorphosis, cytomegaly, angiectasis, and necrosis of the liver; hyperplasia of the transitional epithelium of the kidney pelvis	Fatty metamorphosis, cytomegaly, and necrosis of the liver
Neoplastic effects Hepatocellular neoplastic nodules; pheochromocytomas of the adrenal gland; transitional cell papillomas of the kidney	Hepatocellular neoplastic nodules; mononuclear cell leukemia
Level of evidence of carcinogenic activity Clear evidence	Clear evidence
Genetic toxicology Not mutagenic in *S. typhimurium* TA98, TA100, TA1535, or TA1537; did not induce either sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without S9	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Mirex is based on 2-year studies that began in June 1977 or January 1978 and ended in June 1979 or January 1980 at Frederick Cancer Research Center (Frederick, Maryland).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on Mirex on March 4, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF MIREX

On March 4, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of mirex received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Huff, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male or female rats).

Dr. Popp, a principal reviewer, deferred comment on the conclusions until the Panel discussed some of the major issues concerning the studies. These issues included: apparent nonreproducibility of liver neoplasms for female rats fed 50 ppm mirex in the original study and in a second study started several months later at 50 and 100 ppm; and an unusually high incidence of liver neoplasms in control female animals from the original study. Dr. Huff responded that there was no logical explanation either for the differences between studies or the high control tumor incidence in females from the first study.

As a second principal reviewer, Dr. Chinchilli agreed with the conclusions as written. He expressed concern over the less than complete record keeping on certain aspects of the study. He asked that either more details be given about the process used for randomization of animals or that a statement be added that detailed records are not available.

As a third principal reviewer, Dr. Hughes opined that the conclusions should be equivocal evidence of carcinogenic activity because the primary liver effect was increased nodules, the liver response in females was not the same in both studies, adrenal gland responses were mainly increases in benign pheochromocytomas, the renal transitional cell papilloma response in males was weak, and the mononuclear cell leukemia response was weak in females and equivocal in males and there was no evidence of early onset in exposed animals. Further, he questioned whether these were valid studies on which to base conclusions since not all records were available.

In response to the reviewers, Dr. Huff stated that staff had confidence that the data were scientifically valid and reportable and that the spectrum of neoplastic responses taken together supported the category of evidence selected. The liver and kidney lesions are rare occurrences in F344/N rats. Further, these findings in the liver are supported by other long-term studies reported in the literature, and ample evidence exists that the target organ for this nonmetabolized chemical is the liver. He reminded the Panel of other recent peer-reviewed studies with conclusions of clear evidence of carcinogenic activity based on increased incidences of neoplastic nodules and incidences lower than those reported here. Also, the audit revealed that the archived records necessary to support these conclusions are available, as are all the pathology materials and specimens.

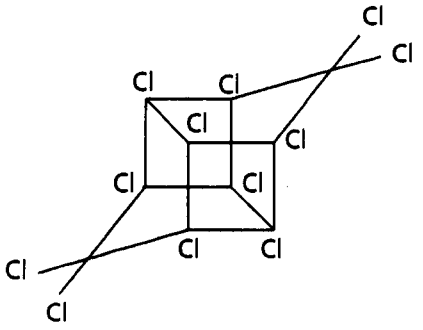
In other discussions, Dr. Gallo also emphasized the liver as a primary target organ, noting that mirex is known to be a potent inducer of cytochrome P450 enzymes. He speculated that cross-contamination between rooms housing exposed and control female animals might have been involved in the high incidence of neoplastic nodules of the liver in control female rats in the first study. Dr. S. Eustis, NIEHS, noted that neoplastic nodules in control animals were primarily composed of basophilic cells, whereas nodules in exposed animals were primarily either clear cell or eosinophilic cell types, a clear indication that mirex caused these effects.

Dr. Hooper moved that the Technical Report on mirex be accepted with the revisions discussed and the conclusions as written for male and female rats, clear evidence of carcinogenic activity. Dr. Sivak seconded the motion, and the Technical Report was accepted by the Panel with six affirmative votes and one negative vote (Dr. Hughes).

I. INTRODUCTION

Physical and Chemical Properties
Degradation and Persistence
Bioaccumulation
Disposition and Metabolism
Toxicity
Reproductive Effects
Mutagenicity
Carcinogenicity
Human Exposure
Study Rationale

I. INTRODUCTION



Mirex

Synonyms and trade names: 1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta[*cd*]pentalene; Hexachloropentadiene dimer; dodecachloropentacyclodecane; perchloropentacyclodecane; hexachlorocyclopentadiene dimer; Dechlorane®; Ferriamicide®

CAS NO. 2385-85-5

$C_{10}Cl_{12}$ Molecular weight 545.6

Mirex is a chlorinated insecticide once used to combat the fire ant Solenopsis sp. First prepared by Prins (1946) by the dimerization of hexachlorocyclopentadiene in the presence of aluminum chloride and carbon tetrachloride, mirex was patented in 1955 and introduced in 1959 by the Allied Chemical Corporation for use in pesticidal formulations (Waters et al., 1977a,b). Although principally used as a pesticide, mirex was also marketed under the trade name Dechlorane® for use in flame-retardant coatings for various materials.

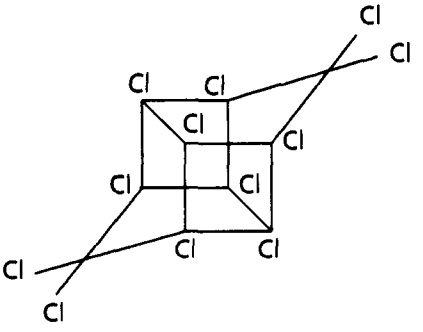
In 1976, the Allied Chemical Corporation ceased production of mirex and formally transferred all registrations on mirex to the Mississippi Department of Agriculture together with the right to manufacture and sell mirex bait (Pest. Chem. News, 1976a). The U.S. Environmental Protection Agency (EPA) and the state of Mississippi agreed to phase out all mirex registrations. Cancellation for mirex 10:5 bait (a dilute form of mirex) became effective at the end of 1977. Selective ground application was permitted only until June 1978 (Holden, 1976). In December 1986, the EPA revoked all existing tolerances for residues of mirex (Fed. Regist., 1986).

A literature collection of 325 abstracts from 1947 to 1976 was published by Waters and Black (1976). Waters et al. (1977a,b) summarized the available information on mirex up to 1977; the International Programme on Chemical Safety published an Environmental Health Criteria Document and a Health and Safety Guide summarizing information on mirex and mirex breakdown products and containing recommendations and evaluations (IPCS, 1984, 1988).

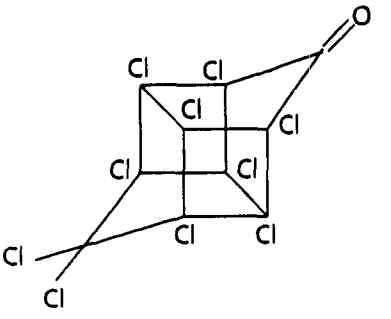
Physical and Chemical Properties

Physically, mirex is an odorless, snow-white crystalline solid that is insoluble in water but soluble in organic solvents such as methyl ethyl ketone, carbon tetrachloride, benzene, xylene, and dioxane. Mirex is reportedly unaffected by sulfuric, hydrochloric, or nitric acids; zinc dust; or sulfur trioxide (Brooks, 1974). Structurally, mirex is closely related to chlordecone (more commonly known as Kepone®); chlordecone and photomirex (8-monohydromirex) have been identified as slow degradation products of mirex.

Mirex, highly lipophilic, acts mainly as a stomach poison after ingestion, having little contact insecticidal activity (Brooks, 1974). It provides effective control of fire ants, harvester ants, and Texas leaf-cutting ants at a relatively low rate of application (Heath and Spann, 1973; Carlson et al., 1976).



Mirex



Chlordecone

(Kepone®)

Degradation and Persistence

Mirex does not occur naturally in the environment. The chemical stability of mirex causes it to be highly persistent in the environment, as illustrated by various experiments (Shapley, 1971). Photodegradation under the influence of ultraviolet radiation is slow, with photomirex being the major product. The environmental half-life of mirex is many years (IPCS, 1984). Exposure to sunlight and ultraviolet light caused only slow degradation; resultant compounds included chlordecone hydrate, undecachloropentacyclodecane, and nonachloropentacyclodecan-5-one hydrate (Ivie et al., 1974a). These breakdown products are as stable as mirex (IPCS, 1984). Mirex was more stable than DDT in the presence of ultraviolet light (Baker and Applegate, 1974) and was not degraded by a variety of soil bacteria (Jones and Hodges, 1974). However, anaerobic sludge organisms appeared to degrade mirex to the 10-monohydro and possibly the 9-monohydro derivatives (Andrade et al., 1975). Unchanged mirex and a number of mirex-related organochlorine compounds (including chlordecone) were detected in two soil samples 12 and 5 years after application of relatively large quantities of mirex (Carlson et al., 1976). In one instance, mirex was applied at a rate of 1 pound per acre (the usual rate of application is 1.7 g per acre) to experimental plots near Gulfport, Mississippi. Analysis of soil samples 12 years later showed that approximately 65% of the mirex was still present unchanged. In a second instance, an aircraft carrying mirex crashed near Sebring, Florida, depositing its entire load in a shallow pond. Five years later, up to 80% of the mirex was still present. In both cases, chlordecone and two monohydro and two dihydro mirex derivatives were identified. Lowe et al. (1971) reported that approximately 34% of the original mirex was still present after fire ant bait had been soaked in open seawater for 9 months.

Bioaccumulation

The accumulation of mirex in an estuarine food web was studied after mirex was applied three times (1.25 pounds of bait per acre) at 6-month intervals (Borthwick et al., 1973). Mirex migrated from treated lands and high marsh to estuarine biota, and significant concentrations were found in predators such as raccoons and birds. Similar results were obtained by Hyde et al. (1973a), who reported accumulation of mirex residues in a variety of species, including animals raised for human consumption, after mirex bait had been applied six times over a 4-year period. Mirex residues ranging from 0.001 to 0.125 ppm were detected in 67/77 (87%) samples of fat taken from beef cattle raised in mirex-treated areas of Mississippi and Georgia (Ford et al., 1973). Mirex was identified in the blubber of 48 beluga whales sampled between 1982 and 1986 in the St. Lawrence River Estuary (Lum et al., 1987). Since there are no known sources of mirex in Quebec, it has been postulated that migrating eels (in which mirex has been measured) and suspended particulate material transported the mirex from Lake Ontario.

Mirex residues were found in birds collected from South Carolina, Georgia, and Florida (Oberheu, 1972; Kreitzer, 1974). Marine unicellular algae species exhibited bioconcentration factors of 3,200-7,300 (Hollister et al., 1975).

In four experiments, each lasting 28 days, mirex leached from bait was applied to an estuarine environment (Tagatz et al., 1975). Toxic responses were highest in summer and lowest in spring. Bioconcentrating factors for mirex were 40,800 for minnows, 10,000 for pink and grass shrimp, and 2,300 for blue crabs.

Disposition and Metabolism

After ingestion, mirex is only partly absorbed; the remainder is generally excreted unaltered in the feces; mirex is also absorbed after inhalation and dermal exposure (IPCS, 1984). Mirex excretion occurs mainly via the feces, with small amounts excreted in urine (Mehendale et al., 1972); traces also have been detected in milk (Gaines and Kimbrough, 1970). Excretion kinetics appear to be biphasic--the initial "fast" phase lasting 38 hours and the "slow" phase projected to last up to 100 days (Mehendale et al., 1972). Mirex binds firmly to soluble liver proteins (Byard et al., 1975) and appears to be retained in fatty tissues (Mehendale et al., 1972; Kutz et al., 1974); these factors may contribute to the long biologic half-life of several months. Mirex was shown to bind to hepatocytes at 37° C and physiologic pH (Rosenbaum and Charles, 1986).

A survey conducted by EPA showed mirex to be present in 52/284 samples of human tissue at levels up to 1.32 ppm on a wet weight basis (Pest. Chem. News, 1976b; USEPA, 1978). Mirex residues of up to 0.16-5.94 ppm were detected in six samples of human adipose tissue from persons living in states where mirex had been used for pest control (Kutz et al., 1974).

Catfish raised in an area that received an application of mirex contained mirex levels from 0.008 to 2.59 ppm (Collins et al., 1973). A build-up of the insecticide was observed in the fish, suggesting that the accumulation occurred via the food chain rather than by direct consumption.

In laying hens fed 1.06 ppm mirex in the diet, the insecticide appeared to be readily absorbed from the digestive tract and distributed throughout the body (Woodham et al., 1975). At 27 weeks, the highest levels were found in fat at a concentration of 15 ppm; levels in other organs were: kidney, 2 ppm; liver, 0.5 ppm; breast, 0.1 ppm. After 39 weeks of dosing, all tissue levels were increased by 60%-300%. In other feed experiments, males often showed higher tissue levels of mirex than did females (Ivie et al., 1974b). Mirex accumulates in egg yolks, indicating that laying hens may lose large quantities of mirex through the eggs. Levels up to 200 ppm mirex in eggs appear to be tolerated without adverse effects on various reproductive indices such as egg hatching and chick growth and survival (Ivie et al., 1974c).

After rats received a single gavage dose of 6 mg/kg of uniformly labeled [^{14}C]mirex, approximately 60% was excreted unchanged in the feces and 0.7% in urine within 48 hours (Mehendale et al., 1972). Of the remainder, about 34% was stored in body tissues: 27.8% in fat, 3.2% in muscle, 1.75% in liver, 0.76% in kidney, and 0.23% in the intestines. Corticosterone and adrenalectomy affect the mirex distribution in rats. Forty-eight hours after administration of a single 100 mg/kg dose of [^{14}C]mirex by gavage, the absorption of [^{14}C] mirex was decreased in the brain of adrenalectomized rats receiving corticosterone supplements and the [^{14}C]mirex concentration per liver was greater in intact than in adrenalectomized rats with or without corticosterone supplements (Brown and Yarborough, 1988).

Rats and Japanese quail fed diets containing [^{14}C]mirex accumulated the [^{14}C]mirex in all body tissues and especially in adipose tissue (Ivie et al., 1974b). After 16 months, the concentration of mirex in fat had increased over dietary levels 120-fold in rats and 185-fold in male quail. No indication of a plateau was noted. A further 10 months on normal diet produced only a 40% decline in tissue concentration. Mirex readily

traverses the placental barrier and accumulates in the rat fetus (Gaines and Kimbrough, 1970).

No metabolic products were identified following incubation of mirex with liver preparations from mice, rats, and rabbits (Mehendale et al., 1972). However, Stein et al. (1976) reported a nonpolar mirex derivative (tentatively identified as undecachloropentacyclodecane) in the feces of monkeys fed [^{14}C]mirex. These investigators suggested that bacteria in the lower gut may have been responsible for the degradation, as no metabolites were detected in other tissues (such as fat) where the level of radioactivity was several orders of magnitude above that in the feces.

Toxicity

Several marine species appear to be extremely sensitive to mirex. Crawfish are susceptible to mirex toxicity (Carter and Graves, 1973), with the third instar stage being the most vulnerable (Ludke et al., 1971). Survival of channel catfish was reduced by 33% after treatment of ponds with mirex bait (1.25 pounds per acre); residues present in the edible parts of the fish averaged 0.018 ppm (Hyde, 1973). In contrast, mirex was reported to have no detrimental effect on honeybee colonies adjacent to treated areas (Glancey et al., 1970). No mirex was detected in bees, honey, or pollen from such colonies.

Toxic effects of mirex in mammalian systems, as studied in laboratory animals, are generally characterized by decreased body weight and increased liver weight (Gaines and Kimbrough, 1970; Davison and Cox, 1974; Abraham et al., 1974; Byard and Pittman, 1975; Larson et al., 1979). The increased liver weight in rats is accompanied by increased ornithine decarboxylase and thymidine kinase activity, as well as by increased incorporation of [^{3}H]thymidine into DNA, 36 or 48 hours after exposure to mirex (Yarbrough et al., 1986). Mirex is not metabolized by the liver; however, several reports indicate that mirex induces liver enzymes. Increased cytochrome P450 (Baker et al., 1972; Davison and Cox, 1974; Fouse and Hodgson, 1987; Crouch and Ebel, 1987), together with proliferation of smooth endoplasmic reticulum and increased numbers of osmiophilic dense bodies, have been reported in rats and mice (Gaines and Kimbrough, 1970; Baker, 1974). Mirex can potentiate hepatotoxic effects of other chemicals. Hepatotoxicity, as measured by the leakage of enzymes from hepatocytes in vitro after in vivo exposure to acetaminophen, was enhanced by prior exposure of male C57BL/6 mice in vivo to mirex (Fouse and Hodgson, 1987). In addition, increased demethylase activity has been observed in mice (Abraham et al., 1974; Baker et al., 1972) as well as increased total DNA, total protein, mitochondrial respiratory activity, and microsomal mixed function oxidase enzyme activity (Byard et al., 1975). Mirex is much weaker than chlordecane in potentiating liver damage in rats caused by chloroform, as measured by histologic examination and serum enymes (Mehendale and Klingensmith, 1988).

Conversely, a decrease in the level of glucose-6-phosphatase activity (Abraham et al., 1974; Byard et al., 1975) as well as glycogen depletion (Abraham et al., 1974; Kendall, 1974a) were measured in both rats and mice. A 60%-65% loss in liver glutamic oxaloacetic transaminase activity was observed in rats receiving 10-200 ppm mirex in the diet for 4 weeks; lactic dehydrogenase (LDH) also was significantly reduced in rats after ingestion of 10 ppm mirex for 4 weeks (Abston and Yarbrough, 1974). A crystalline extract of LDH from rabbit muscle was competitively inhibited by mirex, both with respect to pyruvate (substrate) and NADH (coenzyme) (Hendrickson and Bowden, 1975).

Single doses of mirex which are not toxic to rats cause death in adrenalectomized animals but not in adrenalectomized animals given supplementary doses of corticosterone (Erwin and Yarbrough, 1983).

Toxic reactions following intraperitoneal administrations of mirex in corn oil at LD_{50} levels in rats and mice resemble the signs of DDT intoxication--hair loss, listlessness, and diarrhea. Fatty changes in the liver were manifested as periportal liposis in mice fed mirex, whereas intraperitoneal injection resulted in fibrous white patchy lesions on the liver surface with interior necrosis (Kendall, 1974b).

In humans, symptoms and signs of mirex exposure include gastrointestinal irritation with

nausea, vomiting, diarrhea, malaise, headache, central nervous system excitation (including tremor, paresthesia, ataxia, confusion, convulsions, ventricular fibrillation, central nervous system depression, and central nervous system respiratory paralysis) (National Clearinghouse for Poison Control Centers, 1976).

Reproductive Effects

White leghorn chickens, Coturnix quail (Davison and Cox, 1974), and Japanese quail (Davison et al., 1975) showed normal reproduction after being fed mirex in the diet for 12 weeks (160 ppm for chickens and 80 ppm for quail). However, eggs of mallards fed 1 ppm mirex showed slightly thicker and heavier shells, whereas at 100 ppm, the egg shells were thinner (Hyde, 1973). Reduced survival of the ducklings was observed; no other adverse effects were reported (Hyde et al., 1973b).

Various reproductive effects of mirex have been reported in rats and mice. Female rats fed 5 ppm mirex produced normal litters, whereas dams fed 25 ppm mirex had fewer offspring born alive, fewer offspring survived to weaning, and many pups developed cataracts (Gaines and Kimbrough, 1970). Offspring born to mothers dosed with mirex but nursed by undosed mothers showed normal survival to weaning and fewer cataracts. Thus, mirex appears to be cataractogenic in mouse and rat neonates only after lactogenic exposure (Chernoff et al., 1976). Gas chromatography of milk from dams dosed with mirex showed an average concentration of 11.3 ppm mirex (Gaines and Kimbrough, 1970).

Mirex administration in feed resulted in reduced litter size in BALB/c and CFW mice; additionally, BALB/c mice showed a significant increase in parent mortality (Ware and Good, 1967). In this experiment, fetuses were not evaluated for congenital defects. An investigation of the teratogenic potential of mirex in rats indicated that low doses of mirex (1.5-3.0 mg/kg administered as a single daily oral dose on days 6-15 of gestation) produced no signs of maternal toxicity and no adverse fetal effects (Khera et al., 1976). Maternal toxicity and subsequent fetal visceral abnormalities were noted in offspring of females receiving 6.0 or 12.5 mg/kg; in addition, decreased fetal survival and reduced fetal weight were observed at 12.5 mg/kg. A dominant lethal assay of males given 0, 1.5, 3.0, or 6.0 mg/kg by gavage daily for 10 days showed no significant difference in reproductive indices between experimental and control groups, even though mirex was detected in the testes of the exposed group.

Mutagenicity

The genetic toxicity of mirex has been examined in both prokaryotic and eukaryotic cells. Results of reverse mutation assays with numerous strains of *Salmonella typhimurium* (Hallett et al., 1978; Schoeny et al., 1979; Rinkus and Legator, 1980; Probst and Hill, 1980; Probst et al., 1981) and similar assays using *Escherichia coli* strains WP2 and WP2 uvrA$^-$ (Probst and Hill, 1980; Probst et al., 1981) were uniformly negative; all these bacterial assays were conducted with and without exogenous metabolic activation from induced liver S9 preparations. Likewise, *S. typhimurium*-microsome studies with a preincubation protocol and Salmonella strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 showed no mutagenic activity for mirex at doses of up to 10,000 µg/plate (Mortelmans et al., 1986; National Toxicology Program [NTP] data shown in Table C1).

No unscheduled DNA synthesis was detected in cultured rat, mouse, or hamster hepatocytes after exposure to mirex (Probst and Hill, 1980; Probst et al., 1981; Williams, 1980; Maslansky and Williams, 1981; Telang et al., 1981). Results from experiments on induction of gene mutation at the HGPRT locus in rat hepatocyte-mediated cultured human fibroblasts were negative (Tong et al., 1981). Mirex at exposure concentrations up to 260 µg/ml did not increase the number of sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (NTP data shown in Tables C2 and C3). The only in vivo mutagenicity assay reported for mirex was a dominant lethal study in Wistar rats in which no significant

difference was reported in either viable embryos or deciduomas in pregnant females mated to males dosed by gavage on each of 10 consecutive days with 1.5, 3.0, or 6.0 mg/kg (Khera et al., 1976).

Chlordecone, the keto-analog of mirex, has been evaluated in a series of short-term mutagenicity assays. Like mirex, chlordecone was not mutagenic in the *S. typhimurium*-microsome assay at concentrations up to 10,000 µg/plate (Mortelmans et al., 1986) with or without exogenous metabolic activation. Bacterial reverse mutation assay results from other investigators were also reported to be negative (Hallett et al., 1978; Schoeny et al., 1979; Probst and Hill, 1980; Probst et al., 1981). No unscheduled DNA synthesis was observed after exposure of cultured F344 rat hepatocytes to chlordecone (Williams, 1979, 1980; Probst and Hill, 1980; Probst et al., 1981), and no gene mutations were produced in rat liver epithelial cells after chlordecone treatment (Williams, 1979, 1980; Telang et al., 1981). In in vitro cytogenetic studies (Galloway et al., 1987), treatment of CHO cells with up to 20 µg/ml chlordecone in the presence or absence of Aroclor 1254-induced rat liver S9 did not induce chromosomal aberrations; sister chromatid exchange rates were increased, however, after exposure of the cells to chlordecone at concentrations of 1.6-10 µg/ml only in the absence of exogenous metabolic activation. The only in vivo mutagenicity data for chlordecone were reported in an abstract by Simon et al. (1978) who stated that no dominant lethal mutations were produced in the offspring of male rats orally administered 3.6 or 11.4 mg/kg chlordecone per day for 5 days.

Carcinogenicity

Groups of 18 male and 18 female (C57BL/6×C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6×AKR)F_1 mice were given mirex (98% pure) at doses of 10 mg/kg in 0.5% gelatin by gavage from 7 days to 4 weeks of age; then the mice were fed diets containing 26 ppm mirex (Innes et al., 1969; IARC, 1979). All mice were dead by 70 weeks. "Hepatomas" were observed in 6/18 (33%) males and 8/16 (50%) females of the first strain compared with 8/79 (10%) male and 0/87 female controls and in 5/15 (33%) males and 10/16 (63%) females of the second strain compared with 5/90 (6%) male and 1/82 (1%) female controls. In a companion experiment with the same strains and numbers of mice, 1,000 mg mirex/kg body weight was given by subcutaneous injection in 0.5% gelatin on the 28th day of life (NTIS, 1968). At 78 weeks of age, the remaining mice (16, 17, 17, 15) were killed and necropsies were performed. The incidences of hepatomas in male and female mice were 2/18 and 0/17 in the first strain and 4/17 and 1/18 in the second strain; 1/18 gelatin vehicle control males and 1/161 dimethyl sulfoxide "negative" control males of the second strain had hepatomas, whereas none of the controls of the first strain had liver neoplasia.

Mirex (99% pure) was given in feed at 50 and 100 ppm for 18 months to groups of 26 male and 26 female CD rats (Ulland et al., 1977; IARC, 1979); for the first 10 weeks of the study, the dietary levels were 40 and 80 ppm. The animals were observed for another 6 months, and then survivors were killed and necropsies were performed. Groups of 20 male and 20 female rats were used as controls. Administration of mirex had no appreciable effect on growth rate, but the survival rate in all but the low dose female group was decreased, indicating a dose-related (and possible sex-related) effect. At necropsy, the liver of all animals administered mirex--except for the low dose females--appeared enlarged, mottled, or spotted. A wide spectrum of liver changes was observed, ranging from fatty metamorphosis and megalocytosis of hepatocytes, cystic degeneration and necrosis, and biliary hyperplasia with periportal fibrosis, to circumscribed areas of cellular alteration. Neoplastic nodules of the liver were increased in males (control, 0/20; 50 ppm, 2/26; 100 ppm, 7/26) and in females (0/20; 4/26; 4/26); carcinomas were observed in one low dose and four high dose males and in one high dose female.

In 1979, the International Agency for Research on Cancer (IARC, 1979) evaluated the available data and decided, "There is *sufficient evidence* that mirex is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable for practical purposes to regard mirex as if it presented a carcinogenic risk to

humans." IARC (1987) reevaluated the available data and came to the same conclusion; mirex was placed into the overall evaluation category of Group 2B: possibly carcinogenic to humans.

For the related chemical chlordecone (98% pure), 2-year dietary studies were conducted in groups of 50 male and 50 female Osborne-Mendel rats and B6C3F$_1$ mice (NCI, 1976; IARC, 1979). Doses were reduced during the course of the studies, due to toxicity; time-weighted concentrations for male rats were 0, 8, 24 ppm; for female rats, 0, 18, 26 ppm; for male mice, 0, 20, 23 ppm; and for female mice, 0, 20, 40 ppm. Exposure was discontinued at week 80, and the animals were killed and necropsies performed at week 112 (rats) and week 90 (mice). For rats, hepatocellular carcinomas were found in males (control, 0/105; low dose, 0/50; high dose, 3/44; two low dose males had neoplastic nodules) and in females (0/100; 0/50; 10/45; one control and two high dose females had neoplastic nodules). Extensive hyperplasia, fatty infiltration, and cellular degeneration of the liver were observed in male and female rats in both dose groups. For mice, hepatocellular carcinomas were found in males (6/19; 39/48; 43/49) and in females (0/10; 26/50; 23/49). IARC (1979, 1987) came to the same conclusions for chlordecone as for mirex.

Human Exposure

In early 1974, the EPA expressed concern over the widespread use of mirex because of: (1) adverse effects on reproduction as demonstrated in laboratory animals, (2) detectable amounts found in human adipose tissue from a limited sampling of the population, (3) tumorigenic implications in mice, (4) effects on mammalian energy metabolism, (5) mortality in birds, (6) potential to move in a saltwater environment, (7) effects on certain aquatic organisms, and (8) persistence in the environment (Pest. Chem. News, 1974). In 1978, the EPA issued a report on human population exposure to mirex and kepone. Mirex was detected in human adipose tissue (52/184, 18%), and yet none was found in 1,500 breast milk samples taken throughout the United States (USEPA, 1978).

Study Rationale

Mirex was nominated to the National Cancer Institute for carcinogenesis study in rodents because of widespread environmental exposure. Since there were positive results already in mice, only rats were exposed to mirex in the studies reported in the Technical Report. The dietary route of administration was chosen because this was a likely means of human exposure.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MIREX

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

TWO-YEAR STUDIES

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MIREX

Mirex (1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta[*cd*]pentalene) was obtained from the Agricultural Department of Allied Chemical Company (Baltimore, Maryland) in a 10-pound container as a fine powder (lot no. 083173). Gas chromatographic analysis indicated that the study material was approximately 95% pure. However, because data records for this analysis were incomplete, a retrospective purity analysis was performed on the residual study material by a different analytical laboratory. The identity of the study material was confirmed by infrared (Figure 1) and ultraviolet spectrophotometry and by low and high resolution mass spectrometry (Figure 2). All spectroscopic data were consistent with reference spectra and the structure of mirex. The purity of mirex was determined to be greater than 96% by thin-layer chromatography, capillary gas chromatography, and Karl Fischer water analysis. The residual study material contained 1% water and a 2% impurity that was identified as dechlorane 604 by infrared and ultraviolet spectrophotometry and by low- and high-resolution mass specrometry (Figure 3).

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

No data records were located for the preparation, analysis, or stability of the formulated diets used during the 2-year studies of mirex. A retrospective feed homogeneity and stability study was conducted to confirm that adequate uniform feed blends of mirex could be prepared with relative ease. Results of these studies indicate that homogeneous feed blends of mirex can be prepared easily at 0.1 and 50 ppm by spiking a small premix blend of feed with mirex dissolved in acetone, allowing the acetone to evaporate, and then blending the premix with the approximate amount of feed to yield the required concentration of mirex. These formulated diets were shown to be stable for at least 3 weeks when stored at temperatures ranging from −20° to 25° C. Formulated diets of mirex were analyzed by extraction with hexane followed by gas chromatographic analysis on a GP 4% SE-30/6% SP2401 column with an electron capture detector. Because no records are available, the methods of preparing the diet/mirex mixtures are not known. Nonetheless, available information from the "dose preparation log" shows that the correct amounts of mirex were weighed and mixed with the appropriate amounts of feed to give the target concentrations needed for the different dose groups. Further, numerous entries in the "chemical/vehicle analysis" sheets show that sample analyses of the different dietary concentrations of mirex contained the desired levels of mirex. Moreover, homogenicity samples taken from "left, bottom, right" of the mirex-diet containers for the 0.1-, 1-, 10-, 25-, and 50-ppm mixtures verify uniform and adequate mixtures. Thus, although specific documentation regarding the exact procedure used to incorporate mirex into the feed is not in the archival records, the collective available information is sufficient to support that the mixtures were adequately and accurately prepared and that the animals did receive the appropriate mirex-containing diets.

TWO-YEAR STUDIES

Study Design

Dose selection was based on results of earlier short-term studies (primarily on the reduction of body weights and on differences in survival); although the data and records from these studies are considered incomplete and not adequate enough for reporting, there was enough information present to select the dietary concentrations for the 2-year studies. In brief, groups of five male and five female rats (strain not specified) received diets for 26 weeks containing mirex at concentrations of 0, 25, 50, 80, 100, 150, 200, 400, or 1,000 ppm. Final mean body weights were decreased 11% for the 100-ppm male group, 8% for the 150-ppm male group, 25% for the 400-ppm male group, and 13% or 17% for the 80- to 200-ppm female groups; all animals in the 400- and 1,000-ppm groups died before the end of the 26 weeks.

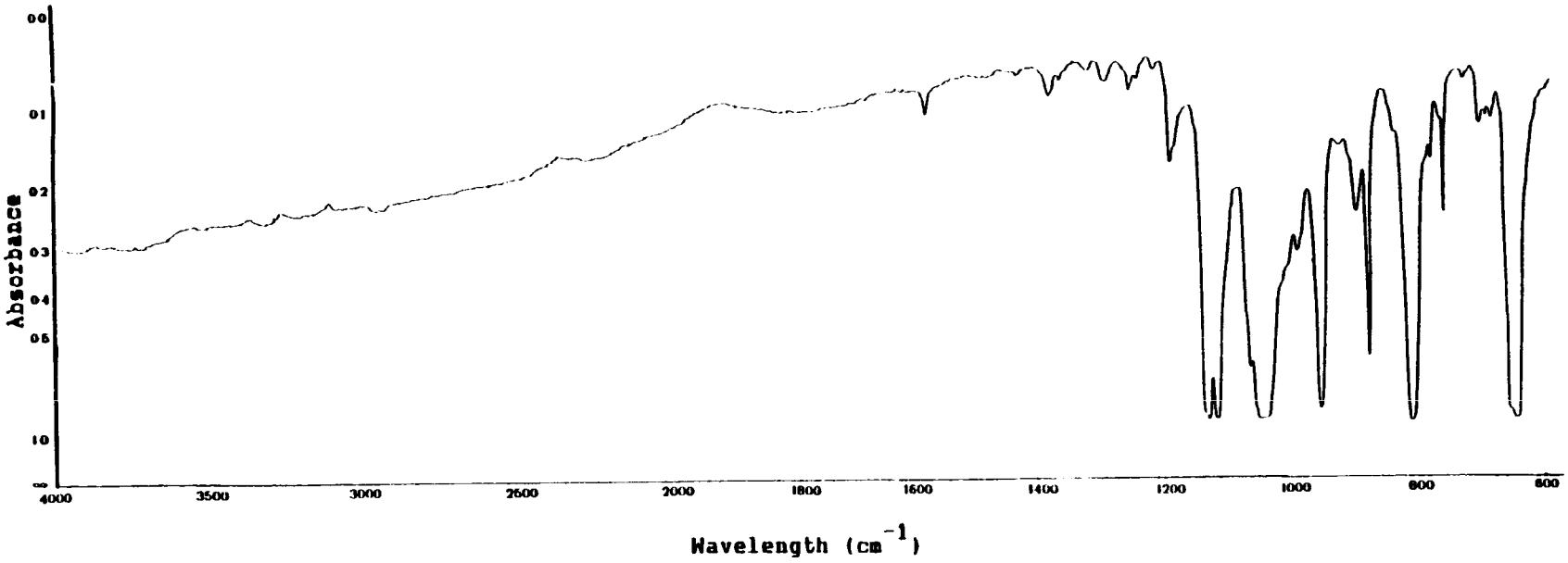

FIGURE 1. INFRARED ABSORPTION SPECTRUM OF MIREX (LOT NO. 083173)

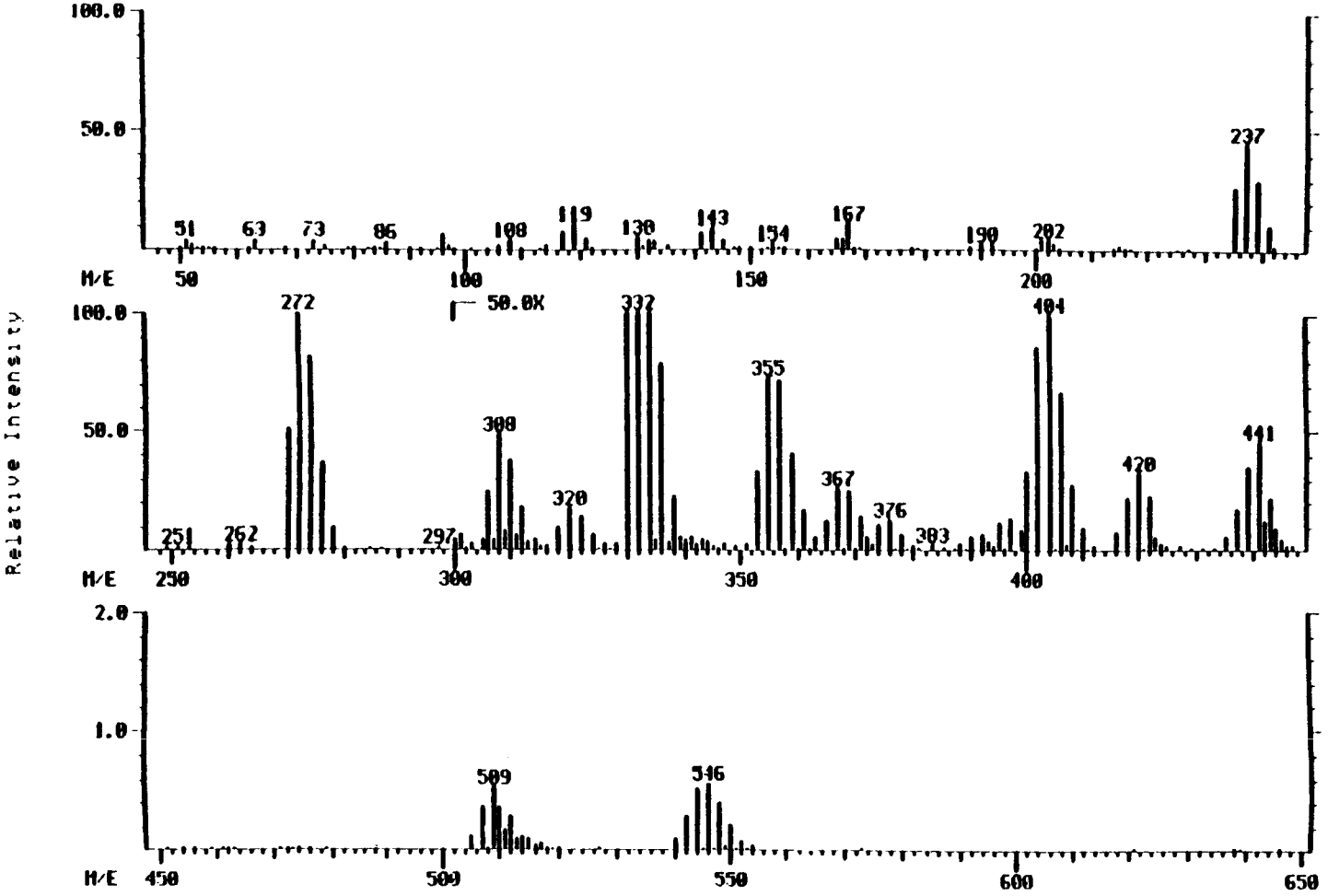

FIGURE 2. MASS SPECTRUM OF MIREX (LOT NO. 083173)

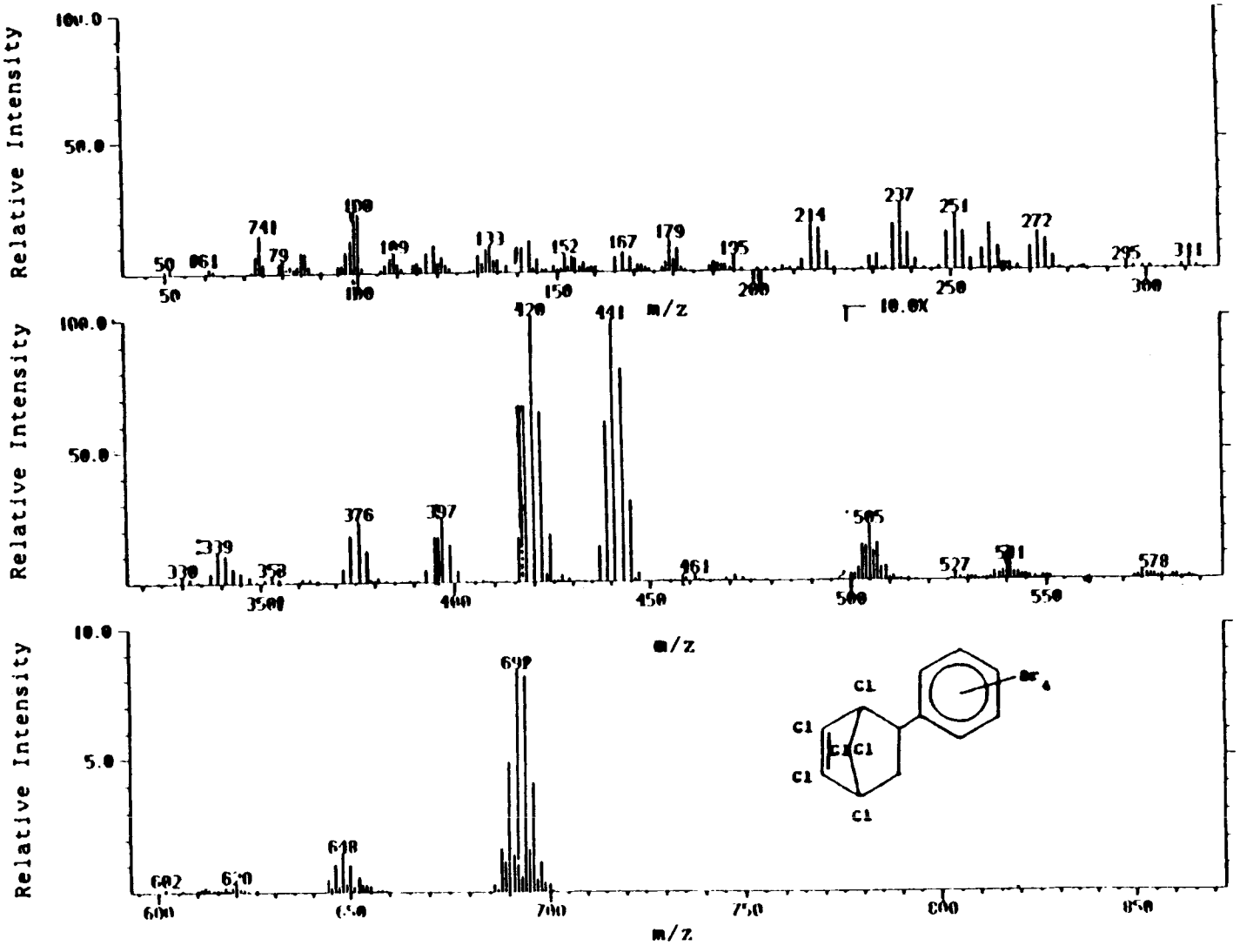

FIGURE 3. MASS SPECTRUM OF THE IMPURITY DECHLORANE 604 FOUND IN MIREX LOT NO. 083173

For the 2-year studies, groups of 52 rats of each sex were fed diets containing 0, 0.1, 1, 10, 25, or 50 ppm mirex in feed for 104 weeks. Several months after the first study had started, it was decided, based on lack of clinical signs and only random and minor variations in the rate of weight gain, that females could tolerate greater concentrations of mirex in feed. In the second study, groups of 52 female rats were fed diets containing 0, 50, or 100 ppm mirex. Further, these dietary concentrations were the same as those used by Ulland et al. (1977) for their study with female CD rats.

Source and Specifications of Animals

The male and female F344/N rats used in this study were produced at Frederick Cancer Research Center or at Harlan Industries (second female rat study). Breeding stock for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were transferred or shipped to the study laboratory at 4 weeks of age. The animals were quarantined at the study facility for 4 weeks. Thereafter, five animals of each sex were killed and given a complete necropsy to assess their health status. The rats were placed on study at 7-8 weeks of age.

Animal Maintenance

Rats were housed four per cage in polycarbonate cages. Feed and water were available ad libitum. Available details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week; the available records on clinical observations were not considered adequate for reporting. Body weights by cage were recorded once per week for the first 12 weeks of the studies and once every 4 weeks thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the studies. A necropsy was performed on all animals, including those found dead. In some cases, a particular organ was not saved or was autolyzed (e.g., pancreas and thyroid gland in male rats). Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed at necropsy. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic evaluation. Tissues examined microscopically are listed in Table 1.

The pathology diagnoses and evaluation of the long-term studies of mirex in rats was first performed by a pathologist at the Frederick Cancer Research Center. Both the pathology quality assessment review and the Pathology Working Group (PWG) review identified major discrepancies and deficiencies, largely in diagnoses, that did not permit an objective evaluation of the studies. As a result, the pathology was reassigned to an independent pathologist (Clement Associates) for a complete re-evaluation. The pathology quality assessment review also identified a marked disparity between the number of liver sections evaluated in some groups of dosed male and female rats and their corresponding control groups. This numerical disparity introduced a potential bias in the interpretation of the pathologic findings, and additional liver sections from control groups were prepared and examined to preclude any possibility of sampling bias. This re-evaluation by a pathologist at Clement Associates was subjected to an independent quality assessment review and a subsequent PWG review and was deemed satisfactory. The pathology data stored in the computerized Carcinogenesis Bioassay Data System and reported in this Technical Report represent a consensus of the opinions of the Clement pathologist and the members of the PWG.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE TWO-YEAR FEED STUDIES OF MIREX

EXPERIMENTAL DESIGN	
Study Laboratory	Frederick Cancer Research Center (Frederick, MD)
Size of Study Groups	52 males and 52 females
Doses	First study: 0, 0.1, 1, 10, 25, or 50 ppm mirex in feed; second study: female rats--0, 50, or 100 ppm mirex in feed
Date of First Dose	First study: 6/7/77; second study: 1/10/78
Duration of Dosing	104 wk
Type and Frequency of Observation	Observed 2 × d; weighed 1 × wk for 12 wk and then 1 × 4 wk
Necropsy and Histologic Examination	Necropsy performed on all animals; the following tissues were examined histologically: adrenal glands, bone marrow, brain, esophagus, heart, kidneys, liver, lungs and bronchi, mammary gland, submandibular and/or mesenteric lymph nodes, pancreas, parathyroid, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small and large intestine, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder
ANIMALS AND ANIMAL MAINTENANCE	
Strain and Species	F344/N rats
Animal Source	Frederick Cancer Research Center (Frederick, MD) (first study); Harlan Industries (Indianapolis, IN) (second study)
Time Held Before Study	4 wk
Age When Placed on Study	7-8 wk
Age When Killed	First study: male--112-113 wk; female--112-114 wk; second study: female--112-114 wk
Necropsy Dates	First study: 6/12/79-6/29/79; second study: female--1/19/80-1/24/80
Method of Animal Distribution	Such that average cage weights were approximately equal; detailed records are not available.
Animal Identification	Ear notch
Feed	Wayne Sterilizable Lab-Blox Mash® (Allied Mills, Chicago, IL); available ad libitum
Water	Tap water acidified to pH 2.5 with 1 N HCl in glass bottles; available ad libitum
Cages	Polycarbonate (Lab Products, Rochelle Park, NJ)
Animals per Cage	4
Other Chemicals on Study in the Same Room	None
Animal Room Environment	Temp--22°-24° C; hum--45%-55%; fluorescent light 12 h/d; 15 room air changes/h

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System.

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. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

In addition to incidental tumor analysis, 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 tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include 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 tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

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 tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS: TWO-YEAR STUDIES

Body Weights and Feed Consumption

Survival

Pathology and Statistical Analyses of Results

Body Weights and Feed Consumption

Mean body weights of male rats that received 25 or 50 ppm mirex were 5%-9% lower than those of the controls beginning at about weeks 12-16, 7%-11% lower at week 60, and 11%-18% lower at week 100 (Table 2; Figure 4). Mean body weights of female rats were 5%-10% lower than those of the controls after week 24 in the 50-ppm group (first study), week 52 in the 50-ppm group (second study), or week 40 in the 100-ppm group; 17% lower after week 84 in the 50-ppm group (first study); and 12%-18% lower after week 64 in the 100-ppm group (Tables 2 and 3; Figures 4 and 5). The average daily feed consumption per rat in the 0.1-ppm, 1-ppm, 10-ppm, 25-ppm and 50-ppm groups in the first studies was 83%, 84%, 87%, 91%, and 89% that by the controls for males and 86%, 99%, 86%, 92%, and 89% for females (Tables D1 and D2). The average amount of mirex consumed per day in the first studies was approximately 0.007, 0.07, 0.7, 1.8, and 3.8 mg/kg for the 0.1-ppm, 1-ppm, 10-ppm, 25-ppm, and 50-ppm groups of male rats and 0.007, 0.08, 0.7, 2.0, and 3.9 mg/kg of female rats. For the second study in female rats, the feed consumption data are incomplete and the available data indicate a wide range of values, and thus, average amounts of mirex per body weight could not be reliably calculated. However, based on the feed consumption data for the first study in female rats, average estimated mirex doses would have been 0, 3.9, and 7.7 mg/kg.

TABLE 2. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE FIRST TWO-YEAR FEED STUDIES OF MIREX

Weeks on Study	Control		0.1 ppm			1 ppm			10 ppm			25 ppm			50 ppm		
	Av. Wt. (grams)	No. of Surv	Av. Wt. (grams)	Wt. (% of Cont)	No. of Surv	Av. Wt. (grams)	Wt. (% of Cont)	No. of Surv	Av. Wt. (grams)	Wt. (% of Cont)	No. of Surv	Av. Wt. (grams)	Wt. (% of Cont)	No. of Surv	Av. Wt. (grams)	Wt. (% of Cont)	No. of Surv
MALE																	
0	121	52	121	100	52	121	100	52	123	102	52	123	102	52	124	102	52
2	205	52	199	97	52	206	100	52	206	100	52	205	100	52	200	98	52
4	227	52	225	99	52	227	100	52	225	99	52	230	101	52	231	102	52
6	263	52	258	98	52	262	100	52	260	99	52	264	100	52	255	97	52
8	273	52	267	98	52	270	99	52	269	99	52	272	100	52	264	97	52
10	297	52	285	96	52	289	97	52	293	99	52	295	99	52	288	97	52
12	308	52	296	96	52	301	98	52	300	97	52	299	97	52	290	94	52
16	327	52	315	96	52	320	98	52	318	97	52	311	95	52	298	91	52
20	345	52	333	97	52	338	98	52	337	98	52	325	94	52	314	91	52
24	364	52	352	97	52	357	98	52	359	99	52	348	96	52	334	92	52
28	381	52	366	96	52	372	98	52	375	98	52	363	95	52	346	91	52
32	393	52	378	96	52	381	97	52	389	99	52	373	95	52	355	90	51
36	398	52	386	97	52	391	98	52	395	99	52	380	95	52	364	91	50
40	401	52	391	98	52	394	98	52	401	100	52	382	95	52	368	92	50
44	405	52	394	97	52	397	98	52	400	99	52	382	94	52	370	91	50
48	415	52	406	98	52	411	99	52	412	99	51	393	95	52	375	90	50
52	416	52	413	99	52	416	100	52	421	101	51	397	95	52	378	91	50
60	413	52	412	100	52	415	100	50	418	101	51	395	96	51	377	91	50
68	432	52	426	99	51	426	99	49	433	100	50	403	93	50	386	89	48
76	419	51	420	100	51	424	101	47	420	100	50	385	92	47	360	86	48
84	411	49	411	100	51	416	101	45	412	100	49	379	92	42	343	83	44
92	423	49	423	100	49	425	100	40	420	99	45	392	93	38	360	85	39
100	418	47	415	99	46	425	102	38	405	97	42	371	89	27	344	82	23
FEMALE																	
0	100	52	100	100	52	100	100	52	100	100	52	100	100	52	100	100	52
2	146	52	145	99	52	144	99	52	142	97	52	142	97	52	142	97	52
4	156	52	155	99	52	154	99	52	153	98	52	159	102	52	158	101	52
6	174	52	173	99	52	172	99	52	171	98	52	170	98	52	172	99	52
8	175	52	173	99	52	172	98	52	170	97	52	170	97	52	172	98	52
10	190	52	183	96	52	182	96	52	180	95	52	182	96	52	183	96	52
12	194	52	191	98	52	188	97	52	185	95	52	186	96	52	185	95	52
16	209	52	207	99	52	206	99	52	200	96	52	203	97	52	200	96	52
20	211	52	208	99	52	209	99	52	203	96	52	207	98	52	200	95	52
24	219	52	216	99	52	217	99	52	211	96	52	215	98	52	204	93	52
28	227	52	223	98	52	225	99	52	218	96	52	219	96	52	213	94	52
32	231	52	227	98	52	230	100	52	223	97	52	225	97	52	216	94	52
36	238	52	232	97	52	234	98	52	228	96	52	229	96	52	220	92	52
40	243	52	237	98	52	240	99	52	233	96	52	235	97	52	224	92	52
44	246	52	241	98	52	244	99	52	239	97	52	239	97	52	228	93	52
48	246	52	239	97	52	243	99	52	239	97	52	238	97	52	229	93	52
52	249	52	243	98	52	248	100	52	243	98	52	244	98	51	232	93	51
60	264	52	256	97	52	261	99	52	257	97	52	257	97	51	242	92	51
68	285	52	278	98	51	282	99	52	275	96	52	272	95	50	256	90	51
76	287	52	283	99	51	286	100	52	280	98	52	279	97	50	258	90	50
84	302	49	288	95	48	284	94	49	288	95	49	284	94	50	255	84	47
92	315	45	298	95	46	303	96	43	302	96	47	299	95	49	267	85	45
100	320	40	298	93	43	307	96	39	298	93	44	296	93	48	267	83	38

TABLE 3. MEAN BODY WEIGHTS AND SURVIVAL OF FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX

Weeks on Study	Control		50 ppm			100 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
0	128	52	130	102	52	133	104	52
4	147	52	147	100	52	150	102	52
8	164	52	165	101	52	168	102	52
12	168	52	172	102	52	174	104	52
16	179	52	180	101	52	184	103	52
20	187	52	189	101	52	188	101	52
24	195	52	193	99	52	193	99	52
28	199	52	198	99	52	197	99	52
32	206	52	205	100	52	202	98	52
36	213	52	208	98	52	207	97	52
40	224	52	213	95	52	209	93	52
44	231	52	222	96	52	216	94	52
48	235	52	225	96	52	218	93	52
52	244	51	233	95	52	224	92	52
56	250	50	237	95	52	226	90	52
60	259	50	246	95	52	232	90	52
64	269	50	252	94	52	238	88	52
68	276	50	260	94	52	243	88	52
72	282	50	266	94	52	249	88	52
76	282	50	270	96	51	252	89	52
80	287	50	273	95	51	255	89	52
84	290	49	273	94	51	251	87	50
88	298	48	278	93	51	253	85	48
92	285	48	265	93	51	242	85	47
96	296	46	275	93	50	247	83	44
100	289	44	264	91	49	247	85	40
104	289	44	267	92	44	238	82	39

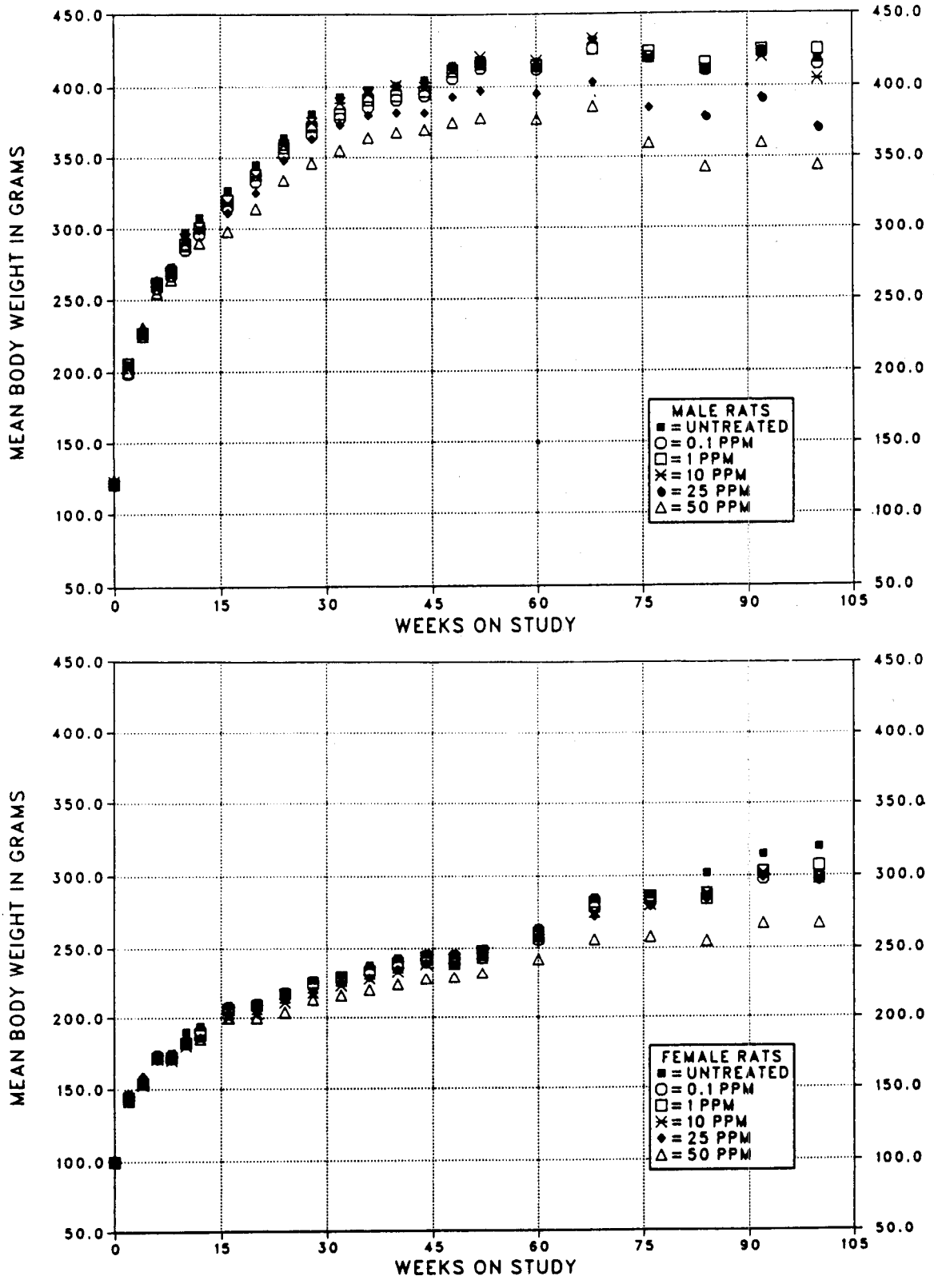

FIGURE 4. GROWTH CURVES FOR RATS FED DIETS CONTAINING MIREX FOR TWO YEARS (FIRST STUDY)

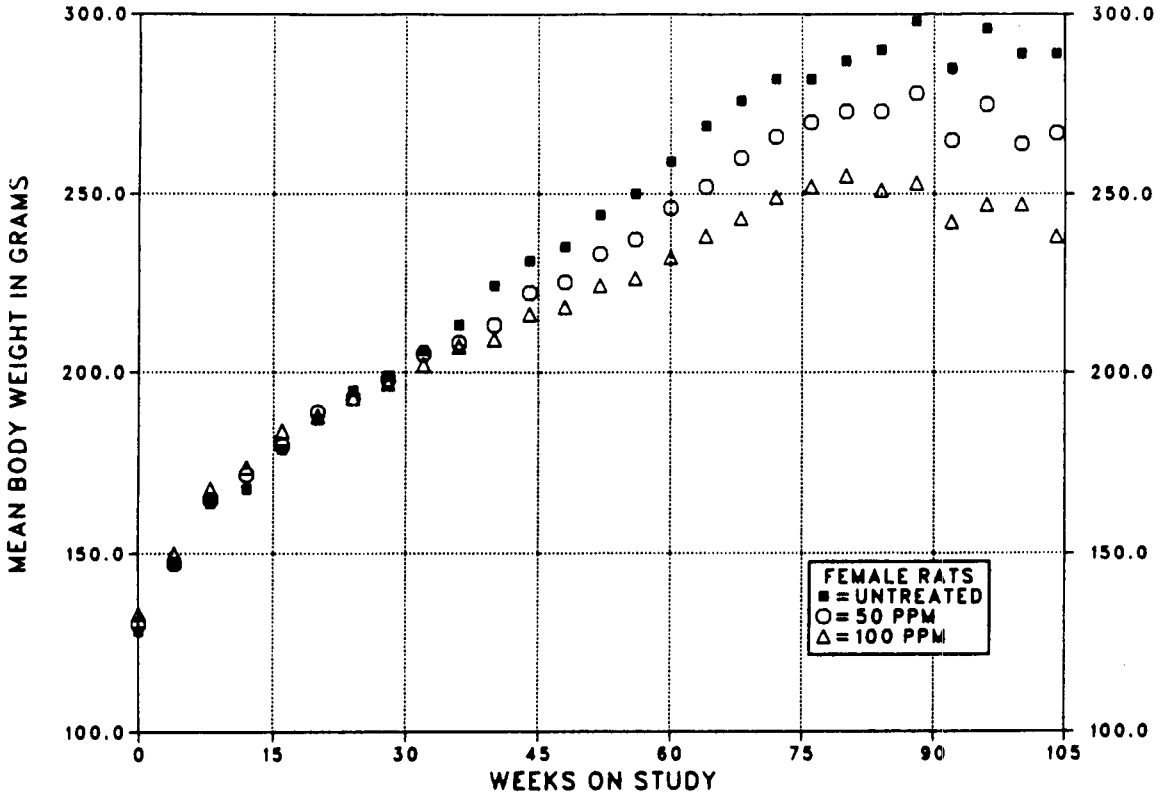

FIGURE 5. GROWTH CURVES FOR FEMALE RATS FED DIETS CONTAINING MIREX FOR TWO YEARS (SECOND STUDY)

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing mirex and for controls are shown in Table 4 and in the Kaplan and Meier curves in Figures 6 and 7. The survival of the 25- and 50-ppm groups of male rats was lower ($P<0.001$) than that of the controls after week 86 and week 87, respectively. No significant differences in survival were observed between any groups of female rats in either the first or second studies.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the liver, adrenal gland, kidney, hematopoietic system, pituitary gland, and thyroid gland. For two lesions (adrenal gland benign and malignant pheochromocytomas and mononuclear cell leukemia), the incidence data from the two studies in female rats were combined for statistical purposes.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 4. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm	100 ppm
MALE (a)							
Animals initially in study	52	52	52	52	52	52	
Nonaccidental deaths before termination (b)	8	15	16	15	33	37	
Killed at termination	42	32	33	34	15	11	
Died during termination period	2	5	3	3	4	4	
Survival P values (c)	<0.001	0.159	0.072	0.140	<0.001	<0.001	
FEMALE (FIRST STUDY) (a)							
Animals initially in study	52	52	52	52	52	52	
Nonaccidental deaths before termination (b)	14	14	17	17	11	17	
Killed at termination	36	33	30	34	35	32	
Died during termination period	2	5	5	1	6	3	
Survival P values (c)	0.933	0.946	0.676	0.812	0.530	0.670	
FEMALE (SECOND STUDY) (d)							
Animals initially in study	52					52	52
Nonaccidental deaths before termination (b)	8					8	13
Killed at termination	43					43	37
Died during termination period	1					1	2
Survival P values (c)	0.266					0.897	0.358

(a) Termination period for the first study: male--weeks 105-107; female--weeks 107-109
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.
(d) Termination period for the second study: weeks 105-106

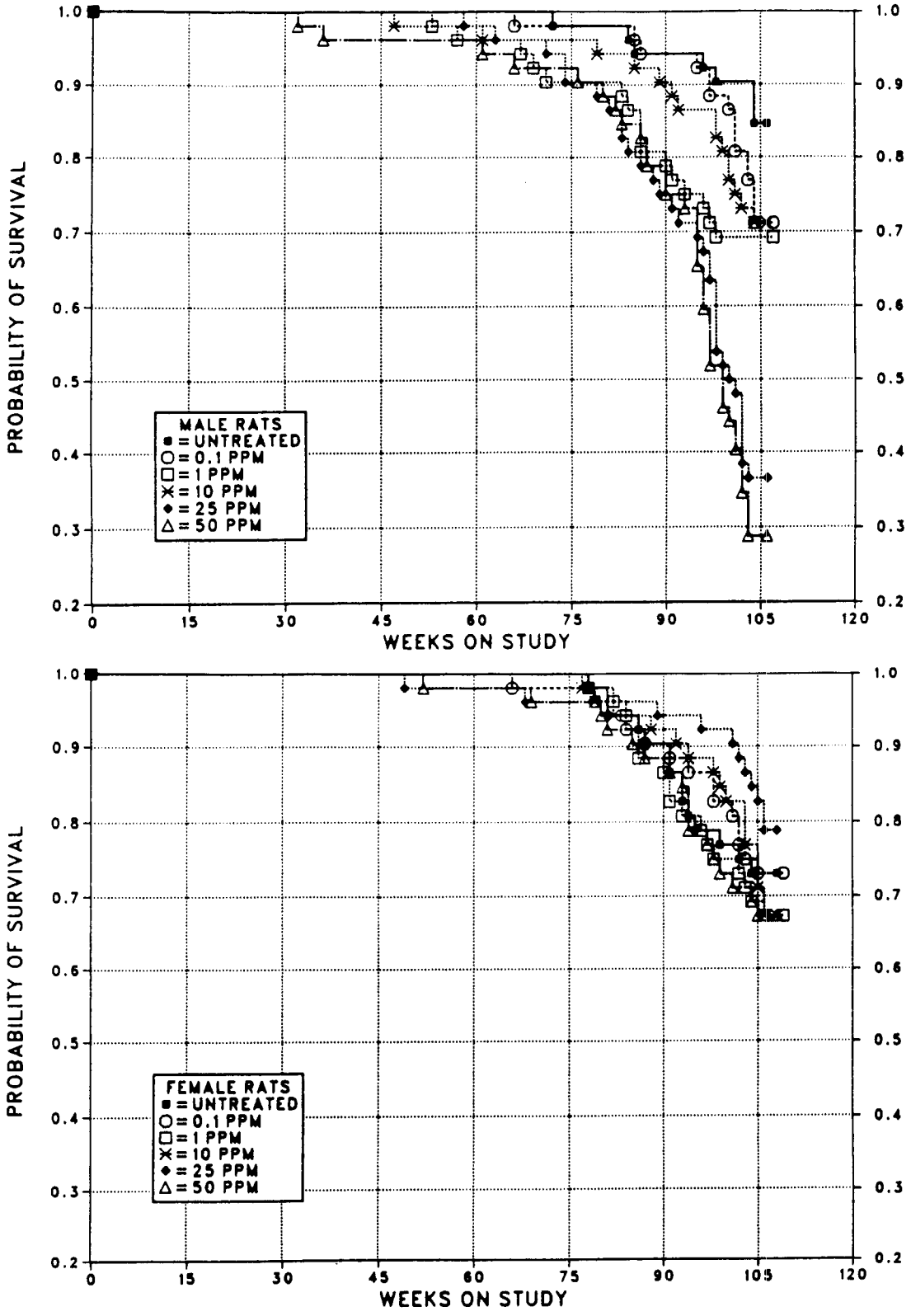

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING MIREX FOR TWO YEARS (FIRST STUDY)

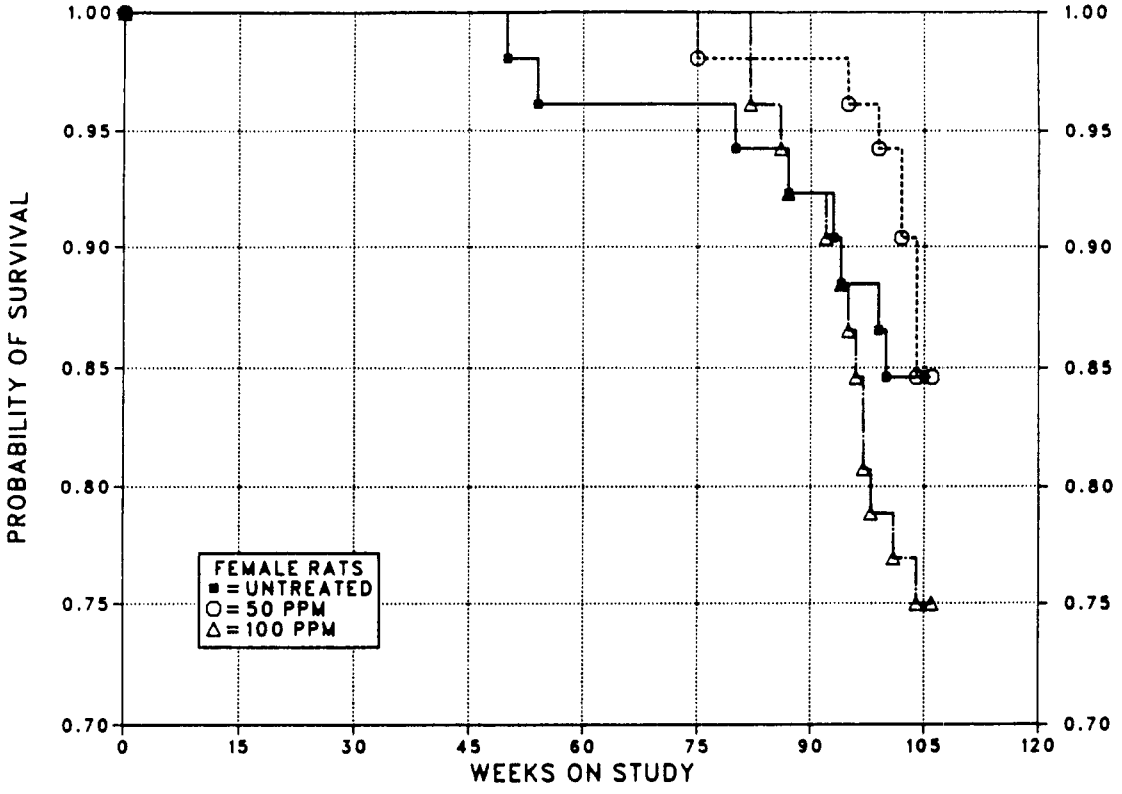

FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR FEMALE RATS FED DIETS CONTAINING MIREX FOR TWO YEARS (SECOND STUDY)

Liver: Several lesions attributable to the administration of mirex were present in the liver (Table 5). These consisted of cytomegaly, fatty metamorphosis, angiectasis (males only), and cellular necrosis. Cytomegaly was observed at increased incidences in the 10-, 25-, and 50-ppm groups of males and the 10-, 25-, 50-, and 100-ppm groups of females. The lesion consisted of generalized centrilobular cytomegaly that increased in both incidence and severity with increased dose. In more severely affected rats, there was bridging of centrilobular areas with involvement of virtually the entire hepatic lobules. Variable atrophy of periportal hepatocytes was associated with the centrilobular change and resulted in some distortion of the hepatic lobular architecture. The enlarged hepatocytes (cytomegaly) had abundant eosinophilic cytoplasm, and some had clear or vacuolated cytoplasm. The presence of cytoplasmic vacuoles is consistent with the intracellular accumulation of fat, and the lesion was diagnosed as fatty metamorphosis. Necrosis of hepatocytes, either focal and/or centrilobular, was observed at increased incidences in dosed groups of male and female rats. Angiectasis, consisting of dilated sinusoids filled with blood or proteinaceous material, occurred more frequently in dosed groups of male rats. This lesion often occurred within foci of cellular alteration or neoplastic nodules.

Neoplastic nodules of the liver in male and female (second study) rats, hepatocellular carcinomas in males, and neoplastic nodules or hepatocellular carcinomas (combined) in males and females (second study) occurred with positive trends, and the incidences in the 10-, 25-, and 50-ppm groups of males and the 50- and 100-ppm

TABLE 5. NUMBER OF RATS WITH LIVER LESIONS IN THE TWO-YEAR FEED STUDIES OF MIREX

Lesion	Concentration (ppm)						
	Control	0.1	1	10	25	50	100
MALE (a)							
Fatty metamorphosis	10	11	13	*20	**21	**26	--
Hepatocytomegaly	2	**12	2	**40	**43	**44	--
Necrosis	7	11	10	12	**28	**38	--
Angiectasis	20	20	19	**42	**38	**39	--
Neoplastic nodule	3	5	5	**14	**15	**26	--
Hepatocellular carcinoma	3	0	2	2	3	4	--
FEMALE (a)							
Fatty metamorphosis							
First study	11	13	18	**36	**45	**43	--
Second study	14	--	--	--	--	**34	**39
Hepatocytomegaly							
First study	4	2	3	*14	**39	**45	--
Second study	4	--	--	--	--	**49	**49
Necrosis							
First study	3	4	3	**15	8	**13	--
Second study	4	--	--	--	--	7	**17
Angiectasis							
First study	3	8	3	2	2	*9	--
Second study	6	--	--	--	--	7	10
Neoplastic nodule							
First study	10	5	4	5	9	7	--
Second study	2	--	--	--	--	**23	**30
Hepatocellular carcinoma							
First study	0	0	0	0	1	2	--
Second study	0	--	--	--	--	0	1

(a) Fifty-two rats were examined in each group.
*P<0.05 vs. controls
**P<0.01 vs. controls

groups of females (second study) were greater than those in the controls (Table 6). There were no differences in incidences of liver neoplasia in the first study in female rats; the number of benign tumors in the control group was unusually high compared with the historical incidence for female F344/N rats (3% ± 3%; 57/2,015; Table B7). The possibility exists that the

TABLE 6. LIVER TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX (a,b)

MALE	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Neoplastic Nodule (c)						
Overall Rates	3/52 (6%)	5/52 (10%)	5/52 (10%)	14/52 (27%)	15/52 (29%)	26/52 (50%)
Adjusted Rates	6.8%	12.6%	13.9%	36.5%	60.6%	81.4%
Terminal Rates	3/44 (7%)	4/37 (11%)	5/36 (14%)	13/37 (35%)	10/19 (53%)	10/15 (67%)
Week of First Observation	105	85	105	91	98	66
Life Table Tests	P<0.001	P=0.279	P=0.251	P=0.001	P< 0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.278	P=0.251	P=0.002	P< 0.001	P<0.001
Hepatocellular Carcinoma (d)						
Overall Rates	3/52 (6%)	0/52 (0%)	2/52 (4%)	2/52 (4%)	3/52 (6%)	4/52 (8%)
Adjusted Rates	6.8%	0.0%	5 6%	5.4%	12 4%	20.3%
Terminal Rates	3/44 (7%)	0/37 (0%)	2/36 (6%)	2/37 (5%)	1/19 (5%)	2/15 (13%)
Week of First Observation	105		105	105	100	95
Life Table Tests	P=0.002	P=0.153N	P=0.591N	P=0.579N	P=0.302	P=0.094
Incidental Tumor Tests	P=0.047	P=0.153N	P=0.591N	P=0.579N	P=0.601	P=0.297
Neoplastic Nodule or Hepatocellular Carcinoma (e)						
Overall Rates	6/52 (12%)	5/52 (10%)	6/52 (12%)	15/52 (29%)	16/52 (31%)	28/52 (54%)
Adjusted Rates	13 6%	12.6%	16 7%	39.2%	62 1%	86.1%
Terminal Rates	6/44 (14%)	4/37 (11%)	6/36 (17%)	14/37 (38%)	10/19 (53%)	11/15 (73%)
Week of First Observation	105	85	105	91	98	66
Life Table Tests	P<0.001	P=0.607N	P=0.475	P=0.008	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.609N	P=0.475	P=0.010	P<0.001	P<0.001
FEMALE (FIRST STUDY)						
Neoplastic Nodule (f)						
Overall Rates	10/52 (19%)	5/52 (10%)	4/52 (8%)	5/52 (10%)	9/52 (17%)	7/52 (13%)
Adjusted Rates	25 3%	13.2%	11.4%	14.3%	21.2%	19.0%
Terminal Rates	9/38 (24%)	5/38 (13%)	4/35 (11%)	5/35 (14%)	8/41 (20%)	6/35 (17%)
Week of First Observation	87	107	107	107	96	94
Life Table Tests	P=0.329	P=0.130N	P=0.098N	P=0 165N	P=0.424N	P=0.356N
Incidental Tumor Tests	P=0 326	P=0.135N	P=0.090N	P=0 180N	P=0.500N	P=0.347N
Hepatocellular Carcinoma						
Overall Rates	0/52 (0%)	0/52 (0%)	0/52 (0%)	0/52 (0%)	1/52 (2%)	2/52 (4%)
Neoplastic Nodule or Hepatocellular Carcinoma (g)						
Overall Rates	10/52 (19%)	5/52 (10%)	4/52 (8%)	5/52 (10%)	10/52 (19%)	9/52 (17%)
Adjusted Rates	25 3%	13 2%	11 4%	14.3%	23 0%	24.6%
Terminal Rates	9/38 (24%)	5/38 (13%)	4/35 (11%)	5/35 (14%)	8/41 (20%)	8/35 (23%)
Week of First Observation	87	107	107	107	96	94
Life Table Tests	P=0 117	P=0 130N	P=0.098N	P=0 165N	P=0.518N	P=0 571N
Incidental Tumor Tests	P=0 119	P=0 135N	P=0.090N	P=0 180N	P=0.593N	P=0.563N

FEMALE (SECOND STUDY)	Control	50 ppm	100 ppm
Neoplastic Nodule (f)			
Overall Rates	2/52 (4%)	23/52 (44%)	30/52 (58%)
Adjusted Rates	4 5%	49 8%	69.4%
Terminal Rates	2/44 (5%)	21/44 (48%)	26/39 (67%)
Week of First Observation	105	95	82
Life Table Tests	P<0.001	P<0.001	P<0 001
Incidental Tumor Tests	P<0 001	P<0.001	P<0.001
Hepatocellular Carcinoma			
Overall Rates	0/52 (0%)	0/52 (0%)	1/52 (2%)
Neoplastic Nodule or Hepatocellular Carcinoma (g)			
Overall Rates	2/52 (4%)	23/52 (44%)	31/52 (60%)
Adjusted Rates	4.5%	49.8%	70.0%
Terminal Rates	2/44 (5%)	21/44 (48%)	26/39 (67%)
Week of First Observation	105	95	82
Life Table Tests	P<0.001	P<0 001	P<0.001
Incidental Tumor Tests	P<0.001	P<0 001	P<0.001

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes); the incidence of hepatocellular neoplasms in controls in the first study in female rats was significantly different from that in the second study, and therefore, the two control groups were not combined for analysis.
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights and Feed Consumption) and in Appendix D.
(c) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 83/1,969 (4% ± 5%)
(d) Historical incidence in NTP studies (mean ± SD): 19/1,969 (1% ± 1%)
(e) Historical incidence in NTP studies (mean ± SD): 101/1,969 (5% ± 5%)
(f) Historical incidence in NTP studies (mean ± SD): 57/2,015 (3% ± 3%)
(g) Historical incidence in NTP studies (mean ± SD): 59/2,015 (3% ± 3%)

additional sampling of liver sections may have contributed to this higher incidence. The two studies are not reported with combined statistical analyses because the two control groups were different ($P=0.008$); however, the combined analyses did show a positive trend ($P<0.0012$), and the incidences in both the 50-ppm and 100-ppm groups were significantly increased ($P<0.001$) compared with that in the control composite (control: 12/104, 11%; 0.1 ppm: 5/52, 10%; 1 ppm: 4/52, 8%; 10 ppm: 5/52, 10%; 25 ppm: 10/52, 19%; 50 ppm: 32/104, 31%; 100 ppm: 31/52, 58%).

The neoplastic nodules observed in dosed rats usually consisted of enlarged hepatocytes with eosinophilic or clear cytoplasm arranged in irregular distorted cords one or two cell layers thick. The eosinophilic cell type predominated in males, and the clear cell type was more common in females. Neoplastic nodules consisting of cells with basophilic cytoplasm were seen in small numbers in control and dosed groups.

Adrenal Gland: The incidences of medullary hyperplasia of the adrenal gland were not increased in dosed male or female rats (Table 7). The incidences of pheochromocytomas or malignant pheochromocytomas (combined) occurred with positive trends in male rats, and the incidences in both the 25- and 50-ppm groups of male rats were significantly increased compared with that in controls. The incidence in the 50-ppm group of female rats (first study) was of borderline significance compared with that in controls; this was not observed in the second study, and combining the two studies for statistical analyses showed no differences among groups. Most neoplasms were benign pheochromocytomas; malignant pheochromocytomas were diagnosed in two control and one 10- and one 50-ppm males and in one 50-ppm (first study) and one 100-ppm female. For this lesion, the most appropriate analyses are for the combination of benign and malignant pheochromocytomas (McConnell et al., 1986).

TABLE 7. ADRENAL GLAND LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

MALE	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Medullary Hyperplasia						
Overall Rates	8/51 (16%)	4/52 (8%)	2/52 (4%)	10/52 (19%)	6/51 (12%)	9/51 (18%)
Pheochromocytoma or Malignant Pheochromocytoma (a)						
Overall Rates	10/51 (20%)	7/52 (13%)	13/52 (25%)	12/52 (23%)	18/51 (35%)	20/51 (39%)
Adjusted Rates	22.7%	16.4%	32.0%	29.2%	61.5%	66.4%
Terminal Rates	10/44 (23%)	4/37 (11%)	9/36 (25%)	9/37 (24%)	9/19 (47%)	7/15 (47%)
Week of First Observation	105	86	86	79	86	80
Life Table Tests	P<0.001	P=0.423N	P=0.164	P=0.258	P<0.001	P<0.001
Incidental Tumor Tests	P<0 001	P=0.334N	P=0.236	P=0.336	P=0.008	P=0.009
FEMALE (FIRST STUDY)						
Medullary Hyperplasia						
Overall Rates	1/51 (2%)	1/52 (2%)	2/52 (4%)	5/51 (10%)	0/5 l (0%)	2/52 (4%)
Pheochromocytoma or Malignant Pheochromocytoma (b)						
Overall Rates	1/51 (2%)	3/52 (6%)	5/52 (10%)	1/51 (2%)	2/51 (4%)	6/52 (12%)
Adjusted Rates	2.6%	7 2%	13.7%	2.9%	5.0%	16.6%
Terminal Rates	1/38 (3%)	2/38 (5%)	4/35 (11%)	1/35 (3%)	2/40 (5%)	5/35 (14%)
Week of First Observation	107	87	102	107	107	104
Life Table Tests	P=0.096	P=0.307	P=0.089	P=0.743	P=0.518	P=0.048
Incidental Tumor Tests	P=0 096	P=0.291	P=0.094	P=0.743	P=0.518	P=0.056

FEMALE (SECOND STUDY)	Control	50 ppm	100 ppm
Medullary Hyperplasia			
Overall Rates	1/52 (2%)	0/52 (0%)	0/52 (0%)
Pheochromocytoma or Malignant Pheochromocytoma (b)			
Overall Rates	3/52 (6%)	2/52 (4%)	2/52 (4%)
Adjusted Rates	6.8%	4.0%	5.1%
Terminal Rates	3/44 (7%)	0/44 (0%)	2/39 (5%)
Week of First Observation	105	99	105
Life Table Tests	P=0.455N	P=0.483N	P=0.555N
Incidental Tumor Tests	P=0.363N	P=0 400N	P=0.555N

COMBINED ANALYSIS (c)	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm	100 ppm
Pheochromocytoma or Malignant Pheochromocytoma							
Overall Rates	4/103 (4%)	3/52 (6%)	5/52 (10%)	1/51 (2%)	2/51 (4%)	8/104 (8%)	2/52 (4%)
Adjusted Rates	4.9%	7.1%	13.4%	2 5%	4.7%	9.5%	5.1%
Terminal Rates	4/82 (5%)	2/39 (5%)	4/36 (11%)	1/40 (3%)	2/43 (5%)	5/80 (6%)	2/39 (5%)
Week of First Observation	105	87	102	108	107	99	105
Life Table Tests	P=0 539	P=0 423	P=0 098	P=0 446N	P=0 649N	P=0.182	P=0.651
Incidental Tumor Tests	P=0.561N	P=0 441	P=0 109	P=0.446N	P=0.649N	P=0.223	P=0.651

(a) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 452/1,950 (23% ± 12%)
(b) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 94/2,001 (5% ± 4%)
(c) Results of comparison of the 0.1-, 1-, 10-, 25-, 50- (combined incidence from first and second studies), and 100-ppm groups with controls (combined incidence from first and second studies)

Kidney: Nephropathy occurred at similar incidences in control and dosed groups of male and female rats. However, the severity was judged to be dose related and greater in groups of male and female rats receiving 25 ppm or more mirex (Table 8). Parathyroid hyperplasia is likely a secondary physiologic response to the nephropathy, and male rats showed dose-related incidences of this lesion (6/32; 12/39; 13/39; 18/40; 22/50; 24/45). Hyperplasia of the transitional epithelium overlying the renal pelvis was observed at increased incidences in dosed male rats (Table 9). This lesion has also been shown to accompany severe nephropathy.

TABLE 8. INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm	100 ppm
MALE							
Incidence of nephropathy	50/51	50/51	45/52	49/52	51/51	52/52	
Severity (a)							
No grade (autolysis)	2	2	1	2	11	6	
Mild	7	4	5	1	5	1	
Moderate	31	39	32	14	10	3	
Marked	10	5	7	32	25	42	
Mean severity (b)	3.1	3.0	3.0	3.7	3.5	3.9	
FEMALE (FIRST STUDY)							
Incidence of nephropathy	34/51	35/52	44/52	47/51	46/50	42/52	
Severity (a)							
No grade (autolysis)	--	--	--	3	1	1	
Mild	17	17	15	22	9	8	
Moderate	16	17	24	16	29	28	
Marked	1	1	5	6	7	5	
Mean severity (b)	2.5	2.5	2.8	2.6	3.0	2.9	
FEMALE (SECOND STUDY)							
Incidence of nephropathy	45/51					51/52	52/52
Severity (a)							
Mild	15					7	7
Moderate	27					35	28
Marked	3					9	17
Mean severity (b)	2.7					3.0	3.2

(a) Number of animals with indicate severity
(b) Mean severity of animals with lesion of diagnosed severity; 2 = mild; 3 = moderate; 4 = marked.

TABLE 9. KIDNEY LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

	Concentration (ppm)					
	Control	0.1	1	10	25	50
Epithelial Hyperplasia of the Renal Pelvis						
Overall Rates	0/51 (0%)	2/51 (4%)	2/52 (4%)	5/52 (10%)	14/51 (27%)	9/52 (17%)
Transitional Cell Papilloma (a)						
Overall Rates	0/51 (0%)	0/51 (0%)	0/52 (0%)	0/52 (0%)	1/51 (2%)	3/52 (6%)
Adjusted Rates	0.0%	0.0%	0.0%	0.0%	3.0%	15.7%
Terminal Rates	0/44 (0%)	0/37 (0%)	0/36 (0%)	0/37 (0%)	0/19 (0%)	1/15 (7%)
Week of First Observation					98	101
Life Table Tests	P<0.001	(b)	(b)	(b)	P=0.425	P=0.018
Incidental Tumor Tests	P=0.018	(b)	(b)	(b)	P=0.742	P=0.193

(a) No 2-year studies by this laboratory are included in the historical data base; historical incidence of transitional cell neoplasms in NTP studies (mean ± SD): 5/1,968 (0.3% ± 0.7%)
(b) No P value is reported because no tumors were observed in the dosed and control groups.

Transitional cell papillomas in male rats occurred with a positive trend (Table 9). The incidence in the 50-ppm group was significantly greater than that in controls by the life table test but not by the incidental tumor test, which is the more appropriate analysis. These papillomas are uncommon in untreated male F344/N rats (historical incidence, 0.3%). The transitional cell papillomas differed from hyperplasia primarily by their complexity of structure. The transitional cell papillomas consisted of a single or stratified epithelium arranged in branching, papillary formations.

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with positive trends in both studies (Table 10). The incidences of mononuclear cell leukemia in the 25-ppm group of males and in the 25- and 50 ppm groups of females in the first study and in the 100-ppm group of females in the second study were greater ($P<0.05$) than those in controls. Because this is most often a life-threatening or lethal lesion, the life table analysis is given preference; in the first study in female rats, most leukemia (except in the 25-ppm group) occurred before the end of the study (40/77, 52%). In the second study in females, most of these lesions were observed incidentally at the end of the study (23/29, 79%); yet in each study, both types of analyses showed positive trends and marginal increases in the 25- and 50-ppm (first study) and in the 100-ppm (second study) groups. Since the incidences in female control groups in both studies were similar, combined statistical analyses were done; the marginal positive trends remained, and the 10-, 25-, 50-, and 100-ppm groups showed increased incidences compared with controls.

TABLE 10. HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

MALE	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Mononuclear Cell Leukemia (a)						
Overall Rates	16/52 (31%)	17/52 (33%)	15/52 (29%)	22/52 (42%)	21/52 (40%)	10/52 (19%)
Adjusted Rates	35.4%	38.5%	36.9%	48.6%	60.7%	31.1%
Terminal Rates	15/44 (34%)	11/37 (30%)	11/36 (31%)	14/37 (38%)	8/19 (42%)	1/15 (7%)
Week of First Observation	85	85	84	91	58	66
Life Table Tests	P=0.046	P=0.317	P=0.420	P=0.066	P=0.001	P=0.264
Incidental Tumor Tests	P=0.101N	P=0.484	P=0.573	P=0.160	P=0.152	P=0.195N
FEMALE (FIRST STUDY)						
Mononuclear Cell Leukemia (b)						
Overall Rates	8/52 (15%)	8/52 (15%)	11/52 (21%)	14/52 (27%)	18/52 (35%)	18/52 (35%)
Adjusted Rates	18.3%	18.0%	23.4%	30.4%	39.3%	40.6%
Terminal Rates	4/38 (11%)	3/38 (8%)	1/35 (3%)	5/35 (14%)	14/41 (34%)	10/35 (29%)
Week of First Observation	91	79	82	77	49	69
Life Table Tests	P=0.005	P=0.586N	P=0.296	P=0.132	P=0.044	P=0.023
Incidental Tumor Tests	P=0.003	P=0.581N	P=0.398	P=0.183	P=0.039	P=0.027

FEMALE (SECOND STUDY)	Control	50 ppm	100 ppm
Mononuclear Cell Leukemia (b)			
Overall Rates	6/52 (12%)	9/52 (17%)	14/52 (27%)
Adjusted Rates	12.8%	18.8%	34.9%
Terminal Rates	4/44 (9%)	6/44 (14%)	13/39 (33%)
Week of First Observation	80	95	98
Life Table Tests	P=0.018	P=0.314	P=0.024
Incidental Tumor Tests	P=0.039	P=0.287	P=0.042

COMBINED ANALYSIS (c)	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm	100 ppm
Mononuclear Cell Leukemia							
Overall Rates	14/104 (13%)	8/52 (15%)	11/52 (21%)	14/52 (27%)	18/52 (35%)	27/104 (26%)	14/52 (27%)
Adjusted Rates	15.4%	18.0%	23.3%	29.5%	37.2%	29.0%	34.9%
Terminal Rates	8/82 (10%)	4/39 (10%)	1/36 (3%)	8/40 (20%)	14/44 (32%)	16/80 (20%)	13/39 (33%)
Week of First Observation	80	79	82	77	49	69	98
Life Table Tests	P=0.044	P=0.445	P=0.130	P=0.041	P=0.006	P=0.025	P=0.030
Incidental Tumor Tests	P=0.035	P=0.548	P=0.331	P=0.042	P=0.002	P=0.024	P=0.045

(a) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 583/1,977 (29% ± 12%)
(b) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 375/2,021 (19% ± 7%)
(c) Results of comparison of the 0.1-, 1-, 10-, 25-, 50- (combined incidence from first and second studies), and 100-ppm groups with controls (combined incidence from first and second studies)

Pituitary Gland: The incidences of adenomas (20/52; 24/51; 31/50; 24/51; 30/52; 22/50) and adenomas or carcinomas (combined) in the 1- and 25-ppm groups of females were greater ($P<0.05$) than those in controls in the first study; however, there was no dose response effect (Tables B5 and B6). The incidences in male rats and in females in the second study indicated negative ($P<0.05$) trends (adenomas or carcinomas, combined--male: 12/52; 11/52; 13/51; 10/50; 9/52; 3/47; female: 32/52; 26/52; 22/52). Almost all lesions were adenomas.

Thyroid Gland: The incidences of follicular cell adenomas and follicular cell adenomas or carcinomas (combined) occurred with a positive trend in dosed male rats, and the incidence of adenomas or carcinomas (combined) in the 50-ppm group of male rats was marginally ($P=0.048$) greater than that in controls (Table 11).

The incidences of C-cell adenomas and C-cell adenomas or carcinomas (combined) occurred with negative trends in male ($P=0.043$) and female ($P=0.003$) rats (in the first study but not in the second study) (Table 11). The incidence of C-cell adenomas or carcinomas (combined) in the 50-ppm group of females was lower ($P=0.009$) than that in controls in the first study but not in the second study. Statistical analyses of the two female rat studies combined showed a negative trend ($P=0.009$), and the 50-ppm groups were marginally decreased ($P=0.026$) but not the 100-ppm group.

TABLE 11. THYROID GLAND LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
MALE						
Follicular Cell Hyperplasia						
Overall Rates	0/51 (0%)	0/50 (0%)	0/47 (0%)	0/47 (0%)	0/35 (0%)	1/49 (2%)
Follicular Cell Adenoma						
Overall Rates	0/51 (0%)	0/50 (0%)	0/47 (0%)	1/47 (2%)	0/35 (0%)	3/49 (6%)
Adjusted Rates	0.0%	0.0%	0.0%	2.7%	0.0%	14.4%
Terminal Rates	0/44 (0%)	0/37 (0%)	0/36 (0%)	1/37 (3%)	0/18 (0%)	1/15 (7%)
Week of First Observation				105		99
Life Table Tests	P<0.001	(a)	(a)	P=0.465	(a)	P=0.024
Incidental Tumor Tests	P=0.017	(a)	(a)	P=0.465	(a)	P=0.193
Follicular Cell Carcinoma						
Overall Rates	0/51 (0%)	1/50 (2%)	0/47 (0%)	0/47 (0%)	0/35 (0%)	1/49 (2%)
Follicular Cell Adenoma or Carcinoma (b)						
Overall Rates	0/51 (0%)	1/50 (2%)	0/47 (0%)	1/47 (2%)	0/35 (0%)	4/49 (8%)
Adjusted Rates	0.0%	2.7%	0.0%	2.7%	0.0%	20.5%
Terminal Rates	0/44 (0%)	1/37 (3%)	0/36 (0%)	1/37 (3%)	0/18 (0%)	2/15 (13%)
Week of First Observation		105		105		99
Life Table Tests	P<0.001	P=0.465	(a)	P=0.465	(a)	P=0.005
Incidental Tumor Tests	P=0.004	P=0.465	(a)	P=0.465	(a)	P=0.048
C-Cell Hyperplasia						
Overall Rates	9/51 (18%)	3/50 (6%)	1/47 (2%)	1/47 (2%)	1/35 (3%)	2/49 (4%)
C-Cell Adenoma or Carcinoma						
Overall Rates	8/51 (16%)	6/50 (12%)	4/47 (9%)	7/47 (15%)	3/35 (9%)	0/49 (0%)
Adjusted Rates	18.2%	15.6%	11.1%	17.7%	16.7%	0.0%
Terminal Rates	8/44 (18%)	5/37 (14%)	4/36 (11%)	5/37 (14%)	3/18 (17%)	0/15 (0%)
Week of First Observation	105	103	105	100	105	
Life Table Tests	P=0.126N	P=0.521N	P=0.287N	P=0.580	P=0.588N	P=0.092N
Incidental Tumor Tests	P=0.043N	P=0.476N	P=0.287N	P=0.604N	P=0.588N	P=0.092N
FEMALE (FIRST STUDY)						
Follicular Cell Adenoma or Carcinoma						
Overall Rates	1/50 (2%)	2/50 (4%)	0/48 (0%)	2/47 (4%)	0/48 (0%)	1/46 (2%)
C-Cell Hyperplasia						
Overall Rates	4/50 (8%)	2/50 (4%)	3/48 (6%)	1/47 (2%)	4/48 (8%)	5/46 (11%)
C-Cell Adenoma						
Overall Rates	10/50 (20%)	9/50 (18%)	6/48 (13%)	5/47 (11%)	6/48 (13%)	2/46 (4%)
Adjusted Rates	25.3%	22.7%	17.0%	14.3%	14.1%	5.9%
Terminal Rates	9/38 (24%)	8/38 (21%)	5/34 (15%)	5/35 (14%)	4/39 (10%)	2/34 (6%)
Week of First Observation	91	91	104	107	96	107
Life Table Tests	P=0.018N	P=0.500N	P=0.276N	P=0.165N	P=0.185N	P=0.024N
Incidental Tumor Tests	P=0.022N	P=0.541N	P=0.259N	P=0.189N	P=0.237N	P=0.027N
C-Cell Carcinoma						
Overall Rates	3/50 (6%)	4/50 (8%)	1/48 (2%)	4/47 (9%)	0/48 (0%)	0/46 (0%)
Adjusted Rates	7.9%	9.9%	2.9%	10.5%	0.0%	0.0%
Terminal Rates	3/38 (8%)	3/38 (8%)	1/34 (3%)	3/35 (9%)	0/39 (0%)	0/34 (0%)
Week of First Observation	107	94	107	92		
Life Table Tests	P=0.029N	P=0.505	P=0.345N	P=0.467	P=0.116N	P=0.141N
Incidental Tumor Tests	P=0.034N	P=0.512	P=0.345N	P=0.410	P=0.116N	P=0.141N
C-Cell Adenoma or Carcinoma (c)						
Overall Rates	12/50 (24%)	13/50 (26%)	7/48 (15%)	9/47 (19%)	6/48 (13%)	2/46 (4%)
Adjusted Rates	30.5%	32.0%	19.9%	24.5%	14.1%	5.9%
Terminal Rates	11/38 (29%)	11/38 (29%)	6/34 (18%)	8/35 (23%)	4/39 (10%)	2/34 (6%)
Week of First Observation	91	91	104	92	96	107
Life Table Tests	P=0.002N	P=0.503	P=0.220N	P=0.377N	P=0.084N	P=0.008N
Incidental Tumor Tests	P=0.003N	P=0.470	P=0.205N	P=0.445N	P=0.112N	P=0.009N

TABLE 11. THYROID GLAND LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF MIREX (Continued)

	Control	50 ppm	100 ppm
FEMALE (SECOND STUDY)			
Follicular Cell Adenoma			
Overall Rates	1/49 (2%)	1/49 (2%)	1/49 (2%)
C-Cell Hyperplasia			
Overall Rates	5/49 (10%)	3/49 (6%)	3/49 (6%)
C-Cell Adenoma			
Overall Rates	5/49 (10%)	3/49 (6%)	5/49 (10%)
C-Cell Carcinoma			
Overall Rates	2/49 (4%)	3/49 (6%)	0/49 (0%)
C-Cell Adenoma or Carcinoma			
Overall Rates	7/49 (14%)	6/49 (12%)	5/49 (10%)

(a) No P value is presented because no tumors were observed in the control and the indicated dose groups.
(b) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 27/1,928 (1% ± 2%)
(c) No 2-year studies by this laboratory are included in the historical data base; historical incidence in NTP studies (mean ± SD): 182/1,952 (9% ± 5%)

IV. DISCUSSION AND CONCLUSIONS

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Long-term toxicology and carcinogenesis studies were initiated by administering diets containing 0, 0.1, 1, 10, 25, or 50 ppm mirex to groups of 52 male and 52 female F344/N rats. During the first few months of the studies, there was concern that the doses selected for the female rats could perhaps have been higher. At that time, no chemical-related clinical signs were observed and no effects on body weight gain or survival were present. Thus, a second study was begun approximately 6 months after the first study was initiated. The second study was designed with two dose groups (50 and 100 ppm) and a control group, providing a top dose twice that used in the first study, a low dose that duplicated the top dose of the first study, and a second concurrent control group.

No studies were done in mice because at the time these studies were begun in F344/N rats, sufficient evidence was available that mirex was carcinogenic for the liver in mice (Innes et al., 1969; IARC, 1979); during the early phases of the rat studies, Ulland et al. (1977) reported that mirex caused liver neoplasms in CD rats (IARC, 1979). Because relatively small numbers of animals were used (26 per group), because dietary exposure lasted just 18 months, followed by a 6-month observation period with no exposure (likely due to reduced survival), and because few neoplasms were observed, the studies in F344/N rats were continued to better define the effects overall, especially at lower exposures (Ulland et al. used dietary concentrations of 50 and 100 ppm mirex).

Mean body weights of male rats that received 25 or 50 ppm were lower than those of controls throughout much of the study, whereas body weights of dosed female rats were similar to those of controls until about week 68 of the first study, after which the 50-ppm group had body weights of 82%-90% those of controls. In the second study, weight gains of the 50-ppm group were affected less than in the first study, and the 100-ppm group had mean body weights 82%-90% those of controls after about week 56. Survival of male rats that received 25 or 50 ppm mirex was lower than that of controls only after weeks 86-87 of the study. Many of these male rats dying of "natural causes" had neoplasms of the liver and/or adrenal gland as well as severe nephropathy. Survival of dosed females was similar to that of controls in both studies.

The most notable compound-related effects were observed in the liver of male and female rats. Fatty metamorphosis, cytomegaly, angiectasis (males only), and necrosis were dose related. No significant differences in incidences of hepatocellular carcinomas were observed, but the incidences of neoplastic nodules of the liver were markedly increased in both dosed male and female rats. Particularly strong dose-response relationships were evident in neoplastic nodules in male rats and in female rats in the second study (see Table 6). The incidence of neoplastic nodules was unusually high in the first study control group (19%), approximately sevenfold greater than the mean historical incidence (2.9%) and twice the highest incidence observed in any previous untreated control group (Table B7a). Comparison of both concurrent female control groups shows clearly that they are statistically different with respect to the number of animals with liver neoplasms. The rats were obtained from different sources for the first and second studies, but uniformly high incidences were not observed across the dose groups in the first study, suggesting that the control incidence represented either a chance clustering of naturally occurring neoplastic nodules (so-called "spontaneous" or background neoplasms of unknown etiology) or the incidence could have been influenced by the additional sections taken from the controls to avoid sample bias, since the higher exposed groups had more sections.

In another study of mirex, in male and female CD rats, similar patterns of increased incidences with dose were reported for both nonneoplastic and neoplastic liver effects at comparable exposure levels (Ulland et al., 1977). In mice, the liver was also shown to be the target organ for toxic effects of mirex (Innes et al., 1968; IARC, 1979). For the related chemical chlordecone, 2-year dietary studies in Osborne-Mendel and $B6C3F_1$ mice at lower doses showed increased incidences in carcinomas of the liver in both sexes of both species, particularly in mice (NCI, 1976).

The incidences of pheochromocytomas or malignant pheochromocytomas (combined) of the adrenal gland increased with a dose-related trend in male rats, and the incidences in the 25- and 50-ppm groups were greater than those in controls. The magnitude and dose response of the lesions in males were considered sufficient to make an association with mirex administration. The control incidence agreed well with the mean historical incidence for untreated control male rats (Table A4e), and the increases at the two top doses occurred despite lessened survival. In females, however, the incidence of pheochromocytomas in the 50-ppm group was marginally increased in the first study and not observed in the second study, suggesting that the neoplasms in females were unrelated to mirex administration.

Transitional cell papillomas of the kidney occurred with a positive trend in male rats (see Table 9). These lesions were observed in the two top dose groups (25 ppm, 1/51, and 50 ppm, 3/52). Transitional cell papillomas and carcinomas are uncommon in historical controls (0.3%; Table A4c). Transitional cell hyperplasia was also increased in dosed male rats. Although this finding strengthens the association of mirex administration with proliferative lesions of the transitional epithelium in the kidney, the biologic importance of these lesions is somewhat uncertain because the rarity of neoplasia has made it difficult to fully assess the potential for progression from hyperplasia to papilloma and from papilloma to carcinoma. In addition, the occurrence of transitional cell hyperplasia may also be associated with the increased severity of nephropathy observed in dosed rats in the current studies. Nonetheless, these hyperplastic and neoplastic lesions are considered to be related to the dietary administration of mirex.

Mononuclear cell leukemia in female rats showed positive dose-related trends in both studies. Increased incidences were observed in the 25- and 50-ppm groups in the first study, and the incidence in the 100-ppm group was increased in the second study (see Table 10). An association of mononuclear cell leukemia with mirex administration is indicated primarily because the rather marginal increases occurred in both studies. If one combines the two studies, since the incidences of leukemia did not differ statistically between the two control groups (13% and 15%), the incidences in the 10-, 25-, 50-, and 100-ppm groups were greater than the combined control incidence, lending further support to the association of mononuclear cell leukemia with mirex administration. In male rats, the increase observed in the 25-ppm group and the slight increase in the 10-ppm group were not supported by the incidence in the 50-ppm animals (see Table 10). Poor survival in the 25- and 50-ppm groups may have limited the expression of mononuclear cell leukemia in these groups, but the present evidence was considered to be insufficient to relate the incidences of mononuclear cell leukemia in male rats with mirex administration.

The incidence of follicular cell neoplasms in the thyroid gland was marginally increased in the top dose group of male rats (see Table 11). Even though the historical control incidence of these neoplasms is low (1.4%; Table A4d), the absence of an effect in the next lower dose group of males and the lack of an increase in either study in female rats make an association between follicular cell tumors and exposure to mirex unlikely. Conversely, negative trends (i.e., decreases in neoplasms in the exposed groups compared with controls) were observed for C-cell neoplasia in male rats and in female rats (first study). These decreases could be related to mirex administration; yet the biologic reasoning for this is unclear. In addition, the decrease in males was very marginal, and the decrease in females was due largely to the relatively low incidence in the top dose group compared with the higher than average control incidence; and neither the 50- nor the 100-ppm female group in the second study exhibited a decreased incidence.

Neither mirex nor the structural analog chlordecone has been shown to induce any consistent effects in genetic toxicity assays in the presence or absence of exogenous metabolic activation, with the exception of one study in which an increase in the rates of sister chromatid exchanges was observed after exposure of CHO cells to chlordecone (Galloway et al., 1987). Mirex has generally been classified as metabolically inert (Waters and Black, 1976), but reductive dechlorination has been predicted as a pathway of degradation in vivo (Rinkus and Legator, 1980). McCann and Ames (1976) have

suggested that microsomal enzymes in S9 fractions may be unable to dechlorinate pesticides such as mirex, chlordecone, and dieldrin, which are carcinogenic and yet lack activity in the Ames assay (Schoeny et al., 1979).

Under the conditions of these 2-year feed studies of mirex, there is *clear evidence of carcinogenic activity** for male and female F344/N rats, as primarily indicated by marked increased incidences of benign neoplastic nodules of the liver, as well as by increased incidences of pheochromocytomas of the adrenal gland and transitional cell papillomas of the kidney in males and by increased incidences of mononuclear cell leukemia in females.

Nonneoplastic effects induced by mirex administration include cytomegaly, fatty metamorphosis, angiectasis (males only), and cellular necrosis in the liver.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ANIMALS INITIALLY IN STUDY	52	52	52	52	52	52
ANIMALS NECROPSIED	52	52	52	52	52	52
ANIMALS EXAMINED HISTOPATH	52	52	52	52	52	52
INTEGUMENTARY SYSTEM						
*Skin	(52)	(52)	(52)	(52)	(52)	(52)
Papilloma, NOS	1 (2%)		1 (2%)			
Squamous cell papilloma	2 (4%)			1 (2%)		
Squamous cell carcinoma					1 (2%)	
Basal cell carcinoma		1 (2%)				
Trichoepithelioma	1 (2%)					
Sebaceous adenoma				1 (2%)		
Sebaceous adenocarcinoma	1 (2%)					
Keratoacanthoma	2 (4%)			1 (2%)		1 (2%)
Fibrosarcoma			1 (2%)			
*Subcutaneous tissue	(52)	(52)	(52)	(52)	(52)	(52)
Sarcoma, NOS				1 (2%)		
Fibroma	4 (8%)	4 (8%)	3 (6%)	7 (13%)	3 (6%)	1 (2%)
Fibrosarcoma					1 (2%)	
RESPIRATORY SYSTEM						
#Lung	(52)	(52)	(52)	(52)	(52)	(51)
Carcinoma, NOS, metastatic					1 (2%)	
Squamous cell carcinoma, metasta					1 (2%)	
Alveolar/bronchiolar adenoma						1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)	2 (4%)		1 (2%)
Sebaceous adenocarcinoma, metast	1 (2%)					
Pheochromocytoma, metastatic				1 (2%)		
HEMATOPOIETIC SYSTEM						
*Multiple organs	(52)	(52)	(52)	(52)	(52)	(52)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	1 (2%)		1 (2%)	
Malig lymphoma, histiocytic type		1 (2%)		1 (2%)		
Leukemia, mononuclear cell	15 (29%)	17 (33%)	15 (29%)	20 (38%)	19 (37%)	9 (17%)
#Spleen	(52)	(51)	(50)	(51)	(48)	(52)
Fibrosarcoma				2 (4%)		
Malignant lymphoma, NOS						1 (2%)
Leukemia, mononuclear cell	1 (2%)			2 (4%)	2 (4%)	1 (2%)
#Mediastinal lymph node	(51)	(52)	(52)	(52)	(48)	(48)
Alveolar/bronchiolar carcinoma, meta				1 (2%)		
#Thymus	(47)	(47)	(42)	(40)	(42)	(41)
Papillary carcinoma				1 (3%)		1 (2%)
CIRCULATORY SYSTEM						
*Eye/lacrimal gland	(52)	(52)	(52)	(52)	(52)	(52)
Hemangioma	1 (2%)					
#Spleen	(52)	(51)	(50)	(51)	(48)	(52)
Hemangiosarcoma		1 (2%)				
*Mesenteric artery	(52)	(52)	(52)	(52)	(52)	(52)
Hemangiosarcoma, invasive		1 (2%)				
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Hemangioma	1 (2%)					
#Kidney	(51)	(51)	(52)	(52)	(51)	(52)
Hemangiosarcoma		1 (2%)				
DIGESTIVE SYSTEM						
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Neoplastic nodule	3 (6%)	5 (10%)	5 (10%)	14 (27%)	15 (29%)	26 (50%)
Hepatocellular carcinoma	3 (6%)		2 (4%)	2 (4%)	3 (6%)	4 (8%)
Pheochromocytoma, metastatic	1 (2%)					
#Pancreas	(51)	(50)	(51)	(47)	(48)	(51)
Acinar cell adenoma	3 (6%)			1 (2%)	2 (4%)	1 (2%)
*Oropharynx	(52)	(52)	(52)	(52)	(52)	(52)
Squamous cell carcinoma			1 (2%)			
#Stomach	(51)	(51)	(48)	(51)	(44)	(44)
Papillomatosis						1 (2%)
#Ileum	(50)	(47)	(47)	(46)	(38)	(35)
Leiomyosarcoma		1 (2%)				

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
URINARY SYSTEM						
#Kidney	(51)	(51)	(52)	(52)	(51)	(52)
Tubular cell adenoma	1 (2%)					
Tubular cell adenocarcinoma	1 (2%)					
Sarcoma, NOS					1 (2%)	
Liposarcoma		1 (2%)				
#Kidney/pelvis	(51)	(51)	(52)	(52)	(51)	(52)
Transitional cell papilloma					1 (2%)	3 (6%)
ENDOCRINE SYSTEM						
#Pituitary	(52)	(52)	(51)	(50)	(52)	(47)
Carcinoma, NOS			1 (2%)			
Adenoma, NOS	12 (23%)	11 (21%)	12 (24%)	10 (20%)	9 (17%)	3 (6%)
#Pituitary intermedia	(52)	(52)	(51)	(50)	(52)	(47)
Adenoma, NOS						1 (2%)
#Adrenal	(51)	(52)	(52)	(52)	(51)	(51)
Cortical adenoma		2 (4%)	2 (4%)			1 (2%)
Cortical carcinoma		1 (2%)		1 (2%)		
Pheochromocytoma	8 (16%)	7 (13%)	13 (25%)	11 (21%)	18 (35%)	19 (37%)
Pheochromocytoma, malignant	2 (4%)			1 (2%)		1 (2%)
Ganglioneuroma		1 (2%)				
#Adrenal/capsule	(51)	(52)	(52)	(52)	(51)	(51)
Adenoma, NOS			1 (2%)			
#Thyroid	(51)	(50)	(47)	(47)	(35)	(49)
Follicular cell adenoma				1 (2%)		3 (6%)
Follicular cell carcinoma		1 (2%)				1 (2%)
C-cell adenoma	5 (10%)	4 (8%)	2 (4%)	5 (11%)	3 (9%)	
C-cell carcinoma	3 (6%)	2 (4%)	2 (4%)	2 (4%)		
#Parathyroid	(32)	(39)	(39)	(40)	(50)	(45)
Adenoma, NOS	1 (3%)	1 (3%)			2 (4%)	1 (2%)
#Pancreatic islets	(51)	(50)	(51)	(47)	(48)	(51)
Islet cell adenoma	8 (16%)	3 (6%)	7 (14%)	4 (9%)	1 (2%)	5 (10%)
Islet cell carcinoma	6 (12%)	15 (30%)	4 (8%)	9 (19%)	5 (10%)	1 (2%)
REPRODUCTIVE SYSTEM						
*Mammary gland	(52)	(52)	(52)	(52)	(52)	(52)
Fibroadenoma	1 (2%)	1 (2%)	1 (2%)	5 (10%)	1 (2%)	
*Preputial gland	(52)	(52)	(52)	(52)	(52)	(52)
Carcinoma, NOS			1 (2%)		1 (2%)	
Papillomatosis	1 (2%)					
Adenoma, NOS	1 (2%)		1 (2%)	1 (2%)	2 (4%)2	
#Prostate	(50)	(50)	(50)	(52)	(52)	(47)
Carcinoma, NOS				1 (2%)		
Adenoma, NOS	2 (4%)	6 (12%)	4 (8%)	2 (4%)		3 (6%)
#Testis	(52)	(52)	(51)	(52)	(52)	(51)
Interstitial cell tumor	50 (96%)	51 (98%)	43 (84%)	48 (92%)	39 (75%)	42 (82%)
*Epididymis	(52)	(52)	(52)	(52)	(52)	(52)
Mesothelioma, NOS		1 (2%)				
NERVOUS SYSTEM						
#Brain	(52)	(52)	(52)	(51)	(52)	(50)
Carcinoma, NOS, invasive			1 (2%)			
Glioma, NOS					2 (4%)	
Astrocytoma	1 (2%)					
Oligodendroglioma				1 (2%)		
SPECIAL SENSE ORGANS						
*Eye	(52)	(52)	(52)	(52)	(52)	(52)
Undifferentiated carcinoma			1 (2%)			
*Harderian gland	(52)	(52)	(52)	(52)	(52)	(52)
Carcinoma, NOS					1 (2%)	
*Zymbal gland	(52)	(52)	(52)	(52)	(52)	(52)
Carcinoma, NOS				1 (2%)	1 (2%)	
Squamous cell carcinoma					1 (2%)	
Sebaceous adenoma		1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
MUSCULOSKELETAL SYSTEM						
*Vertebra	(52)	(52)	(52)	(52)	(52)	(52)
Liposarcoma						1 (2%)
Osteosarcoma	1 (2%)					
*Femur	(52)	(52)	(52)	(52)	(52)	(52)
Fibrosarcoma			1 (2%)			
BODY CAVITIES						
*Abdominal cavity	(52)	(52)	(52)	(52)	(52)	(52)
Sarcoma, NOS		1 (2%)				
*Tunica vaginalis	(52)	(52)	(52)	(52)	(52)	(52)
Mesothelioma, NOS	2 (4%)	1 (2%)			1 (2%)	
ALL OTHER SYSTEMS						
*Multiple organs	(52)	(52)	(52)	(52)	(52)	(52)
Undiff. carcinoma, metastatic			1 (2%)			
Mesothelioma, NOS						1 (2%)
ANIMAL DISPOSITION SUMMARY						
Animals initially in study	52	52	52	52	52	52
Natural death	5	19	13	17	31	38
Moribund sacrifice	5	1	6	1	6	3
Terminal sacrifice	42	32	33	34	15	11
TUMOR SUMMARY						
Total animals with primary tumors**	52	51	49	51	51	48
Total primary tumors	147	143	127	160	137	135
Total animals with benign tumors	52	51	48	50	44	46
Total benign tumors	105	92	91	99	82	87
Total animals with malignant tumors	28	36	26	35	33	19
Total malignant tumors	37	44	31	47	39	21
Total animals with secondary tumors##	2	1	2	2	2	
Total secondary tumors	2	1	2	2	2	
Total animals with tumors uncertain--benign or malignant	5	7	5	14	16	27
Total uncertain tumors	5	7	5	14	16	27

*Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
**Primary tumors: all tumors except secondary tumors
#Number of animals examined microscopically at this site
##Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: UNTREATED CONTROL

ANIMAL NUMBER	0111	0179	0207	0335	0221	0339	0443	0551	0001	0003	0005	0007	0009	0113	0115	0117	0119	0223	0225	0229	0331	0333	0337	0441	0445	0447
WEEKS ON STUDY	072	084	085	096	098	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+
Papilloma, NOS																										
Squamous cell papilloma														X												
Trichoepithelioma																										
Sebaceous adenocarcinoma									X																	
Keratoacanthoma				X																						
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+
Fibroma		X				X	X																			
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma								X							X											
Sebaceous adenocarcinoma, metastatic									X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																										
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X							
Hepatocellular carcinoma																	X				X	X				
Pheochromocytoma, metastatic																										
Hemangioma																										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma								X												X						
Esophagus	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																										
Tubular cell adenocarcinoma																										
Urinary bladder	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X	X	X			X	X			X			X								X	X
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma									X	X						X		X							X	
Pheochromocytoma, malignant																										
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X												
C-cell carcinoma																										
Parathyroid	+	+	−	+	−	−	−	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS																										
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X					X					X				X	X									
Islet cell carcinoma					X								X											X		
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	N	+	+	+	+	N	+	+	N	N	N	+	+	+	+	N	N	+	+	+	N
Fibroadenoma																									X	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	+	X
Prostate	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																										X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillomatosis											X															
Adenoma, NOS													X													
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																										
SPECIAL SENSE ORGANS																										
Lacrimal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																										
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																										
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																	X									
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS				X																						
Leukemia, mononuclear cell			X							X			X	X			X				X					X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	049	053	055	057	059	061	063	065	067	069	071	073	075	077	081	083	085	087	089	091	093	095	097	099	101	103	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Papilloma, NOS		X																									1
Squamous cell papilloma							X																				2
Trichoepithelioma						X																					1
Sebaceous adenocarcinoma																											1
Keratoacanthoma										X																	2
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma																		X									4
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																											2
Sebaceous adenocarcinoma, metas																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leukemia, mononuclear cell																							X				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule						X										X											3
Hepatocellular carcinoma																											3
Pheochromocytoma, metastatic			X																								1
Hemangioma					X																						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell adenoma				X																							3
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tubular cell adenoma			X																								1
Tubular cell adenocarcinoma					X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS			X										X									X					12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma										X												X	X				8
Pheochromocytoma, malignant			X												X												2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C cell adenoma			X	X					X								X										5
C cell carcinoma		X									X		X														3
Parathyroid	−	+	+	−	+	+	+	+	+	−	−	+	−	+	+	−	−	−	+	−	−	+	−	+	−	+	32
Adenoma, NOS									X																		1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islet cell adenoma										X	X				X												8
Islet cell carcinoma			X													X			X								6
REPRODUCTIVE SYSTEM																											
Mammary gland	N	+	+	+	+	N	N	N	N	+	N	N	+	N	+	N	N	N	N	+	+	+	+	N	+	+	*52
Fibroadenoma																											1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Interstitial cell tumor	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X																								2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Papillomatosis																											1
Adenoma, NOS																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Astrocytoma					X																						1
SPECIAL SENSE ORGANS																											
Lacrimal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Hemangioma																					X						1
MUSCULOSKELETAL SYSTEM																											
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Osteosarcoma					X																						1
BODY CAVITIES																											
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Mesothelioma, NOS	X																										2
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malignant lymphoma, NOS																											1
Leukemia, mononuclear cell			X								X	X	X				X					X		X		X	15

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: 0.1 ppm

ANIMAL NUMBER	199	219	171	245	231	235	221	209	223	227	173	179	163	197	217	177	189	147	165	175	145	149	151	153	155	157
WEEKS ON STUDY	066	085	086	095	097	097	100	101	101	101	103	103	104	104	104	105	105	106	106	106	107	107	107	107	107	107
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	
Basal cell carcinoma																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	
Fibroma									X				X						X							
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma											X															
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Hemangiosarcoma, invasive											X															
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Neoplastic nodule		X																X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pancreas	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Small intestine	+	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Leiomyosarcoma																										
Large intestine	−	−	−	−	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	
URINARY SYSTEM																										
Kidney	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liposarcoma						X																				
Hemangiosarcoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS						X								X				X	X				X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cortical adenoma		X				X																				
Cortical carcinoma												X														
Pheochromocytoma			X	X							X					X		X	X							
Ganglioneuroma																										
Thyroid	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell carcinoma																			X							
C cell adenoma												X						X								
C cell carcinoma																										
Parathyroid	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	+	−	+	+	+	+	+	+	
Adenoma, NOS				X																						
Pancreatic islets	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islet cell adenoma																										
Islet cell carcinoma					X							X		X	X	X	X				X		X	X		X
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	
Fibroadenoma																										
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Adenoma, NOS												X			X			X					X			
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Mesothelioma, NOS				X																						
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Sebaceous adenoma																										
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Sarcoma, NOS																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma, NOS																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Malignant lymphoma, NOS			X																							
Malignant lymphoma, histiocytic type																										
Leukemia, mononuclear cell		X			X		X	X		X				X		X			X			X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 0.1 ppm (Continued)

ANIMAL NUMBER	159	161	167	169	181	183	185	187	191	193	195	201	203	205	207	211	213	215	225	229	233	237	239	241	243	247	TOTAL:
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*52
Basal cell carcinoma									X																		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*52
Fibroma																								X			4
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Hemangiosarcoma, invasive																											1
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule										X						X		X									5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma						X																					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liposarcoma																											1
Hemangiosarcoma																						X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS			X	X									X					X						X			11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma																											2
Cortical carcinoma																											1
Pheochromocytoma																				X							7
Ganglioneuroma																								X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																											1
C cell adenoma			X				X																				4
C cell carcinoma										X	X																2
Parathyroid	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	−	−	39
Adenoma, NOS																											1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma						X										X		X									3
Islet cell carcinoma					X								X						X					X	X		15
REPRODUCTIVE SYSTEM																											
Mammary gland	N	+	+	N	+	+	+	N	N	+	N	N	N	+	+	+	N	N	+	+	+	+	+	+	N	N	*52
Fibroadenoma														X													1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	51
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X																								6
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Mesothelioma, NOS																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
SPECIAL SENSE ORGANS																											
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	*52
Sebaceous adenoma																										X	1
BODY CAVITIES																											
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Sarcoma, NOS												X															1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Mesothelioma, NOS																				X							1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malignant lymphoma, NOS																											1
Malig. lymphoma, histiocytic type																								X			1
Leukemia, mononuclear cell							X		X				X			X		X	X			X				X	17

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: 1 ppm

ANIMAL NUMBER	251	255	345	327	335	271	331	283	315	339	259	261	317	263	273	351	265	299	307	249	253	257	287	269	275	277
WEEKS ON STUDY	053	057	067	069	071	083	084	086	086	086	090	091	093	096	097	098	105	105	105	106	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																										
Fibrosarcoma																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																	X									
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										
Trachea	–	–	–	–	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	–	–	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																			X							
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					X		X			X
Hepatocellular carcinoma																										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	–	+	+	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	–	+	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X																
Adenoma, NOS							X					X			X						X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X					
Cortical adenoma																X										
Pheochromocytoma									X	X			X		X	X	X	X	X		X					X
Thyroid	–	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma																						X				
C cell carcinoma																										
Parathyroid	–	–	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Islet cell adenoma											X				X			X						X		
Islet cell carcinoma																					X					
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	N	N	+	+	N	+	N	+	N	+	+	N	+	N	N	+	N	N	N	N
Fibroadenoma												X														
Testis	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X			X		X	X		X		X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adenoma, NOS																										X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																										
Adenoma NOS		X																								
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive										X																
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Undifferentiated carcinoma												X														
Zymbal gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sebaceous adenoma				X																						
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma						X																				
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Undifferentiated carcinoma, metastatic												X														
Malignant lymphoma, NOS								X																		
Leukemia, mononuclear cell							X		X				X	X							X	X			X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1 ppm (Continued)

ANIMAL NUMBER	279	281	285	287	289	291	293	295	297	301	303	305	309	311	313	319	321	323	325	329	333	337	341	343	347	349	TOTAL TISSUES TUMORS
WEEKS ON STUDY	106	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Papilloma, NOS																	X										1
Fibrosarcoma													X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma									X						X												3
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma	X																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+		42
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Squamous cell carcinoma																											1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule								X									X										5
Hepatocellular carcinoma																	X					X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, NOS																											1
Adenoma, NOS		X		X		X			X			X			X		X				X						12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS																											1
Cortical adenoma												X															2
Pheochromocytoma			X	X						X							X										13
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C cell adenoma													X														2
C cell carcinoma		X													X												2
Parathyroid	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islet cell adenoma		X																							X	X	7
Islet cell carcinoma						X						X									X						4
REPRODUCTIVE SYSTEM																											
Mammary gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	+	+	*52
Fibroadenoma																											1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X		X															X						4
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Carcinoma, NOS												X															1
Adenoma, NOS																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																											1
SPECIAL SENSE ORGANS																											
Eye	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Undifferentiated carcinoma																											1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Sebaceous adenoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Fibrosarcoma																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Undiff carcinoma, metastatic																											1
Malignant lymphoma, NOS																											1
Leukemia, mononuclear cell					X		X	X		X		X					X					X			X	15

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: 10 ppm

ANIMAL NUMBER	445	395	419	431	443	387	403	399	433	413	407	439	449	389	425	361	535	555	557	599	633	655	687	699	711	733
WEEKS ON STUDY	047	061	079	085	089	091	092	098	098	099	100	100	101	102	104	105	106	106	106	106	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																										
Skin	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X	
Sebaceous adenoma																										
Keratoacanthoma																										
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS		X																								
Fibroma			X							X			X									X				
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma														X			X									
Pheochromocytoma, metastatic																										
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																										
Leukemia, mononuclear cell														X										X		
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																	X									
Thymus	+	−	−	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	−	+
Papillary carcinoma																							X			
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X														X	X					
Hepatocellular carcinoma																			X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+
Acinar cell adenoma																										
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Small intestine	−	−	+	+	−	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	
Large intestine	+	−	+	−	−	−	−	−	−	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X											X		X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																										
Pheochromocytoma			X						X	X						X		X			X				
Pheochromocytoma, malignant																										
Thyroid	−	−	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X								
C cell adenoma														X			X									
C cell carcinoma											X									X						
Parathyroid	+	+	+	+	+	+	−	+	+	+	−	−	+	−	−	+	+	+	+	−	+	+	+	−	−	+
Pancreatic islets	−	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+
Islet cell adenoma												X														
Islet cell carcinoma														X				X								
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	N	+	+	+	N	+	+	N	+	+	N	N	+	N	+	N	+	+	+	N	N
Fibroadenoma												X											X	X		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																										
Adenoma, NOS																										
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																										
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																										
Sebaceous adenoma																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type																					X					
Leukemia, mononuclear cell						X	X	X		X	X	X	X					X							X	

+ Tissue examined microscopically
− Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
No tissue information submitted
C Necropsy, no histology due to protocol
A Autolysis
M Animal missing
B No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 10 ppm (Continued)

ANIMAL NUMBER	375	377	379	381	383	385	391	393	397	401	405	409	411	415	417	421	423	427	429	435	437	441	447	451	453	455	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell papilloma																											1
Sebaceous adenoma												X															1
Keratoacanthoma											X																1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Sarcoma, NOS																											1
Fibroma	X								X			X															7
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																											2
Pheochromocytoma, metastatic																X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma															X							X					2
Leukemia, mononuclear cell																											2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma, met																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	–	+	+	40
Papillary carcinoma																											1
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X	X		X		X	X			X				X				X	X		X	X					14
Hepatocellular carcinoma																		X									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Acinar cell adenoma														X													1
Esophagus	+	+	+	+	+	+	+	–	+	–	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	50
Adenoma, NOS			X				X								X	X		X	X								10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical carcinoma													X														1
Pheochromocytoma			X	X							X								X		X						11
Pheochromocytoma, malignant																X											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																											1
C cell adenoma		X																							X	X	5
C cell carcinoma																											2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	–	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma							X					X			X												4
Islet cell carcinoma			X						X							X		X	X			X				X	9
REPRODUCTIVE SYSTEM																											
Mammary gland	N	N	+	N	+	N	N	N	N	N	+	N	N	N	+	+	N	N	+	N	N	N	N	N	N	N	*52
Fibroadenoma					X														X								5
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS	X																										1
Adenoma, NOS					X											X											2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Adenoma, NOS						X																					1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	51
Oligodendroglioma						X																					1
SPECIAL SENSE ORGANS																											
Zymbal gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*52
Carcinoma, NOS																				X							1
Sebaceous adenoma			X																								1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malig. lymphoma, histiocytic type																											1
Leukemia, mononuclear cell				X		X	X	X	X	X	X				X					X		X	X				20

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: 25 ppm

ANIMAL NUMBER	50 05	58 55	50 01	49 99	52 92	58 81	53 35	52 27	59 97	52 25	50 07	55 57	54 47	53 33	58 89	58 87	55 59	56 69	59 99	50 03	54 49	56 67	57 75	59 91	54 43	51 11
WEEKS ON STUDY	05 58	06 63	07 71	07 74	07 74	07 79	08 81	08 83	08 83	08 84	08 86	08 88	08 89	09 91	09 92	09 95	09 96	09 97	09 97	09 98	09 98	09 98	09 98	09 98	09 99	10 00
INTEGUMENTARY SYSTEM																										
Skin	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																										
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma					X					X																
Fibrosarcoma			X																							
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic														X												
Squamous cell carcinoma, metastatic		X																								
Trachea	+	–	–	–	–	–	–	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	–	+	–	+	–	+	–	–	+	+	–	+	+	+	–	–	–	+	+	–	+	+	+	+	+
Spleen	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																										
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Thymus	+	–	–	–	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																				X			X			
Hepatocellular carcinoma																										X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																										
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	–	–	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Small intestine	+	–	–	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	+	–	–	+	+	–	+
Large intestine	+	–	–	–	+	–	+	–	+	–	+	–	+	+	+	–	–	–	+	+	–	–	+	+	–	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Transitional cell papilloma																				X						
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X				X												X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X					X		X	X					X		X
Thyroid	+	–	+	–	+	–	+	–	+	–	+	–	+	–	+	–	–	–	+	+	–	–	+	+	–	+
C-cell adenoma																										
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenoma, NOS																			X				X			
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Islet cell adenoma																										
Islet cell carcinoma			X					X																		
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	N	+	N	+	N	N	N	N	+	+	N	+	+	+	N	N	+	+	+	+	N	+
Fibroadenoma																										
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor										X		X		X	X	X	X	X	X	X	X	X	X	X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																										X
Adenoma, NOS																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																					X					
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS														X												
Zymbal gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N
Carcinoma, NOS																			X							
Squamous cell carcinoma		X																								
Sebaceous adenoma																			X							
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																										X
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																										
Leukemia, mononuclear cell	X			X			X	X	X			X			X					X			X		X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 25 ppm (Continued)

ANIMAL NUMBER	537	497	513	523	565	571	583	539	573	593	509	515	517	519	521	531	541	545	551	553	555	561	563	577	579	595	TOTAL
WEEKS ON STUDY	101	102	102	102	102	102	103	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell carcinoma										X																	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma										X																	3
Fibrosarcoma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, metastatic																											1
Squamous cell carcinoma, metastati																											1
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	40
HEMATOPOIETIC SYSTEM																											
Bone marrow	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia, mononuclear cell		X														X											2
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X		X	X							X	X			X	X	X	X	X	X			X			X	15
Hepatocellular carcinoma				X							X																3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma							X										X										2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	48
Stomach	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Large intestine	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma, NOS																											1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Transitional cell papilloma																											1
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS											X			X				X			X			X			9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma				X		X	X		X	X	X		X		X		X			X						X	18
Thyroid	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
C cell adenoma											X			X											X		3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																											2
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																	X										1
Islet cell carcinoma														X	X			X									5
REPRODUCTIVE SYSTEM																											
Mammary gland	N	+	N	+	+	+	+	N	N	+	N	N	+	N	N	N	+	N	+	N	N	N	N	+	N	N	*52
Fibroadenoma																			X								1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Interstitial cell tumor	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Carcinoma, NOS																											1
Adenoma, NOS													X		X												2
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Glioma, NOS													X														2
SPECIAL SENSE ORGANS																											
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Carcinoma, NOS																											1
Zymbal gland	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*52
Carcinoma, NOS																											1
Squamous cell carcinoma																											1
Sebaceous adenoma																											1
BODY CAVITIES																											
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Mesothelioma, NOS																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malignant lymphoma, NOS	X																										1
Leukemia, mononuclear cell			X			X		X						X				X	X	X			X	X			19

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX: 50 ppm

ANIMAL NUMBER	88585	80383	82929	82767	81717	88811	79595	86699	79797	80909	81919	81151	87171	87979	80505	84141	85959	87575	79999	80101	87717	83131	83737	84249	88787	80707
WEEKS ON STUDY	03252	03636	06161	06666	07606	08080	08252	08383	08686	08787	08787	09090	09090	09393	09595	09595	09595	09595	09696	09696	09696	09697	09797	09797	09797	09999
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X			
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										X
Alveolar/bronchiolar carcinoma																									X	
Trachea	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																X										
Leukemia, mononuclear cell																										
Lymph nodes	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	+	−	+	−	+	−	−	+	+	+	+	+	−	+	+	−	+	+	+	+	−	−	+
Papillary carcinoma																										
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Neoplastic nodule				X					X						X	X	X	X	X			X		X	X	
Hepatocellular carcinoma																X										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																										
Esophagus	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+	+
Papillomatosis																				X						
Small intestine	+	+	−	+	−	+	−	−	−	−	+	+	−	−	+	−	+	+	−	+	+	−	−	−	+	+
Large intestine	+	−	+	+	+	+	−	−	−	−	+	+	−	−	+	−	−	−	−	+	−	−	−	−	−	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																										
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	−	−	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																										
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X	
Pheochromocytoma						X				X	X				X					X	X				X	
Pheochromocytoma, malignant																						X				
Thyroid	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																										X
Follicular cell carcinoma																										
Parathyroid	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Adenoma, NOS																									X	
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																										
Islet cell carcinoma																										
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	N	N	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	N	+
Testis	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								X	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X
Prostate	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS													X													
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N
Sebaceous adenoma																		X								
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Liposarcoma																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																										X
Leukemia, mononuclear cell				X	X						X		X								X		X			

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 ppm (Continued)

ANIMAL NUMBER	8 3 9	8 6 7	8 4 3	8 4 5	8 7 3	7 9 3	8 5 5	8 5 7	8 1 3	8 5 3	8 9 5	8 2 1	8 6 1	8 6 3	8 1 1	8 2 3	8 2 5	8 3 3	8 3 5	8 4 7	8 5 1	8 6 5	8 8 3	8 8 9	8 9 1	8 9 3	TOTAL:
WEEKS ON STUDY	0 9 9	0 9 9	1 0 0	1 0 1	1 0 1	1 0 2	1 0 2	1 0 2	1 0 3	1 0 3	1 0 3	1 0 5	1 0 5	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Keratoacanthoma																											1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																											1
Alveolar/bronchiolar carcinoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Malignant lymphoma, NOS																											1
Leukemia, mononuclear cell							X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	41
Papillary carcinoma		X																									1
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X		X			X	X		X	X				X	X	X		X	X	X			X	X	X	X	26
Hepatocellular carcinoma											X										X				X		4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell adenoma																					X						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Stomach	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Papillomatosis																											1
Small intestine	+	+	+	+	+	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	35
Large intestine	+	+	+	+	+	–	+	+	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	–	+	30
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional cell papilloma					X					X									X								3
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS				X		X												X			X						4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cortical adenoma																											1
Pheochromocytoma	X		X				X	X	X			X	X	X	X			X							X	X	19
Pheochromocytoma, malignant																											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma							X							X													3
Follicular cell carcinoma																			X								1
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	45
Adenoma, NOS																											1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islet cell adenoma														X		X	X	X							X		5
Islet cell carcinoma																						X					1
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	N	N	+	+	+	N	+	N	+	N	N	+	+	N	N	N	+	N	N	+	N	N	+	N	*52
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	42
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X											X															3
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																											
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Sebaceous adenoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Liposarcoma																						X					1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Mesothelioma, NOS																											1
Leukemia, mononuclear cell				X						X							X										9

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Skin: Papilloma or Squamous Cell Papilloma or Carcinoma						
Overall Rates (a)	3/52 (6%)	0/52 (0%)	1/52 (2%)	1/52 (2%)	1/52 (2%)	0/52 (0%)
Adjusted Rates (b)	6.8%	0.0%	2.8%	2.7%	5.3%	0.0%
Terminal Rates (c)	3/44 (7%)	0/37 (0%)	1/36 (3%)	1/37 (3%)	1/19 (5%)	0/15 (0%)
Week of First Observation	105		105	105	105	
Life Table Tests (d)	P=0.458N	P=0.153N	P=0.379N	P=0.369N	P=0.629N	P=0.361N
Incidental Tumor Tests (d)	P=0.458N	P=0.153N	P=0.379N	P=0.369N	P=0.629N	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.197N					
Fisher Exact Test (d)		P=0.121N	P=0.309N	P=0.309N	P=0.309N	P=0.121N
Subcutaneous Tissue: Fibroma						
Overall Rates (a)	4/52 (8%)	4/52 (8%)	3/52 (6%)	7/52 (13%)	3/52 (6%)	1/52 (2%)
Adjusted Rates (b)	8.3%	9.8%	8.3%	16.8%	9.4%	3.2%
Terminal Rates (c)	1/44 (2%)	2/37 (5%)	3/36 (8%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	84	101	105	79	74	97
Life Table Tests (d)	P=0.452N	P=0.568	P=0.609N	P=0.196	P=0.527	P=0.463N
Incidental Tumor Tests (d)	P=0.041N	P=0.440N	P=0.511N	P=0.414	P=0.136N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.102N					
Fisher Exact Test (d)		P=0.642	P=0.500N	P=0.263	P=0.500N	P=0.181N
Subcutaneous Tissue: Fibroma or Fibrosarcoma						
Overall Rates (a)	4/52 (8%)	4/52 (8%)	3/52 (6%)	7/52 (13%)	4/52 (8%)	1/52 (2%)
Adjusted Rates (b)	8.3%	9.8%	8.3%	16.8%	11.2%	3.2%
Terminal Rates (c)	1/44 (2%)	2/37 (5%)	3/36 (8%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	84	101	105	79	71	97
Life Table Tests (d)	P=0.513N	P=0.568	P=0.609N	P=0.196	P=0.376	P=0.463N
Incidental Tumor Tests (d)	P=0.054N	P=0.440N	P=0.511N	P=0.414	P=0.182N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.131N					
Fisher Exact Test (d)		P=0.642	P=0.500N	P=0.263	P=0.642	P=0.181N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma						
Overall Rates (a)	4/52 (8%)	4/52 (8%)	3/52 (6%)	8/52 (15%)	4/52 (8%)	1/52 (2%)
Adjusted Rates (b)	8.3%	9.8%	8.3%	18.4%	11.2%	3.2%
Terminal Rates (c)	1/44 (2%)	2/37 (5%)	3/36 (8%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	84	101	105	61	71	97
Life Table Tests (d)	P=0.490N	P=0.568	P=0.609N	P=0.132	P=0.376	P=0.463N
Incidental Tumor Tests (d)	P=0.047N	P=0.440N	P=0.511N	P=0.300	P=0.182N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.125N					
Fisher Exact Test (d)		P=0.642	P=0.500N	P=0.179	P=0.642	P=0.181N
Integumentary System: Fibroma or Fibrosarcoma						
Overall Rates (a)	4/52 (8%)	4/52 (8%)	4/52 (8%)	7/52 (13%)	4/52 (8%)	1/52 (2%)
Adjusted Rates (b)	8.3%	9.8%	11.1%	16.8%	11.2%	3.2%
Terminal Rates (c)	1/44 (2%)	2/37 (5%)	4/36 (11%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	84	101	105	79	71	97
Life Table Tests (d)	P=0.471N	P=0.568	P=0.526	P=0.196	P=0.376	P=0.463N
Incidental Tumor Tests (d)	P=0.046N	P=0.440N	P=0.623	P=0.414	P=0.182N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.105N					
Fisher Exact Test (d)		P=0.642	P=0.642	P=0.263	P=0.642	P=0.181N
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma						
Overall Rates (a)	4/52 (8%)	4/52 (8%)	4/52 (8%)	8/52 (15%)	4/52 (8%)	1/52 (2%)
Adjusted Rates (b)	8.3%	9.8%	11.1%	18.4%	11.2%	3.2%
Terminal Rates (c)	1/44 (2%)	2/37 (5%)	4/36 (11%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	84	101	105	61	71	97
Life Table Tests (d)	P=0.451N	P=0.568	P=0.526	P=0.132	P=0.376	P=0.463N
Incidental Tumor Tests (d)	P=0.040N	P=0.440N	P=0.623	P=0.300	P=0.182N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.100N					
Fisher Exact Test (d)		P=0.642	P=0.642	P=0.179	P=0.642	P=0.181N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Hematopoietic System: Mononuclear Cell Leukemia						
Overall Rates (a)	16/52 (31%)	17/52 (33%)	15/52 (29%)	22/52 (42%)	21/52 (40%)	10/52 (19%)
Adjusted Rates (b)	35.4%	38.5%	36.9%	48.6%	60.7%	31.1%
Terminal Rates (c)	15/44 (34%)	11/37 (30%)	11/36 (31%)	14/37 (38%)	8/19 (42%)	1/15 (7%)
Week of First Observation	85	85	84	91	58	66
Life Table Tests (d)	P=0.046	P=0.317	P=0.420	P=0.066	P=0.001	P=0.264
Incidental Tumor Tests (d)	P=0.101N	P=0.484	P=0.573	P=0.160	P=0.152	P=0.195N
Cochran-Armitage Trend Test (d)	P=0.122N					
Fisher Exact Test (d)		P=0.500	P=0.500N	P=0.154	P=0.206	P=0.129N
Liver: Neoplastic Nodule						
Overall Rates (a)	3/52 (6%)	5/52 (10%)	5/52 (10%)	14/52 (27%)	15/52 (29%)	26/52 (50%)
Adjusted Rates (b)	6.8%	12.6%	13.9%	36.5%	60.6%	81.4%
Terminal Rates (c)	3/44 (7%)	4/37 (11%)	5/36 (14%)	13/37 (35%)	10/19 (53%)	10/15 (67%)
Week of First Observation	105	85	105	91	98	66
Life Table Tests (d)	P<0.001	P=0.279	P=0.251	P=0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.278	P=0.251	P=0.002	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001					
Fisher Exact Test (d)		P=0.358	P=0.358	P=0.003	P=0.002	P<0.001
Liver: Hepatocellular Carcinoma						
Overall Rates (a)	3/52 (6%)	0/52 (0%)	2/52 (4%)	2/52 (4%)	3/52 (6%)	4/52 (8%)
Adjusted Rates (b)	6.8%	0.0%	5.6%	5.4%	12.4%	20.3%
Terminal Rates (c)	3/44 (7%)	0/37 (0%)	2/36 (6%)	2/37 (5%)	1/19 (5%)	2/15 (13%)
Week of First Observation	105		105	105	100	95
Life Table Tests (d)	P=0.002	P=0.153N	P=0.591N	P=0.579N	P=0.302	P=0.094
Incidental Tumor Tests (d)	P=0.047	P=0.153N	P=0.591N	P=0.579N	P=0.601	P=0.297
Cochran-Armitage Trend Test (d)	P=0.105					
Fisher Exact Test (d)		P=0.121N	P=0.500N	P=0.500N	P=0.661	P=0.500
Liver: Neoplastic Nodule or Hepatocellular Carcinoma						
Overall Rates (a)	6/52 (12%)	5/52 (10%)	6/52 (12%)	15/52 (29%)	16/52 (31%)	28/52 (54%)
Adjusted Rates (b)	13.6%	12.6%	16.7%	39.2%	62.1%	86.1%
Terminal Rates (c)	6/44 (14%)	4/37 (11%)	6/36 (17%)	14/37 (38%)	10/19 (53%)	11/15 (73%)
Week of First Observation	105	85	105	91	98	66
Life Table Tests (d)	P<0.001	P=0.607N	P=0.475	P=0.008	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.609N	P=0.475	P=0.010	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001					
Fisher Exact Test (d)		P=0.500N	P=0.620	P=0.024	P=0.015	P<0.001
Pancreas: Acinar Cell Adenoma						
Overall Rates (a)	3/51 (6%)	0/50 (0%)	0/51 (0%)	1/47 (2%)	2/48 (4%)	1/51 (2%)
Adjusted Rates (b)	6.6%	0.0%	0.0%	2.8%	10.0%	6.7%
Terminal Rates (c)	2/44 (5%)	0/37 (0%)	0/35 (0%)	1/36 (3%)	1/19 (5%)	1/15 (7%)
Week of First Observation	104			105	103	105
Life Table Tests (d)	P=0.170	P=0.155N	P=0.169N	P=0.384N	P=0.497	P=0.719N
Incidental Tumor Tests (d)	P=0.472	P=0.100N	P=0.166N	P=0.330N	P=0.539N	P=0.457N
Cochran-Armitage Trend Test (d)	P=0.524					
Fisher Exact Test (d)		P=0.125N	P=0.121N	P=0.340N	P=0.529N	P=0.309N
Kidney: Transitional Cell Papilloma						
Overall Rates (a)	0/51 (0%)	0/51 (0%)	0/52 (0%)	0/52 (0%)	1/51 (2%)	3/52 (6%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	0.0%	3.0%	15.7%
Terminal Rates (c)	0/44 (0%)	0/37 (0%)	0/36 (0%)	0/37 (0%)	0/19 (0%)	1/15 (7%)
Week of First Observation					98	101
Life Table Tests (d)	P<0.001	(e)	(e)	(e)	P=0.425	P=0.018
Incidental Tumor Tests (d)	P=0.018	(e)	(e)	(e)	P=0.742	P=0.193
Cochran-Armitage Trend Test (d)	P=0.002					
Fisher Exact Test (d)		(e)	(e)	(e)	P=0.500	P=0.125

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Pituitary Gland: Adenoma						
Overall Rates (a)	12/52 (23%)	11/52 (21%)	12/51 (24%)	10/50 (20%)	9/52 (17%)	3/47 (6%)
Adjusted Rates (b)	25.4%	27.8%	30.3%	26.7%	34.8%	15.0%
Terminal Rates (c)	9/44 (20%)	9/37 (24%)	9/36 (25%)	9/36 (25%)	5/19 (26%)	1/15 (7%)
Week of First Observation	98	97	84	98	83	101
Life Table Tests (d)	P=0.381N	P=0.517	P=0.372	P=0.586	P=0.205	P=0.373N
Incidental Tumor Tests (d)	P=0.025N	P=0.452N	P=0.434	P=0.488N	P=0.434N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.009N					
Fisher Exact Test (d)		P=0.500N	P=0.571	P=0.446N	P=0.313N	P=0.019N
Pituitary Gland: Adenoma or Carcinoma						
Overall Rates (a)	12/52 (23%)	11/52 (21%)	13/51 (25%)	10/50 (20%)	9/52 (17%)	3/47 (6%)
Adjusted Rates (b)	25.4%	27.8%	31.9%	26.7%	34.8%	15.0%
Terminal Rates (c)	9/44 (20%)	9/37 (24%)	9/36 (25%)	9/36 (25%)	5/19 (26%)	1/15 (7%)
Week of First Observation	98	97	84	98	83	101
Life Table Tests (d)	P=0.338N	P=0.517	P=0.293	P=0.586	P=0.205	P=0.373N
Incidental Tumor Tests (d)	P=0.018N	P=0.452N	P=0.394	P=0.488N	P=0.434N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.007N					
Fisher Exact Test (d)		P=0.500N	P=0.478	P=0.446N	P=0.313N	P=0.019N
Adrenal Gland: Adenoma or Cortical Adenoma						
Overall Rates (a)	0/51 (0%)	2/52 (4%)	3/52 (6%)	0/52 (0%)	0/51 (0%)	1/51 (2%)
Adjusted Rates (b)	0.0%	4.0%	8.3%	0.0%	0.0%	3.2%
Terminal Rates (c)	0/44 (0%)	0/37 (0%)	3/36 (8%)	0/37 (0%)	0/19 (0%)	0/15 (0%)
Week of First Observation		85	105			97
Life Table Tests (d)	P=0.524N	P=0.242	P=0.088	(e)	(e)	P=0.413
Incidental Tumor Tests (d)	P=0.245N	P=0.332	P=0.088	(e)	(e)	P=0.807
Cochran-Armitage Trend Test (d)	P=0.327N					
Fisher Exact Test (d)		P=0.252	P=0.125	(e)	(e)	P=0.500
Adrenal Gland: Cortical Adenoma or Carcinoma						
Overall Rates (a)	0/51 (0%)	3/52 (6%)	2/52 (4%)	1/52 (2%)	0/51 (0%)	1/51 (2%)
Adjusted Rates (b)	0.0%	6.3%	5.6%	2.7%	0.0%	3.2%
Terminal Rates (c)	0/44 (0%)	0/37 (0%)	2/36 (6%)	1/37 (3%)	0/19 (0%)	0/15 (0%)
Week of First Observation		85	105	105		97
Life Table Tests (d)	P=0.523N	P=0.119	P=0.195	P=0.465	(e)	P=0.413
Incidental Tumor Tests (d)	P=0.171N	P=0.231	P=0.195	P=0.465	(e)	P=0.807
Cochran-Armitage Trend Test (d)	P=0.300N					
Fisher Exact Test (d)		P=0.125	P=0.252	P=0.505	(e)	P=0.500
Adrenal Gland: Adenoma or Cortical Adenoma or Carcinoma						
Overall Rates (a)	0/51 (0%)	3/52 (6%)	3/52 (6%)	1/52 (2%)	0/51 (0%)	1/51 (2%)
Adjusted Rates (b)	0.0%	6.3%	8.3%	2.7%	0.0%	3.2%
Terminal Rates (c)	0/44 (0%)	0/37 (0%)	3/36 (8%)	1/37 (3%)	0/19 (0%)	0/15 (0%)
Week of First Observation		85	105	105		97
Life Table Tests (d)	P=0.451N	P=0.119	P=0.088	P=0.465	(e)	P=0.413
Incidental Tumor Tests (d)	P=0.143N	P=0.231	P=0.088	P=0.465	(e)	P=0.807
Cochran-Armitage Trend Test (d)	P=0.226N					
Fisher Exact Test (d)		P=0.125	P=0.125	P=0.505	(e)	P=0.500
Adrenal Gland: Pheochromocytoma						
Overall Rates (a)	8/51 (16%)	7/52 (13%)	13/52 (25%)	11/52 (21%)	18/51 (35%)	19/51 (37%)
Adjusted Rates (b)	18.2%	16.4%	32.0%	26.6%	61.5%	65.2%
Terminal Rates (c)	8/44 (18%)	4/37 (11%)	9/36 (25%)	8/37 (22%)	9/19 (47%)	7/15 (47%)
Week of First Observation	105	86	86	79	86	80
Life Table Tests (d)	P<0.001	P=0.599	P=0.075	P=0.192	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.524N	P=0.117	P=0.263	P=0.003	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001					
Fisher Exact Test (d)		P=0.484N	P=0.177	P=0.323	P=0.020	P=0.012

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma						
Overall Rates (a)	10/51 (20%)	7/52 (13%)	13/52 (25%)	12/52 (23%)	18/51 (35%)	20/51 (39%)
Adjusted Rates (b)	22.7%	16.4%	32.0%	29.2%	61.5%	66.4%
Terminal Rates (c)	10/44 (23%)	4/37 (11%)	9/36 (25%)	9/37 (24%)	9/19 (47%)	7/15 (47%)
Week of First Observation	105	86	86	79	86	80
Life Table Tests (d)	P<0.001	P=0.423N	P=0.164	P=0.258	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.334N	P=0.236	P=0.336	P=0.008	P=0.009
Cochran-Armitage Trend Test (d)	P=0.001					
Fisher Exact Test (d)		P=0.283N	P=0.338	P=0.425	P=0.060	P=0.025
Thyroid Gland: Follicular Cell Adenoma						
Overall Rates (a)	0/51 (0%)	0/50 (0%)	0/47 (0%)	1/47 (2%)	0/35 (0%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	2.7%	0.0%	14.4%
Terminal Rates (c)	0/44 (0%)	0/37 (0%)	0/36 (0%)	1/37 (3%)	0/18 (0%)	1/15 (7%)
Week of First Observation				105		99
Life Table Tests (d)	P<0.001	(e)	(e)	P=0.465	(e)	P=0.024
Incidental Tumor Tests (d)	P=0.017	(e)	(e)	P=0.465	(e)	P=0.193
Cochran-Armitage Trend Test (d)	P=0.006					
Fisher Exact Test (d)		(e)	(e)	P=0.480	(e)	P=0.114
Thyroid Gland: Follicular Cell Adenoma or Carcinoma						
Overall Rates (a)	0/51 (0%)	1/50 (2%)	0/47 (0%)	1/47 (2%)	0/35 (0%)	4/49 (8%)
Adjusted Rates (b)	0.0%	2.7%	0.0%	2.7%	0.0%	20.5%
Terminal Rates (c)	0/44 (0%)	1/37 (3%)	0/36 (0%)	1/37 (3%)	0/18 (0%)	2/15 (13%)
Week of First Observation		105		105		99
Life Table Tests (d)	P<0.001	P=0.465	(e)	P=0.465	(e)	P=0.005
Incidental Tumor Tests (d)	P=0.004	P=0.465	(e)	P=0.465	(e)	P=0.048
Cochran-Armitage Trend Test (d)	P=0.005					
Fisher Exact Test (d)		P=0.495	(e)	P=0.480	(e)	P=0.054
Thyroid Gland: C-Cell Adenoma						
Overall Rates (a)	5/51 (10%)	4/50 (8%)	2/47 (4%)	5/47 (11%)	3/35 (9%)	0/49 (0%)
Adjusted Rates (b)	11.4%	10.3%	5.6%	13.1%	16.7%	0.0%
Terminal Rates (c)	5/44 (11%)	3/37 (8%)	2/36 (6%)	4/37 (11%)	3/18 (17%)	0/15 (0%)
Week of First Observation	105	103	105	102	105	
Life Table Tests (d)	P=0.338N	P=0.603N	P=0.304N	P=0.517	P=0.442	P=0.206N
Incidental Tumor Tests (d)	P=0.181N	P=0.550N	P=0.304N	P=0.541	P=0.442	P=0.206N
Cochran-Armitage Trend Test (d)	P=0.059N					
Fisher Exact Test (d)		P=0.513N	P=0.253N	P=0.576	P=0.580N	P=0.031N
Thyroid Gland: C-Cell Carcinoma						
Overall Rates (a)	3/51 (6%)	2/50 (4%)	2/47 (4%)	2/47 (4%)	0/35 (0%)	0/49 (0%)
Adjusted Rates (b)	6.8%	5.4%	5.6%	5.0%	0.0%	0.0%
Terminal Rates (c)	3/44 (7%)	2/37 (5%)	2/36 (6%)	1/37 (3%)	0/18 (0%)	0/15 (0%)
Week of First Observation	105	105	105	100		
Life Table Tests (d)	P=0.149N	P=0.579N	P=0.591N	P=0.573N	P=0.316N	P=0.361N
Incidental Tumor Tests (d)	P=0.093N	P=0.579N	P=0.591N	P=0.546N	P=0.316N	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.051N					
Fisher Exact Test (d)		P=0.509N	P=0.539N	P=0.539N	P=0.203N	P=0.129N
Thyroid Gland: C-Cell Adenoma or Carcinoma						
Overall Rates (a)	8/51 (16%)	6/50 (12%)	4/47 (9%)	7/47 (15%)	3/35 (9%)	0/49 (0%)
Adjusted Rates (b)	18.2%	15.6%	11.1%	17.7%	16.7%	0.0%
Terminal Rates (c)	8/44 (18%)	5/37 (14%)	4/36 (11%)	5/37 (14%)	3/18 (17%)	0/15 (0%)
Week of First Observation	105	103	105	100	105	
Life Table Tests (d)	P=0.126N	P=0.521N	P=0.287N	P=0.580	P=0.588N	P=0.092N
Incidental Tumor Tests (d)	P=0.043N	P=0.476N	P=0.287N	P=0.604N	P=0.588N	P=0.092N
Cochran-Armitage Trend Test (d)	P=0.008N					
Fisher Exact Test (d)		P=0.403N	P=0.220N	P=0.569N	P=0.265N	P=0.003N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Pancreatic Islets: Islet Cell Adenoma						
Overall Rates (a)	8/51 (16%)	3/50 (6%)	7/51 (14%)	4/47 (9%)	1/48 (2%)	5/51 (10%)
Adjusted Rates (b)	17.1%	8.1%	18.5%	10.5%	5.3%	33.3%
Terminal Rates (c)	6/44 (14%)	3/37 (8%)	5/35 (14%)	3/36 (8%)	1/19 (5%)	5/15 (33%)
Week of First Observation	84	105	90	100	105	105
Life Table Tests (d)	P=0.246	P=0.161N	P=0.540	P=0.283N	P=0.155N	P=0.248
Incidental Tumor Tests (d)	P=0.537	P=0.130N	P=0.541N	P=0.198N	P=0.046N	P=0.473
Cochran-Armitage Trend Test (d)	P=0.235N					
Fisher Exact Test (d)		P=0.106N	P=0.500N	P=0.220N	P=0.019N	P=0.277N
Pancreatic Islets: Islet Cell Carcinoma						
Overall Rates (a)	6/51 (12%)	15/50 (30%)	4/51 (8%)	9/47 (19%)	5/48 (10%)	1/51 (2%)
Adjusted Rates (b)	13.2%	36.2%	11.4%	24.2%	19.3%	6.7%
Terminal Rates (c)	5/44 (11%)	11/37 (30%)	4/35 (11%)	8/36 (22%)	3/19 (16%)	1/15 (7%)
Week of First Observation	98	97	105	102	71	105
Life Table Tests (d)	P=0.171N	P=0.011	P=0.521N	P=0.170	P=0.315	P=0.366N
Incidental Tumor Tests (d)	P=0.021N	P=0.027	P=0.518N	P=0.202	P=0.639	P=0.216N
Cochran-Armitage Trend Test (d)	P=0.004N					
Fisher Exact Test (d)		P=0.021	P=0.370N	P=0.232	P=0.543N	P=0.056N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma						
Overall Rates (a)	14/51 (27%)	18/50 (36%)	11/51 (22%)	13/47 (28%)	6/48 (13%)	6/51 (12%)
Adjusted Rates (b)	29.5%	43.6%	29.4%	33.9%	24.4%	40.0%
Terminal Rates (c)	11/44 (25%)	14/37 (38%)	9/35 (26%)	11/36 (31%)	4/19 (21%)	6/15 (40%)
Week of First Observation	84	97	90	100	71	105
Life Table Tests (d)	P=0.429N	P=0.133	P=0.570N	P=0.455	P=0.472N	P=0.474
Incidental Tumor Tests (d)	P=0.053N	P=0.249	P=0.454N	P=0.572	P=0.109N	P=0.439N
Cochran-Armitage Trend Test (d)	P=0.003N					
Fisher Exact Test (d)		P=0.239	P=0.323N	P=0.580	P=0.054N	P=0.040N
Mammary: Fibroadenoma						
Overall Rates (a)	1/52 (2%)	1/52 (2%)	1/52 (2%)	5/52 (10%)	1/52 (2%)	0/52 (0%)
Adjusted Rates (b)	2.3%	2.7%	2.4%	12.9%	5.3%	0.0%
Terminal Rates (c)	1/44 (2%)	1/37 (3%)	0/36 (0%)	4/37 (11%)	1/19 (5%)	0/15 (0%)
Week of First Observation	105	105	91	100	105	
Life Table Tests (d)	P=0.538N	P=0.723	P=0.718	P=0.072	P=0.564	P=0.714N
Incidental Tumor Tests (d)	P=0.354N	P=0.723	P=0.663N	P=0.089	P=0.564	P=0.714N
Cochran-Armitage Trend Test (d)	P=0.226N					
Fisher Exact Test (d)		P=0.752	P=0.752	P=0.102	P=0.752	P=0.500N
Preputial Gland: Adenoma or Carcinoma						
Overall Rates (a)	(f) 2/52 (4%)	0/52 (0%)	2/52 (4%)	1/52 (2%)	3/52 (6%)	0/52 (0%)
Adjusted Rates (b)	4.5%	0.0%	4.7%	2.7%	13.8%	0.0%
Terminal Rates (c)	2/44 (5%)	0/37 (0%)	1/36 (3%)	1/37 (3%)	2/19 (11%)	0/15 (0%)
Week of First Observation	105		57	105	100	
Life Table Tests (d)	P=0.522	P=0.277N	P=0.637	P=0.560N	P=0.180	P=0.494N
Incidental Tumor Tests (d)	P=0.543N	P=0.277N	P=0.633N	P=0.560N	P=0.302	P=0.494N
Cochran-Armitage Trend Test (d)	P=0.382N					
Fisher Exact Test (d)		P=0.248N	P=0.691	P=0.500N	P=0.500	P=0.248N
Prostate: Adenoma						
Overall Rates (a)	2/50 (4%)	6/50 (12%)	4/50 (8%)	2/52 (4%)	0/52 (0%)	3/47 (6%)
Adjusted Rates (b)	4.7%	15.4%	11.4%	5.4%	0.0%	12.3%
Terminal Rates (c)	2/43 (5%)	4/36 (11%)	4/35 (11%)	2/37 (5%)	0/19 (0%)	1/15 (7%)
Week of First Observation	105	103	105	105		90
Life Table Tests (d)	P=0.464	P=0.091	P=0.246	P=0.640	P=0.431N	P=0.187
Incidental Tumor Tests (d)	P=0.387N	P=0.155	P=0.246	P=0.640	P=0.431N	P=0.433
Cochran-Armitage Trend Test (d)	P=0.236N					
Fisher Exact Test (d)		P=0.134	P=0.339	P=0.676N	P=0.238N	P=0.470

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Prostate: Adenoma or Carcinoma						
Overall Rates (a)	2/50 (4%)	6/50 (12%)	4/50 (8%)	3/52 (6%)	0/52 (0%)	3/47 (6%)
Adjusted Rates (b)	4.7%	15.4%	11.4%	8.1%	0.0%	12.3%
Terminal Rates (c)	2/43 (5%)	4/36 (11%)	4/35 (11%)	3/37 (8%)	0/19 (0%)	1/15 (7%)
Week of First Observation	105	103	105	105		90
Life Table Tests (d)	P=0.457	P=0.091	P=0.246	P=0.431	P=0.431N	P=0.187
Incidental Tumor Tests (d)	P=0.396N	P=0.155	P=0.246	P=0.431	P=0.431N	P=0.433
Cochran-Armitage Trend Test (d)	P=0.225N					
Fisher Exact Test (d)		P=0.134	P=0.339	P=0.519	P=0.238N	P=0.470
Testis: Interstitial Cell Tumor						
Overall Rates (a)	50/52 (96%)	51/52 (98%)	43/51 (84%)	48/52 (92%)	39/52 (75%)	42/51 (82%)
Adjusted Rates (b)	96.2%	100.0%	100.0%	98.0%	97.5%	100.0%
Terminal Rates (c)	42/44 (95%)	37/37 (100%)	36/36 (100%)	36/37 (97%)	18/19 (95%)	15/15 (100%)
Week of First Observation	72	85	69	85	84	83
Life Table Tests (d)	P<0.001	P=0.060	P=0.391	P=0.158	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.183N	P=0.540	P=0.234N	P=0.531N	P=0.080N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.003N					
Fisher Exact Test (d)		P=0.500	P=0.043N	P=0.339N	P=0.002N	P=0.024N
All Sites: Benign Tumors						
Overall Rates (a)	52/52 (100%)	51/52 (98%)	48/52 (92%)	50/52 (96%)	44/52 (85%)	46/52 (88%)
Adjusted Rates (b)	100.0%	100.0%	100.0%	100.0%	97.8%	100.0%
Terminal Rates (c)	44/44 (100%)	37/37 (100%)	36/36 (100%)	37/37 (100%)	18/19 (95%)	15/15 (100%)
Week of First Observation	72	85	57	79	74	80
Life Table Tests (d)	P<0.001	P=0.110	P=0.148	P=0.135	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.091N	P=0.500N	P=0.366N	P=0.500N	P=0.060N	P=0.223N
Cochran-Armitage Trend Test (d)	P=0.005N					
Fisher Exact Test (d)		P=0.500N	P=0.059N	P=0.248N	P=0.003N	P=0.014N
All Sites: Malignant Tumors						
Overall Rates (a)	28/52 (54%)	36/52 (69%)	26/52 (50%)	35/52 (67%)	33/52 (63%)	19/52 (37%)
Adjusted Rates (b)	58.2%	74.7%	58.6%	75.9%	80.4%	59.4%
Terminal Rates (c)	24/44 (55%)	25/37 (68%)	18/36 (50%)	26/37 (70%)	12/19 (63%)	5/15 (33%)
Week of First Observation	85	85	83	61	58	66
Life Table Tests (d)	P=0.010	P=0.023	P=0.351	P=0.027	P<0.001	P=0.057
Incidental Tumor Tests (d)	P=0.016N	P=0.097	P=0.489N	P=0.081	P=0.247	P=0.117N
Cochran-Armitage Trend Test (d)	P=0.010N					
Fisher Exact Test (d)		P=0.079	P=0.422N	P=0.114	P=0.213	P=0.058N
All Sites: All Tumors						
Overall Rates (a)	52/52 (100%)	51/52 (98%)	49/52 (94%)	51/52 (98%)	51/52 (98%)	48/52 (92%)
Adjusted Rates (b)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Terminal Rates (c)	44/44 (100%)	37/37 (100%)	36/36 (100%)	37/37 (100%)	19/19 (100%)	15/15 (100%)
Week of First Observation	72	85	57	61	58	66
Life Table Tests (d)	P<0.001	P=0.110	P=0.106	P=0.097	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.575	P=0.500N	P=0.500N	(g)	P=0.814N	P=0.534N
Cochran-Armitage Trend Test (d)	P=0.074N					
Fisher Exact Test (d)		P=0.500N	P=0.122N	P=0.500N	P=0.500N	P=0.059N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups.
(f) Includes one diagnosis of papillomatosis
(g) No P value is presented because the tumor incidences in the control and 10-ppm groups were 100% in each of the four time intervals during which tumors were observed

TABLE A4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Overall Historical Incidence			
TOTAL	83/1,969 (4.2%)	19/1,969 (1.0%)	101/1,969 (5.1%)
SD (c)	4.54%	1.37%	4.60%
Range (d)			
High	12/50	3/50	12/50
Low	0/50	0/90	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by this laboratory are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence of Leukemia in Controls
Overall Historical Incidence	
TOTAL	583/1,977 (29.5%)
SD (c)	11.59%
Range (d)	
High	30/50
Low	5/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by this laboratory are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF KIDNEY TRANSITIONAL CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence of Papillomas or Carcinomas in Controls
Overall Historical Incidence	
TOTAL	(d) 5/1,968 (0.3%)
SD (c)	0.69%
Range (e)	
High	1/48
Low	0/90

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by this laboratory are included in the historical data base.
(c) Standard deviation
(d) Includes three papillomas and two carcinomas. One carcinoma, NOS, was also observed; the inclusion of this tumor would not affect the reported range.
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
TOTAL	(c) 16/1,928 (0.8%)	(d) 11/1,928 (0.6%)	(c,d) 27/1,928 (1.4%)
SD (e)	1.41%	0.91%	1.75%
Range (f)			
High	2/49	2/89	3/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by this laboratory are included in the historical data base.
(c) Includes one cystadenoma and one papillary cystadenoma
(d) Includes one papillary adenocarcinoma
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4e. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Overall Historical Incidence			
TOTAL	427/1,950 (21.9%)	30/1,950 (1.5%)	452/1,950 (23.2%)
SD (c)	12.41%	2.00%	12.39%
Range (d)			
High	31/49	4/49	32/49
Low	2/50	0/50	3/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by this laboratory are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF IN MALE RATS IN NONNEOPLASTIC LESIONS IN THE TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ANIMALS INITIALLY IN STUDY	52	52	52	52	52	52
ANIMALS NECROPSIED	52	52	52	52	52	52
ANIMALS EXAMINED HISTOPATH	52	52	52	52	52	52
INTEGUMENTARY SYSTEM						
*Skin	(52)	(52)	(52)	(52)	(52)	(52)
Epidermal inclusion cyst				1 (2%)		1 (2%)
Ulcer, NOS				1 (2%)		
Inflammation, acute					1 (2%)	
Hyperplasia, epithelial					1 (2%)	
RESPIRATORY SYSTEM						
*Nasal cavity	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, acute					1 (2%)	
#Lung	(52)	(52)	(52)	(52)	(52)	(51)
Congestion, chronic passive		1 (2%)	3 (6%)	8 (15%)	6 (12%)	4 (8%)
Inflammation, NOS						1 (2%)
Inflammation, interstitial	1 (2%)	1 (2%)		3 (6%)		1 (2%)
Inflammation, acute focal					1 (2%)	
Pneumonia, chronic murine		6 (12%)				
Inflammation, granulomatous focal	1 (2%)					
Necrosis, focal					1 (2%)	
Hyperplasia, alveolar epithelium	7 (13%)		1 (2%)	2 (4%)	1 (2%)	
Metaplasia, cartilaginous	1 (2%)					
HEMATOPOIETIC SYSTEM						
#Bone marrow	(52)	(49)	(48)	(47)	(40)	(51)
Fibrosis				1 (2%)		
Fibrosis, focal				3 (6%)		
#Spleen	(52)	(51)	(50)	(51)	(48)	(52)
Fibrosis		4 (8%)	1 (2%)	7 (14%)	6 (13%)	9 (17%)
Fibrosis, focal	2 (4%)	1 (2%)			1 (2%)	1 (2%)
Adhesion, NOS				1 (2%)		
Necrosis, NOS		1 (2%)				
Infarct, NOS	1 (2%)					
Hemosiderosis		1 (2%)	2 (4%)			
Atrophy, NOS						1 (2%)
Hyperplasia, lymphoid					1 (2%)	
Hematopoiesis			2 (4%)		2 (4%)	
#Splenic capsule	(52)	(51)	(50)	(51)	(48)	(52)
Fibrosis			1 (2%)			
Fibrosis, focal	2 (4%)		1 (2%)			
#Mesenteric lymph node	(51)	(52)	(52)	(52)	(48)	(48)
Fibrosis			1 (2%)			
Necrosis, focal	1 (2%)					
#Thymus	(47)	(47)	(42)	(40)	(42)	(41)
Cyst, NOS	3 (6%)		1 (2%)	2 (5%)	1 (2%)	1 (2%)
Hyperplasia, epithelial	15 (32%)	10 (21%)	7 (17%)	2 (5%)	8 (19%)	7 (17%)
CIRCULATORY SYSTEM						
*Mediastinum	(52)	(52)	(52)	(52)	(52)	(52)
Periarteritis						1 (2%)
#Lung	(52)	(52)	(52)	(52)	(52)	(51)
Thrombosis, NOS						1 (2%)
#Heart	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, acute/chronic			1 (2%)			
Inflammation, chronic	50 (96%)	51 (98%)	50 (96%)	50 (96%)	50 (96%)	46 (88%)
#Left atrium	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS	1 (2%)	7 (13%)	6 (12%)	7 (13%)	8 (15%)	5 (10%)
#Left ventricle	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS						1 (2%)
#Cardiac valve	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, chronic	1 (2%)					
#Mitral valve	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS		1 (2%)				
Inflammation, chronic	1 (2%)	1 (2%)				
*Aorta	(52)	(52)	(52)	(52)	(52)	(52)
Mineralization	3 (6%)	1 (2%)				1 (2%)
*Renal artery	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis	1 (2%)					
*Hepatic artery	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS				1 (2%)		
*Superior mesenteric vein	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis	1 (2%)					

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
CIRCULATORY SYSTEM (Continued)						
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis	1 (2%)					
*Mesentery	(52)	(52)	(52)	(52)	(52)	(52)
Periarteritis	3 (6%)	4 (8%)		3 (6%)	4 (8%)	
DIGESTIVE SYSTEM						
#Salivary gland	(52)	(52)	(52)	(52)	(50)	(51)
Calculus, unkn gross or micro			1 (2%)			
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, acute focal	1 (2%)					
Fibrosis		1 (2%)	1 (2%)			2 (4%)
Degeneration, NOS		1 (2%)	1 (2%)			
Necrosis, NOS		2 (4%)	1 (2%)	2 (4%)	4 (8%)	18 (35%)
Necrosis, focal	6 (12%)	9 (17%)	7 (13%)	5 (10%)	17 (33%)	8 (15%)
Metamorphosis, fatty	10 (19%)	11 (21%)	13 (25%)	20 (38%)	21 (40%)	26 (50%)
Pigmentation, NOS		1 (2%)				
Cytoplasmic change, NOS			1 (2%)			
Basophilic cyto change	47 (90%)	38 (73%)	41 (79%)	39 (75%)	27 (52%)	22 (42%)
Eosinophilic cyto change			1 (2%)	2 (4%)	2 (4%)	
Hepatocytomegaly	2 (4%)	12 (23%)	2 (4%)	40 (77%)	43 (83%)	44 (85%)
Atrophy, NOS	3 (6%)			2 (4%)		3 (6%)
Hypertrophy, focal			1 (2%)			
Angiectasis	20 (38%)	20 (38%)	19 (37%)	42 (81%)	38 (73%)	39 (75%)
Regeneration, NOS	1 (2%)					
#Liver/centrilobular	(52)	(52)	(52)	(52)	(52)	(52)
Degeneration, NOS	1 (2%)	3 (6%)	3 (6%)		1 (2%)	1 (2%)
Necrosis, NOS	1 (2%)		1 (2%)	5 (10%)	7 (13%)	12 (23%)
Necrosis, focal			1 (2%)			
Atrophy, NOS	5 (10%)	5 (10%)	2 (4%)	3 (6%)	4 (8%)	1 (2%)
#Bile duct	(52)	(52)	(52)	(52)	(52)	(52)
Cyst, NOS				1 (2%)	1 (2%)	1 (2%)
Hyperplasia, NOS	52 (100%)	51 (98%)	46 (88%)	46 (88%)	50 (96%)	47 (90%)
#Pancreatic duct	(51)	(50)	(51)	(47)	(48)	(51)
Hyperplasia, NOS		1 (2%)				
#Pancreatic acinus	(51)	(50)	(51)	(47)	(48)	(51)
Atrophy, NOS	13 (25%)	7 (14%)	6 (12%)	9 (19%)	5 (10%)	4 (8%)
Hyperplasia, NOS	4 (8%)	2 (4%)		2 (4%)	1 (2%)	3 (6%)
Hyperlasia, focal	3 (6%)					
#Stomach	(51)	(51)	(48)	(51)	(44)	(44)
Diverticulum	1 (2%)					
Inflammation, chronic						1 (2%)
Inflammation, proliferative	1 (2%)					
#Gastric mucosa	(51)	(51)	(48)	(51)	(44)	(44)
Ulcer, NOS	1 2(%)	3 (6%)	2 (4%)			1 (2%)
Erosion	2 (4%)	2 (4%)		2 (4%)	5 (11%)	4 (9%)
Hyperplasia, epithelial		1 (2%)				
Hyperplasia, focal		1 (2%)				
#Forestomach	(51)	(51)	(48)	(51)	(44)	(44)
Ulcer, NOS		1 (2%)	1 (2%)	3 (6%)	4 (9%)	2 (5%)
Inflammation, acute	1 (2%)				1 (2%)	
Inflammation, chronic		1 (2%)				
Erosion						2 (5%)
Hyperplasia, epithelial	2 (4%)	2 (4%)	2 (4%)		1 (2%)	2 (5%)
#Duodenum	(50)	(47)	(47)	(46)	(38)	(35)
Ulcer, NOS					3 (8%)	
Erosion		1 (2%)				
*Rectum	(52)	(52)	(52)	(52)	(52)	(52)
Polyp, inflammatory	1 (2%)					
URINARY SYSTEM						
#Kidney	(51)	(51)	(52)	(52)	(51)	(52)
Inflammation, acute focal			1 (2%)			
Abscess, NOS			1 (2%)	1 (2%)		
Nephropathy	50 (98%)	50 (98%)	45 (87%)	49 (94%)	51 (100%)	52 (100%)
Necrosis, focal					1 (2%)	
Infarct, NOS	1 (2%)	1 (2%)		1 (2%)		
Hyperplasia, tubular cell			1 (2%)		1 (2%)	
#Kidney/pelvis	(51)	(51)	(52)	(52)	(51)	(52)
Inflammation, acute focal					1 (2%)	
Hyperplasia, epithelial		2 (4%)	2 (4%)	5 (10%)	14 (27%)	9 (17%)
#Renal papilla	(51)					
Necrosis	1 (2%)					

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
URINARY SYSTEM (Continued)						
#Urinary bladder	(49)	(51)	(49)	(50)	(50)	(49)
Ulcer, NOS		1 (2%)				
Inflammation, acute necrotizing					1 (2%)	
#Urinary bladder/submucosa	(49)	(51)	(49)	(50)	(50)	(49)
Hemorrhage				1 (2%)		
ENDOCRINE SYSTEM						
#Pituitary	(52)	(52)	(51)	(50)	(52)	(47)
Cyst, NOS	2 (4%)	1 (2%)	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Necrosis, focal						1 (2%)
Pigmentation, NOS	1 (2%)					
Hypertrophy, focal		1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, NOS	3 (6%)	3 (6%)	2 (4%)	1 (2%)		2 (4%)
Hyperplasia, focal	2 (4%)	1 (2%)		3 (6%)	1 (2%)	2 (4%)
Angiectasis		1 (2%)				
#Adrenal	(51)	(52)	(52)	(52)	(51)	(51)
Necrosis, NOS				2 (4%)		
Necrosis, cortical				1 (2%)		
Cytoplasmic change, NOS				1 (2%)		
Hypertrophy, focal	1 (2%)					
Angiectasis	1 (2%)				1 (2%)	
#Adrenal cortex	(51)	(52)	(52)	(52)	(51)	(51)
Degeneration, NOS			1 (2%)	1 (2%)		
Necrosis, focal	1 (2%)					
Metamorphosis, fatty	6 (12%)	8 (15%)	4 (8%)	4 (8%)	9 (18%)	8 (16%)
Hyperplasia, NOS	5 (10%)		1 (2%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal			1 (2%)			
#Zona fasciculata	(51)	(52)	(52)	(52)	(51)	(51)
Hyperplasia, NOS				1 (2%)		
#Adrenal medulla	(51)	(52)	(52)	(52)	(51)	(51)
Hyperplasia, NOS	8 (16%)	4 (8%)	2 (4%)	10 (19%)	6 (12%)	9 (18%)
#Thyroid	(51)	(50)	(47)	(47)	(35)	(49)
Cystic follicles	2 (4%)	1 (2%)		5 (11%)	4 (11%)	6 (12%)
Hyperplasia, C-cell	9 (18%)	3 (6%)	1 (2%)	1 (2%)	1 (3%)	2 (4%)
Hyperplasia, follicular cell						1 (2%)
#Parathyroid	(32)	(39)	(39)	(40)	(50)	(45)
Ectopia	1 (3%)			2 (5%)	4 (8%)	1 (2%)
Hyperplasia, NOS	6 (19%)	12 (31%)	12 (31%)	18 (45%)	22 (44%)	24 (53%)
Hyperplasia, focal			1 (3%)			
#Pancreatic islets	(51)	(50)	(51)	(47)	(48)	(51)
Hyperplasia, NOS	12 (24%)	7 (14%)	8 (16%)	13 (28%)	14 (29%)	3 (6%)
Hyperplasia, focal	1 (2%)					
REPRODUCTIVE SYSTEM						
*Mammary gland	(52)	(52)	(52)	(52)	(52)	(52)
Galactocele		3 (6%)	1 (2%)	2 (4%)		
Cyst, NOS					1 (2%)	
Cystic ducts	9 (17%)	9 (17%)	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Inflammation, granulomatous			1 (2%)	1 (2%)		
*Penis	(52)	(52)	(52)	(52)	(52)	(52)
Ulcer, NOS					1 (2%)	
*Preputial gland	(52)	(52)	(52)	(52)	(52)	(52)
Cyst, NOS						2 (4%)
Cystic ducts					1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)					1 (2%)
Atrophy, NOS						1 (2%)
#Prostate	(50)	(50)	(50)	(52)	(52)	(47)
Inflammation, acute				1 (2%)	1 (2%)	
Inflammation, active chronic		1 (2%)				
Inflammation, chronic	4 (8%)	2 (4%)	7 (14%)	2 (4%)	3 (6%)	
Inflammation, granulomatous		1 (2%)				
Hyperplasia, NOS	13 (26%)	10 (20%)	10 (20%)	4 (8%)	4 (8%)	2 (4%)
Hyperplasia, focal	2 (4%)					
*Seminal vesicle	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, chronic	2 (4%)				2 (4%)	
Atrophy, NOS			1 (2%)			
#Testis	(52)	(52)	(51)	(52)	(52)	(51)
Granuloma, spermatic			1 (2%)	1 (2%)		
Infarct, NOS	1 (2%)					
Atrophy, NOS			1 (2%)	1 (2%)		2 (4%)
Hyperplasia, interstitial cell						4 (8%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
REPRODUCTIVE SYSTEM (Continued)						
*Epididymis	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, chronic		1 (2%)				
*Scrotum	(52)	(52)	(52)	(52)	(52)	(52)
Necrosis, fat						1 (2%)
NERVOUS SYSTEM						
#Brain	(52)	(52)	(52)	(51)	(52)	(50)
Compression, NOS			1 (2%)			
Hydrocephalus, NOS			2 (4%)			
Necrosis, NOS					1 (2%)	
Necrosis, focal			1 (2%)			
Necrosis, hemorrhagic		3 (6%)		1 (2%)	3 (6%)	2 (4%)
*Spinal cord	(52)	(52)	(52)	(52)	(52)	(52)
Necrosis, NOS					1 (2%)	
Malacia	2 (4%)					
Necrosis, hemorrhagic		2 (4%)		1 (2%)		
SPECIAL SENSE ORGANS						
*Eye/lacrimal gland	(52)	(52)	(52)	(52)	(52)	(52)
Atrophy, NOS				1 (2%)		
MUSCULOSKELETAL SYSTEM						
*Vertebra	(52)	(52)	(52)	(52)	(52)	(52)
Fibrous osteodystrophy					2 (4%)	2 (4%)
Exostosis		1 (2%)				
*Intervertebral disc	(52)	(52)	(52)	(52)	(52)	(52)
Rupture	2 (4%)					
BODY CAVITIES						
*Abdominal cavity	(52)	(52)	(52)	(52)	(52)	(52)
Steatitis		2 (4%)	2 (4%)	2 (4%)		3 (6%)
Inflammation, granulomatous				1 (2%)	1 (2%)	
Necrosis, fat	1 (2%)	3 (6%)	1 (2%)	2 (4%)	3 (6%)	
Necrosis, hemorrhagic						1 (2%)
*Mesentery	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, granulomatous	1 (2%)					
Necrosis, fat	1 (2%)					
ALL OTHER SYSTEMS						
*Multiple organs	(52)	(52)	(52)	(52)	(52)	(52)
Mineralization	1 (2%)	1 (2%)	1 (2%)	1 (2%)	5 (10%)	3 (6%)
Congestion, NOS			1 (2%)			
Adipose tissue						
Necrosis, NOS				1		
SPECIAL MORPHOLOGY SUMMARY						
None						

*Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
#Number of animals examined microscopically at this site.

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ANIMALS INITIALLY IN STUDY	52	52	52	52	52	52
ANIMALS NECROPSIED	52	52	52	52	52	52
ANIMALS EXAMINED HISTOPATH	52	52	52	52	52	52
INTEGUMENTARY SYSTEM						
*Subcutaneous tissue	(52)	(52)	(52)	(52)	(52)	(52)
Fibroma	1 (2%)	2 (4%)		1 (2%)		1 (2%)
Fibrosarcoma				1 (2%)	2 (4%)	
RESPIRATORY SYSTEM						
#Trachea	(47)	(47)	(45)	(47)	(46)	(44)
C-cell carcinoma, invasive		1 (2%)				
#Lung	(52)	(52)	(52)	(52)	(52)	(52)
Alveolar/bronchiolar adenoma						1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)			
C-cell carcinoma, metastatic		1 (2%)		2 (4%)		
Fibrosarcoma, metastatic				1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM						
*Multiple organs	(52)	(52)	(52)	(52)	(52)	(52)
Malig. lymphoma, histiocytic type		1 (2%)				
Leukemia, mononuclear cell	8 (15%)	8 (15%)	10 (19%)	13 (25%)	17 (33%)	14 (27%)
#Spleen	(50)	(52)	(52)	(50)	(51)	(50)
Leukemia, mononuclear cell				1 (2%)	1 (2%)	4 (8%)
#Thymus	(42)	(47)	(42)	(42)	(48)	(41)
Carcinoma, NOS			1 (2%)			1 (2%)
CIRCULATORY SYSTEM						
#Spleen	(50)	(52)	(52)	(50)	(51)	(50)
Hemangioma						1 (2%)
Hemangiosarcoma		1 (2%)				
#Pancreas	(50)	(52)	(51)	(49)	(50)	(50)
Hemangiosarcoma, invasive		1 (2%)				
DIGESTIVE SYSTEM						
*Tongue	(52)	(52)	(52)	(52)	(52)	(52)
Squamous cell papilloma	2 (4%)					
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Neoplastic nodule	10 (19%)	5 (10%)	4 (8%)	5 (10%)	9 (17%)	7 (13%)
Hepatocellular carcinoma					1 (2%)	2 (4%)
#Pancreas	(50)	(52)	(51)	(49)	(50)	(50)
Acinar cell adenoma			1 (2%)		1 (2%)	
#Jejunum	(49)	(52)	(49)	(48)	(47)	(47)
Papillary adenoma					1 (2%)	
URINARY SYSTEM						
#Kidney	(51)	(52)	(52)	(51)	(51)	(52)
Sarcoma, NOS						1 (2%)
Lipoma						1 (2%)
#Urinary bladder	(50)	(51)	(52)	(51)	(47)	(50)
Transitional cell carcinoma				1 (2%)		
Sarcoma, NOS, invasive				1 (2%)		
ENDOCRINE SYSTEM						
#Pituitary	(52)	(51)	(50)	(51)	(52)	(50)
Carcinoma, NOS	2 (4%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
Adenoma, NOS	20 (38%)	24 (47%)	31 (62%)	24 (47%)	30 (58%)	22 (44%)
Fibrosarcoma, invasive				1 (2%)		
#Adrenal	(51)	(52)	(52)	(51)	(51)	(52)
Cortical adenoma	3 (6%)	2 (4%)	5 (10%)	3 (6%)	4 (8%)	3 (6%)
Cortical carcinoma						1 (2%)
Pheochromocytoma	1 (2%)	3 (6%)	5 (10%)	1 (2%)	2 (4%)	5 (10%)
Pheochromocytoma, malignant						1 (2%)
Ganglioneuroma	1 (2%)					
#Thyroid	(50)	(50)	(48)	(47)	(48)	(46)
Follicular cell adenoma				1 (2%)		
Follicular cell carcinoma	1 (2%)	2 (4%)		1 (2%)		1 (2%)
C-cell adenoma	10 (20%)	9 (18%)	6 (13%)	5 (11%)	6 (13%)	2 (4%)
C-cell carcinoma	3 (6%)	4 (8%)	1 (2%)	4 (9%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ENDOCRINE SYSTEM (Continued)						
#Pancreatic islets	(50)	(52)	(51)	(49)	(50)	(50)
Islet cell adenoma	2 (4%)		1 (2%)	1 (2%)	4 (8%)	
Islet cell carcinoma	2 (4%)	2 (4%)	1 (2%)	3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM						
*Mammary gland	(52)	(52)	(52)	(52)	(52)	(52)
Adenocarcinoma, NOS	1 (2%)		3 (6%)		1 (2%)	2 (4%)
Fibroma					1 (2%)	
Fibroadenoma	12 (23%)	8 (15%)	11 (21%)	17 (33%)	10 (19%)	3 (6%)
*Preputial gland	(52)	(52)	(52)	(52)	(52)	(52)
Carcinoma, NOS						1 (2%)
*Clitoral gland	(52)	(52)	(52)	(52)	(52)	(52)
Adenoma, NOS		1 (2%)	1 (2%)			
Cystadenoma, NOS			2 (4%)	1 (2%)		
#Uterus	(51)	(51)	(52)	(52)	(52)	(52)
Adenocarcinoma, NOS	2 (4%)		1 (2%)			1 (2%)
Leiomyoma					1 (2%)	1 (2%)
Endometrial stromal polyp	14 (27%)	8 (16%)	10 (19%)	13 (25%)	12 (23%)	15 (29%)
Endometrial stromal sarcoma			1 (2%)		2 (4%)	
#Cervix uteri	(51)	(51)	(52)	(52)	(52)	(52)
Sarcoma, NOS				1 (2%)		
Endometrial stromal polyp					1 (2%)	
#Ovary	(51)	(51)	(52)	(52)	(52)	(51)
Granulosa cell tumor		1 (2%)				
Fibrosarcoma				1 (2%)		
NERVOUS SYSTEM						
#Brain	(52)	(52)	(51)	(52)	(52)	(52)
Carcinoma, NOS, invasive	2 (4%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
Astrocytoma	2 (4%)	1 (2%)		1 (2%)		1 (2%)
SPECIAL SENSE ORGANS						
*Zymbal gland	(52)	(52)	(52)	(52)	(52)	(52)
Sebaceous adenoma						1 (2%)
MUSCULOSKELETAL SYSTEM						
None						
BODY CAVITIES						
*Thoracic cavity	(52)	(52)	(52)	(52)	(52)	(52)
Mesothelioma, NOS	1 (2%)					
*Abdominal cavity	(52)	(52)	(52)	(52)	(52)	(52)
Osteoma				1 (2%)		
Fibrosarcoma	1 (2%)					
ALL OTHER SYSTEMS						
*Multiple organs	(52)	(52)	(52)	(52)	(52)	(52)
Adenocarcinoma, NOS, metastatic						1 (2%)
Fibrosarcoma, metastic	1 (2%)					
ANIMAL DISPOSITION SUMMARY						
Animals initially in study	52	52	52	52	52	52
Natural death	13	10	14	15	16	18
Moribund sacrifice	3	9	8	3	1	2
Terminal sacrifice	36	33	30	34	35	32

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
TUMOR SUMMARY						
Total animals with primary tumors**	48	48	49	47	50	49
Total primary tumors	99	83	98	102	108	93
Total animals with benign tumors	40	37	44	40	43	36
Total benign tumors	66	57	73	68	73	56
Total animals with malignant tumors	19	18	20	26	24	25
Total malignant tumors	22	20	21	29	26	30
Total animals with secondary tumors##	3	3	1	6	2	1
Total secondary tumors	3	4	1	7	2	1
Total animals with tumors uncertain--benign or malignant	11	6	4	5	9	7
Total uncertain tumors	11	6	4	5	9	7

*Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
**Primary tumors: all tumors except secondary tumors
#Number of animals examined microscopically at this site
##Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	50 ppm	100 ppm
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*Skin	(52)	(52)	(52)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma		1 (2%)	
Basal cell tumor	1 (2%)		
*Subcutaneous tissue	(52)	(52)	(52)
Carcinoma, NOS, unclear primary or metastatic	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(52)	(52)	(52)
Squamous cell carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)		1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	3 (6%)
Pheochromocytoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(52)	(52)	(52)
Malignant lymphoma, histiocytic type	1 (2%)		
Leukemia, mononuclear cell	5 (10%)	6 (12%)	12 (23%)
#Spleen	(51)	(52)	(49)
Leukemia, mononuclear cell	1 (2%)	3 (6%)	2 (4%)
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(52)	(52)	(52)
Hemangiosarcoma			1 (2%)
*Vertebra	(52)	(52)	(52)
Hemangiosarcoma			1 (2%)
#Heart	(52)	(52)	(52)
Hemangiosarcoma, metastatic			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(52)	(52)	(52)
Squamous cell papilloma	1 (2%)	1 (2%)	
#Liver	(52)	(52)	(52)
Neoplastic nodule	2 (4%)	23 (44%)	30 (58%)
Hepatocellular carcinoma			1 (2%)
#Pancreas	(50)	(52)	(51)
Acinar cell adenoma			1 (2%)
Mixed tumor, benign		1 (2%)	
#Stomach	(51)	(51)	(52)
Squamous cell papilloma			1 (2%)
URINARY SYSTEM			
#Kidney	(52)	(52)	(52)
Sarcoma, NOS			1 (2%)
#Kidney/pelvis	(52)	(52)	(52)
Transitional cell carcinoma	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Transitional cell papilloma	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	50 ppm	100 ppm
ENDOCRINE SYSTEM			
#Pituitary	(52)	(52)	(52)
Carcinoma, NOS	1 (2%)	3 (6%)	
Adenoma, NOS	31 (60%)	23 (44%)	22 (42%)
#Adrenal	(52)	(52)	(52)
Cortical adenoma	5 (10%)	6 (12%)	
Cortical carcinoma	2 (4%)		
Pheochromocytoma	3 (6%)	2 (4%)	1 (2%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(49)	(49)	(49)
Follicular cell adenoma	1 (2%)	1 (2%)	1 (2%)
C-cell adenoma	5 (10%)	3 (6%)	5 (10%)
C-cell carcinoma	2 (4%)	3 (6%)	
#Pancreatic islets	(50)	(52)	(51)
Islet cell adenoma	1 (2%)	2 (4%)	1 (2%)
Islet cell carcinoma	4 (8%)	9 (17%)	6 (12%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(52)	(52)	(52)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	3 (6%)	6 (12%)	3 (6%)
#Uterus	(52)	(51)	(52)
Undifferentiated carcinoma		1 (2%)	
Papillary adenoma	1 (2%)		
Endometrial stromal polyp	12 (23%)	8 (16%)	8 (15%)
NERVOUS SYSTEM			
#Brain	(52)	(52)	(52)
Carcinoma, NOS, invasive	1 (2%)	2 (4%)	
Osteosarcoma, invasive			1 (2%)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Skull	(52)	(52)	(52)
Osteosarcoma			1 (2%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(52)	(52)	(52)
Undifferentiated carcinoma, metastatic		1 (2%)	
Fibrosarcoma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	52	52	52
Natural death	7	7	14
Moribund sacrifice	2	2	1
Terminal sacrifice	43	43	37

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	50 ppm	100 ppm
TUMOR SUMMARY			
Total animals with primary tumors**	49	47	48
Total primary tumors	90	107	104
Total animals with benign tumors	41	36	31
Total benign tumors	68	54	44
Total animals with malignant tumors	17	24	24
Total malignant tumors	19	30	30
Total animals with secondary tumors##	1	4	3
Total secondary tumors	1	4	3
Total animals with tumors uncertain--benign or malignant	2	23	30
Total uncertain tumors	2	23	30
Total animals with tumors uncertain--primary or metastatic	1		
Total uncertain tumors	1		

*Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
**Primary tumors: all tumors except secondary tumors
#Number of animals examined microscopically at this site
##Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: UNTREATED CONTROL

ANIMAL NUMBER	064	014	050	024	054	012	094	010	098	076	046	004	080	044	002	006	008	016	018	020	022	026	028	030	032	034
WEEKS ON STUDY	078	081	081	086	087	091	091	093	093	094	095	099	102	104	107	107	107	107	107	107	107	107	107	107	107	107
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+
Fibroma																						X				
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	+	+	−	+	+	−	+	+	−	+	+	−	+	−	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	+	+	+	+	+	●	+
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																X										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule					X									X					X	X			X			X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS														X												
Adenoma, NOS		X		X		X			X			X			X					X	X		X		X	
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																										
Pheochromocytoma																										
Ganglioneuroma																X										
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																										
C-cell adenoma							X														X					X
C-cell carcinoma																										
Parathyroid	−	+	−	−	+	−	+	+	+	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	−
Pancreatic islets	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X							
Islet cell carcinoma																									X	
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	N	N	+	+
Adenocarcinoma, NOS																										
Fibroadenoma				X	X																	X				
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X								
Endometrial stromal polyp													X							X				X	X	
Ovary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive														X												
Astrocytoma						X					X															
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS										X																
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma	X																									
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic	X																									
Leukemia, mononuclear cell							X	X	X		X							X								

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
@: Multiple occurrence of morphology

: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	036	038	040	042	048	052	056	058	060	062	066	068	070	072	074	078	082	084	086	088	100	102	104	090	092	096	TOTAL:
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	108	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Squamous cell papilloma										X																	2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule			X				X			X													X				10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS																										X	2
Adenoma, NOS								X	X					X		X	X	X	X	X	X				X		20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cortical adenoma															X									X		X	3
Pheochromocytoma		X																									1
Ganglioneuroma																											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma								X																			1
C-cell adenoma	X					X			X	X					X							X			X		10
C-cell carcinoma				X					X											X							3
Parathyroid	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma												X															2
Islet cell carcinoma										X																	2
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	N	N	+	+	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	−	+	*52
Adenocarcinoma, NOS		X																									1
Fibroadenoma								X		X						X	X		X		X		X		X	X	12
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma, NOS																				X							2
Endometrial stromal polyp				X			X		X	X	X			X	X					X		X			X		14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																										X	2
Astrocytoma																											2
BODY CAVITIES																											
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Mesothelioma, NOS																											1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Fibrosarcoma																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Fibrosarcoma, metastatic																											1
Leukemia, mononuclear cell			X		X									X													8

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: 0.1 ppm

ANIMAL NUMBER	200	218	180	182	210	208	148	152	184	240	216	202	208	186	212	146	150	154	156	158	160	162	164	166	168	170	172
WEEKS ON STUDY	066	079	084	084	087	091	094	098	098	101	102	102	103	105	109	109	109	109	109	109	109	109	109	109	109	109	109
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																											
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																											
Trachea	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive																											
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, invasive			X																								
Esophagus	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS	X																										
Adenoma, NOS				X				X	X		X					X	X	X		X	X	X	X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																											
Pheochromocytoma					X										X												
Thyroid	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																											
C-cell adenoma						X																	X	X			
C-cell carcinoma							X																				
Parathyroid	+	−	+	+	−	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																				X							
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	−	+	+	N	+	N	N	
Fibroadenoma			X		X	X	X									X					X						
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Adenoma, NOS												X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	
Endometrial stromal polyp						X									X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	
Granulosa cell tumor										X																	
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, NOS, invasive	X																										
Astrocytoma																											
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Malignant lymphoma, histiocytic type																											
Leukemia, mononuclear cell		X					X			X			X	X													

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 0.1 ppm (Continued)

ANIMAL NUMBER	174	176	178	188	190	192	194	196	198	202	204	206	214	222	224	226	228	230	232	234	236	238	242	244	246	248	TOTAL:
WEEKS ON STUDY	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	109	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma	X																							X			2
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell carcinoma, metastatic									X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell carcinoma, invasive									X																		1
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+		47
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X						X																X	X			5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma, invasive																											1
Esophagus	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, NOS																											1
Adenoma, NOS			X					X	X	X			X			X	X			X				X	X	X	24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma	X												X														2
Pheochromocytoma										X																	3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma										X	X																2
C-cell adenoma	X				X		X									X		X								X	9
C-cell carcinoma									X						X							X					4
Parathyroid	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell carcinoma										X																	2
REPRODUCTIVE SYSTEM																											
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	N	N	+	N	N	*52
Fibroadenoma								X				X															8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Adenoma, NOS																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endometrial stromal polyp			X	X				X			X							X						X		8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Granulosa cell tumor																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																											1
Astrocytoma														X													1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malig. lymphoma, histiocytic type																	X										1
Leukemia, mononuclear cell				X														X	X								8

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: 1 ppm

ANIMAL NUMBER	336	310	346	314	340	344	270	292	326	320	332	302	260	294	304	308	352	256	282	250	252	254	258	262	264	266
WEEKS ON STUDY	078	082	084	086	086	086	090	091	091	093	096	097	098	102	103	104	106	107	107	108	108	108	108	108	108	108
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										
Trachea	−	−	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell														X												
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																										
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X					X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																										
Esophagus	+	+	+	+	−	−	−	−	+	+	+	−	−	−	+	+	−	+	+	+	+	+	−	−	+	−
Stomach	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																										
Adenoma, NOS		X		X		X			X	X				X	X	X				X	X	X	X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma															X					X						
Pheochromocytoma														X										X		
Thyroid	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
C-cell adenoma																X						X				X
C-cell carcinoma																										
Parathyroid	+	+	−	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X							
Islet cell carcinoma																							X			
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS				X					X																	
Fibroadenoma			X									X		X		X				X	X		X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																										
Cystadenoma, NOS																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																										
Endometrial stromal polyp								X			X							X						X	
Endometrial stromal sarcoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X		X	X		X				X	X	X		X	X				X						

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1 ppm (Continued)

ANIMAL NUMBER	26 68	27 72	31 18	27 74	27 76	27 78	28 80	28 84	28 86	28 88	29 90	29 96	29 98	30 00	30 06	31 12	31 16	32 22	32 24	32 28	33 30	33 34	33 38	34 42	34 48	35 50	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	10 08	10 08	10 08	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	10 09	
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																						X					1
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leukemia, mononuclear cell																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Carcinoma, NOS					X																						1
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule													X							X							4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell adenoma				X																							1
Esophagus	+	–	+	–	+	+	–	+	+	–	–	+	+	–	+	+	–	+	–	–	+	–	–	+	+	–	29
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																			X								1
Adenoma, NOS	X		X		X	X	X			X	X	X	X		X	X	X	X				X	X	X	X		31
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma			X								X	X															5
Pheochromocytoma						X																			X		5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma								X														X	X				6
C-cell carcinoma											X																1
Parathyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islet cell adenoma																											1
Islet cell carcinoma																											1
REPRODUCTIVE SYSTEM																											
Mammary gland	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*52
Adenocarcinoma, NOS																									X		3
Fibroadenoma			X												X				X						X		11
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Adenoma, NOS											X																1
Cystadenoma, NOS																			X					X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma, NOS														X													1
Endometrial stromal polyp					X				X												X		X	X		X	10
Endometrial stromal sarcoma						X																					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, NOS, invasive																			X								1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Leukemia, mononuclear cell																											10

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: 10 ppm

ANIMAL NUMBER	37 42	45 21	36 88	41 66	39 22	44 40	39 00	41 22	35 44	36 00	36 22	45 00	35 66	37 22	39 44	35 88	42 66	36 44	36 66	37 00	37 76	37 88	38 00	38 22	38 44	38 66
WEEKS ON STUDY	07 77	07 99	08 82	08 88	09 22	09 44	09 98	09 99	10 00	10 33	10 33	10 33	10 55	10 55	10 55	10 66	10 66	10 88	10 88	10 80	10 88	10 88	10 80	10 88	10 88	10 88
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																										
Fibrosarcoma													X													
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																										
Fibrosarcoma, metastatic													X													
Trachea	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																X										
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	−	−	+	+	−	+	+	−	+	−	−	−	+	−	−	−	−	+
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	−	−	−	−	+	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																										
Sarcoma, NOS, invasive				X																						
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																X				X						
Adenoma, NOS		X				X	X			X	X		X	X	X		X						X	X	X	
Fibrosarcoma, invasive													X													
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X			X									
Pheochromocytoma																										
Thyroid	−	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																										
Follicular cell carcinoma										X																
C-cell adenoma																				X						
C-cell carcinoma					X																					
Parathyroid	−	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																										
Islet cell carcinoma													X													
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N
Fibroadenoma	X										X			X		X		X	X		X		X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Cystadenoma, NOS																										
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS				X																						
Endometrial stromal polyp						X				X	X						X							X	X	X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																X				X						
Astrocytoma																										
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X	X	X				X	X	X							X		X		X						

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 10 ppm (Continued)

ANIMAL NUMBER	388	396	398	400	402	404	406	408	410	414	418	420	422	424	428	430	432	434	436	438	442	444	446	448	454	456	TOTAL:
WEEKS ON STUDY	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	*52
Fibroma			X																								1
Fibrosarcoma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell carcinoma, metastatic									X	X																	2
Fibrosarcoma, metastatic																											1
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	42
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X		X	X				X											X								5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	−	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	35
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	42
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Transitional cell carcinoma													X														1
Sarcoma, NOS, invasive																											1
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, NOS																											2
Adenoma, NOS						X				X	X		X			X	X	X		X			X	X	X	X	24
Fibrosarcoma, invasive																											1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cortical adenoma	X																										3
Pheochromocytoma									X																		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																								X			1
Follicular cell carcinoma																											1
C-cell *adenoma*			X	X										X			X										5
C-cell carcinoma									X	X																X	4
Parathyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma								X																			1
Islet cell carcinoma									X																X		3
REPRODUCTIVE SYSTEM																											
Mammary gland	N	+	+	+	+	N	+	+	N	+	N	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+	*52
Fibroadenoma							X						X	X		X	X						X	X	X	X	17
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Cystadenoma, NOS																										X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma, NOS																											1
Endometrial stromal polyp	X			X			X					X				X			X								13
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibrosarcoma	X																										1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																											2
Astrocytoma								X																			1
BODY CAVITIES																											
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Osteoma										X																	1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Leukemia, mononuclear cell		X			X									X			X										13

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: 25 ppm

ANIMAL NUMBER	520	518	558	570	504	552	514	566	526	508	512	498	500	510	556	574	576	502	506	516	522	524	528	530	532	534
WEEKS ON STUDY	049	068	089	096	101	102	103	104	105	106	106	107	107	107	107	107	107	108	108	108	108	108	108	108	108	108
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma							X																			
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic							X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																		X								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				X									X										X			
Hepatocellular carcinoma											X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																										X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	+	−	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+
Papillary adenoma										X																
Large intestine	−	−	+	+	−	−	+	−	+	+	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	−	+	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																					
Adenoma, NOS			X			X				X			X		X	X		X	X			X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																	X									
Pheochromocytoma																X				X						
Thyroid	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+
C-cell adenoma				X					X												X					
Parathyroid	+	−	+	+	+	−	−	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+
Pancreatic islets	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X													X		
Islet cell carcinoma							X																			
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	N
Adenocarcinoma, NOS																										
Fibroma											X															
Fibroadenoma						X		X				X													X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Leiomyoma																										
Endometrial stromal polyp							X						X					X					X			
Endometrial stromal sarcoma																		X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive					X																					
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X	X		X				X				X	X	X	X	X	X									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 25 ppm (Continued)

ANIMAL NUMBER	536	538	540	542	544	546	548	550	554	560	562	564	568	572	578	580	582	584	586	588	590	592	594	596	598	600	TOTAL:
WEEKS ON STUDY	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*52
Fibrosarcoma																										X	2
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibrosarcoma, metastatic																											1
Trachea	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia, mononuclear cell																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule												X	X			X	X			X	X						9
Hepatocellular carcinoma																											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																											1
Esophagus	+	+	+	+	+	−	−	+	−	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	42
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papillary adenoma																											1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS																											1
Adenoma, NOS	X			X	X	X		X			X	X			X	X	X	X	X	X		X		X	X	X	30
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cortical adenoma							X										X								X		4
Pheochromocytoma																											2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma					X		X															X					6
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma						X						X															4
Islet cell carcinoma																											1
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	N	N	+	+	+	+	+	+	N	N	+	*52
Adenocarcinoma, NOS																						X					1
Fibroma																											1
Fibroadenoma			X					X					X					X		X					X	10
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leiomyoma																								X			1
Endometrial stromal polyp					X				X				X			X		X@X							X	X	12
Endometrial stromal sarcoma																									X		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Leukemia, mononuclear cell		X			X							X	X								X	X	X				17

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX: 50 ppm

ANIMAL NUMBER	84202	86404	80202	84404	83805	83606	81806	81606	79808	82606	88004	82808	85005	85202	81202	89204	89404	83202	87606	88808	79404	79606	80004	80404	80604	80808
WEEKS ON STUDY	05202	06909	08000	08101	08505	08707	09101	09303	09404	09404	09404	09707	09908	09909	10101	10404	10505	10707	10707	10707	10808	10808	10808	10808	10808	10808
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X				
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Trachea	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Hemangioma								X																		
Leukemia, mononuclear cell														X						X						
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	−	−	+	−	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+
Carcinoma, NOS														X						X						
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X															
Hepatocellular carcinoma																				X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	−	−	−	+	+	−	+	+	−	+	−	+	−	−	−	+	−	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																										
Lipoma																										
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Adenoma, NOS		X			X				X			X			X				X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Cortical adenoma																			X							
Cortical carcinoma																					X					
Pheochromocytoma																X								X		
Pheochromocytoma, malignant																										
Thyroid	+	+	+	−	+	+	+	−	−	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+
Follicular cell carcinoma										X																
C-cell adenoma																		X								
Parathyroid	+	+	+	+	−	+	+	−	+	+	+	+	+	+	−	−	−	−	−	+	+	+	+	−	+	+
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	+	+	N	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																										
Fibroadenoma								X																		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X								
Leiomyoma																										
Endometrial stromal polyp			X			X	X							X	X									X	X	
Ovary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																							X			
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N
Sebaceous adenoma																						X				
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic																		X								
Leukemia, mononuclear cell		X	X				X		X	X	X		X						X						X	

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 ppm (Continued)

ANIMAL NUMBER	8110	8114	8201	8222	8243	8303	8334	8404	8446	8448	8545	8566	8588	8601	8626	8666	8688	8701	8722	8744	8782	8822	8844	8866	8901	8966	TOTAL:
WEEKS ON STUDY	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																						X					1
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+		44
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																											1
Leukemia, mononuclear cell										X				X													4
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	41
Carcinoma, NOS								X																			1
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X			X		X	X														X		X				7
Hepatocellular carcinoma										X																	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	−	+	−	+	+	+	−	+	−	−	−	−	+	+	+	+	−	−	+	+	+	+	38
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma, NOS																							X				1
Lipoma																	X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X		X	X		X	X			X			X		X		X		X		X	X		X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma			X														X										3
Cortical carcinoma																											1
Pheochromocytoma		X							X				X														5
Pheochromocytoma, malignant																X											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell carcinoma																											1
C-cell adenoma														X													2
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																											
Mammary gland	+	N	+	+	+	+	+	N	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	*52
Adenocarcinoma, NOS																		X	X								2
Fibroadenoma			X																	X							3
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Carcinoma, NOS															X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma, NOS																											1
Leiomyoma														X													1
Endometrial stromal polyp									X		X							X	X		X	X	X		X		15
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Astrocytoma																											1
SPECIAL SENSE ORGANS																											
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Sebaceous adenoma																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Adenocarcinoma, NOS, metastatic																											1
Leukemia, mononuclear cell						X		X									X	X							X		14

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX: UNTREATED CONTROL

ANIMAL NUMBER	0402	0222	0288	0722	0444	0884	0092	0770	0004	0006	0008	0010	0112	0114	0116	0118	0220	0224	0226	0330	0332	0334	0336	0338	0422	0466
WEEKS ON STUDY	050	054	080	087	093	094	099	100	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Basal cell tumor																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, unclear prim or metastatic																			X							
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										X
Alveolar/bronchiolar carcinoma																										
Trachea	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									X	
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	−	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	+	~	−	+	+	−	−	+	−	−	−
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																				X						
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																										
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																										
Adenoma, NOS				X	X		X		X	X			X	X	X	X	X	X	X		X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																										X
Cortical carcinoma																				X						
Pheochromocytoma												X														
Thyroid	+	+	+	~	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X													
C-cell adenoma									X						X								X			
C-cell carcinoma																										X
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																										X
Islet cell carcinoma							X															X				
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X								
Fibroadenoma	X									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																										
Endometrial stromal polyp									X						X									X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																										
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type								X																		
Leukemia, mononuclear cell			X			X											X									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	048	050	052	054	056	058	060	062	064	066	068	074	076	078	080	082	086	088	090	092	094	096	098	100	102	104	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell papilloma																					X						1
Basal cell tumor															X												1
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Carcinoma, NOS, unclear pri or met																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																								X			2
Alveolar/bronchiolar carcinoma															X												1
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia, mononuclear cell																											1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Squamous cell papilloma			X																								1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule									X												X						2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	–	–	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	–	–	–	–	32
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional cell carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma		X																									1
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS																							X				1
Adenoma, NOS	X		X	X	X		X		X			X	X				X	X	X	X	X	X		X	X	X	31
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma	X		X		X			X																			5
Cortical carcinoma											X																2
Pheochromocytoma																			X	X							3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																											1
C-cell adenoma																		X					X				5
C-cell carcinoma													X														2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																											1
Islet cell carcinoma										X	X																4
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	*52
Adenocarcinoma, NOS																											1
Fibroadenoma																							X				3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Papillary adenoma			X																								1
Endometrial stromal polyp	X	X		X	X	X		X	X							X			X								12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive																							X				1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malig. lymphoma, histiocytic type																											1
Leukemia, mononuclear cell							X								X												5

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX: 50 ppm

ANIMAL NUMBER	202	166	114	160	174	126	154	190	156	106	108	110	112	118	118	120	122	124	128	130	132	134	136	138	140	142
WEEKS ON STUDY	075	095	099	102	102	104	104	104	105	106	106	106	108	106	106	106	106	106	106	106	106	106	106	106	106	106
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																					
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic					X																					
Alveolar/bronchiolar carcinoma													X												X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell														X												
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																										
Salivary gland	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule		X					X				X		X	X			X	X	X		X		X	X		X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor, benign																				X						
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X											X							
Adenoma, NOS			X		X		X		X						X			X		X		X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X												X
Pheochromocytoma			X		X																					
Thyroid	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																										
C-cell adenoma									X																X	
C-cell carcinoma							X				X							X								
Parathyroid	+	−	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																						X				
Islet cell carcinoma									X	X				X				X								
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Adenoma, NOS															X											
Fibroadenoma	X												X				X						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																										
Endometrial stromal polyp											X						X		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive								X																		
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Undifferentiated carcinoma, metastatic																										
Fibrosarcoma						X																				
Leukemia, mononuclear cell		X		X			X											X							X	

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 ppm (Continued)

ANIMAL NUMBER	144	146	148	150	152	158	162	164	168	170	172	176	178	180	182	184	186	188	192	194	196	198	200	204	206	208	TOTAL:
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell carcinoma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma, metastati																											1
Alveolar/bronchiolar carcinoma		X																									3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leukemia, mononuclear cell																						X				X	3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																											
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Squamous cell papilloma			X																								1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule						X		X	X								X	X	X		X	X	X		X	X	23
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mixed tumor, benign																											1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS		X																									3
Adenoma, NOS			X	X	X	X	X		X						X	X		X	X			X		X		X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma	X				X			X																		X	6
Pheochromocytoma																											2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma					X																						1
C-cell adenoma							X																				3
C-cell carcinoma																											3
Parathyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell adenoma						X																					2
Islet cell carcinoma	X								X				X	X	X												9
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Adenoma, NOS																											1
Fibroadenoma							X																	X			6
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Undifferentiated carcinoma				X																							1
Endometrial stromal polyp	X										X		X	X		X											8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, NOS, invasive		X																									2
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Undiff. carcinoma, metastatic				X																							1
Fibrosarcoma																											1
Leukemia, mononuclear cell																	X										6

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX: 100 ppm

ANIMAL NUMBER	284	310	252	236	226	300	282	280	248	294	272	268	286	210	212	214	216	218	220	222	224	228	230	232	234	238
WEEKS ON STUDY	082	082	086	087	092	094	095	096	097	097	098	101	104	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																								
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																										X
Pheochromocytoma, metastatic																										
Trachea	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																										X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic						X																				
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X	X	X									X		X	X		X		X		X		X		X	X
Hepatocellular carcinoma								X																		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X																
Small intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS	X																									
Urinary bladder	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X						X			X			X	X	X	X		X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																										
Pheochromocytoma, malignant																										
Thyroid	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																										
C-cell adenoma											X						X		X							
Parathyroid	+	+	+	−	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																X										
Islet cell carcinoma																										
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X	X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X			X																		X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, invasive									X																	
Astrocytoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma						X																				
Osteosarcoma									X																	
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell											X						X	X			X			X		

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 ppm (Continued)

ANIMAL NUMBER	240	242	244	246	250	254	256	258	260	262	264	266	270	274	276	278	288	290	292	296	298	302	304	306	308	312	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*52
Hemangiosarcoma																											1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma									X																		1
Alveolar/bronchiolar carcinoma						X																X					3
Pheochromocytoma, metastatic																								X			1
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	47
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																			X								2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma, metastatic																											1
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X	X	X	X		X	X	X	X	X			X			X		X	X	X	X	X			X	X	30
Hepatocellular carcinoma																											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell adenoma									X																		1
Esophagus	−	−	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma																											1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+		48
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma, NOS																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS	X	X	X		X	X	X	X			X	X				X						X			X		22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma							X																				1
Pheochromocytoma, malignant																								X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																						X					1
C-cell adenoma							X																X				5
Parathyroid	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	−	+	−	+	+	42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islet cell adenoma																											1
Islet cell carcinoma			X			X					X	X		X				X									6
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	*52
Fibroadenoma												X															3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endometrial stromal polyp			X		X		X																		X	X	8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Osteosarcoma, invasive																											1
Astrocytoma											X																1
MUSCULOSKELETAL SYSTEM																											
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Hemangiosarcoma																											1
Osteosarcoma																											1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Leukemia, mononuclear cell			X				X						X	X			X				X			X			12

* Animals necropsied

TABLE B5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Hematopoietic System: Mononuclear Cell Leukemia						
Overall Rates (a)	8/52 (15%)	8/52 (15%)	11/52 (21%)	14/52 (27%)	18/52 (35%)	18/52 (35%)
Adjusted Rates (b)	18.3%	18.0%	23.4%	30.4%	39.3%	40.6%
Terminal Rates (c)	4/38 (11%)	3/38 (8%)	1/35 (3%)	5/35 (14%)	14/41 (34%)	10/35 (29%)
Week of First Observation	91	79	82	77	49	69
Life Table Tests (d)	P=0.005	P=0.586N	P=0.296	P=0.132	P=0.044	P=0.023
Incidental Tumor Tests (d)	P=0.003	P=0.581N	P=0.398	P=0.183	P=0.039	P=0.027
Cochran-Armitage Trend Test (d)	P=0.003					
Fisher Exact Test (d)		P=0.607	P=0.306	P=0.115	P=0.020	P=0.020
Liver: Neoplastic Nodule						
Overall Rates (a)	10/52 (19%)	5/52 (10%)	4/52 (8%)	5/52 (10%)	9/52 (17%)	7/52 (13%)
Adjusted Rates (b)	25.3%	13.2%	11.4%	14.3%	21.2%	19.0%
Terminal Rates (c)	9/38 (24%)	5/38 (13%)	4/35 (11%)	5/35 (14%)	8/41 (20%)	6/35 (17%)
Week of First Observation	87	107	107	107	96	94
Life Table Tests (d)	P=0.329	P=0.130N	P=0.098N	P=0.165N	P=0.424N	P=0.356N
Incidental Tumor Tests (d)	P=0.326	P=0.135N	P=0.090N	P=0.180N	P=0.500N	P=0.347N
Cochran-Armitage Trend Test (d)	P=0.345					
Fisher Exact Test (d)		P=0.132N	P=0.075N	P=0.132N	P=0.500N	P=0.298N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma						
Overall Rates (a)	10/52 (19%)	5/52 (10%)	4/52 (8%)	5/52 (10%)	10/52 (19%)	9/52 (17%)
Adjusted Rates (b)	25.3%	13.2%	11.4%	14.3%	23.0%	24.6%
Terminal Rates (c)	9/38 (24%)	5/38 (13%)	4/35 (11%)	5/35 (14%)	8/41 (20%)	8/35 (23%)
Week of First Observation	87	107	107	107	96	94
Life Table Tests (d)	P=0.117	P=0.130N	P=0.098N	P=0.165N	P=0.518N	P=0.571N
Incidental Tumor Tests (d)	P=0.119	P=0.135N	P=0.090N	P=0.180N	P=0.593N	P=0.563N
Cochran-Armitage Trend Test (d)	P=0.130					
Fisher Exact Test (d)		P=0.132N	P=0.075N	P=0.132N	P=0.598	P=0.500N
Pituitary Gland: Adenoma						
Overall Rates (a)	20/52 (38%)	24/51 (47%)	31/50 (62%)	24/51 (47%)	30/52 (58%)	22/50 (44%)
Adjusted Rates (b)	45.7%	58.0%	71.6%	54.0%	68.0%	56.8%
Terminal Rates (c)	15/38 (39%)	20/37 (54%)	23/35 (66%)	15/35 (43%)	27/41 (66%)	17/33 (52%)
Week of First Observation	81	84	82	79	89	69
Life Table Tests (d)	P=0.528	P=0.264	P=0.018	P=0.244	P=0.090	P=0.261
Incidental Tumor Tests (d)	P=0.518N	P=0.243	P=0.015	P=0.278	P=0.021	P=0.293
Cochran-Armitage Trend Test (d)	P=0.454N					
Fisher Exact Test (d)		P=0.247	P=0.014	P=0.247	P=0.038	P=0.357
Pituitary Gland: Adenoma or Carcinoma						
Overall Rates (a)	22/52 (42%)	25/51 (49%)	32/50 (64%)	26/51 (51%)	31/52 (60%)	22/50 (44%)
Adjusted Rates (b)	49.4%	58.8%	73.9%	57.5%	68.7%	56.8%
Terminal Rates (c)	16/38 (42%)	20/37 (54%)	24/35 (69%)	16/35 (46%)	27/41 (66%)	17/33 (52%)
Week of First Observation	81	66	82	79	89	69
Life Table Tests (d)	P=0.408N	P=0.335	P=0.028	P=0.247	P=0.140	P=0.393
Incidental Tumor Tests (d)	P=0.373N	P=0.318	P=0.023	P=0.308	P=0.038	P=0.451
Cochran-Armitage Trend Test (d)	P=0.325N					
Fisher Exact Test (d)		P=0.314	P=0.023	P=0.247	P=0.058	P=0.511
Adrenal Gland: Cortical Adenoma						
Overall Rates (a)	3/51 (6%)	2/52 (4%)	5/52 (10%)	3/51 (6%)	4/51 (8%)	3/52 (6%)
Adjusted Rates (b)	7.9%	5.3%	13.8%	7.8%	10.0%	8.6%
Terminal Rates (c)	3/38 (8%)	2/38 (5%)	4/35 (11%)	1/35 (3%)	4/40 (10%)	3/35 (9%)
Week of First Observation	107	107	103	105	107	107
Life Table Tests (d)	P=0.559	P=0.500N	P=0.316	P=0.637	P=0.528	P=0.625
Incidental Tumor Tests (d)	P=0.548N	P=0.500N	P=0.327	P=0.606N	P=0.528	P=0.625
Cochran-Armitage Trend Test (d)	P=0.551N					
Fisher Exact Test (d)		P=0.491N	P=0.369	P=0.661	P=0.500	P=0.652N

TABLE B5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Adrenal Gland: Cortical Adenoma or Carcinoma						
Overall Rates (a)	3/51 (6%)	2/52 (4%)	5/52 (10%)	3/51 (6%)	4/51 (8%)	4/52 (8%)
Adjusted Rates (b)	7.9%	5.3%	13.8%	7.8%	10.0%	11.4%
Terminal Rates (c)	3/38 (8%)	2/38 (5%)	4/35 (11%)	1/35 (3%)	4/40 (10%)	4/35 (11%)
Week of First Observation	107	107	103	105	107	107
Life Table Tests (d)	P=0.380	P=0.500N	P=0.316	P=0.637	P=0.528	P=0.455
Incidental Tumor Tests (d)	P=0.400	P=0.500N	P=0.327	P=0.606N	P=0.528	P=0.455
Cochran-Armitage Trend Test (d)	P=0.398					
Fisher Exact Test (d)		P=0.491N	P=0.369	P=0.661	P=0.500	P=0.511
Adrenal Gland: Pheochromocytoma						
Overall Rates (a)	1/51 (2%)	3/52 (6%)	5/52 (10%)	1/51 (2%)	2/51 (4%)	5/52 (10%)
Adjusted Rates (b)	2.6%	7.2%	13.7%	2.9%	5.0%	13.8%
Terminal Rates (c)	1/38 (3%)	2/38 (5%)	4/35 (11%)	1/35 (3%)	2/40 (5%)	4/35 (11%)
Week of First Observation	107	87	102	107	107	104
Life Table Tests (d)	P=0.199	P=0.307	P=0.089	P=0.743	P=0.518	P=0.088
Incidental Tumor Tests (d)	P=0.199	P=0.291	P=0.094	P=0.743	P=0.518	P=0.102
Cochran-Armitage Trend Test (d)	P=0.213					
Fisher Exact Test (d)		P=0.316	P=0.107	P=0.752	P=0.500	P=0.107
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma						
Overall Rates (a)	1/51 (2%)	3/52 (6%)	5/52 (10%)	1/51 (2%)	2/51 (4%)	6/52 (12%)
Adjusted Rates (b)	2.6%	7.2%	13.7%	2.9%	5.0%	16.6%
Terminal Rates (c)	1/38 (3%)	2/38 (5%)	4/35 (11%)	1/35 (3%)	2/40 (5%)	5/35 (14%)
Week of First Observation	107	87	102	107	107	104
Life Table Tests (d)	P=0.096	P=0.307	P=0.089	P=0.743	P=0.518	P=0.048
Incidental Tumor Tests (d)	P=0.096	P=0.291	P=0.094	P=0.743	P=0.518	P=0.056
Cochran-Armitage Trend Test (d)	P=0.106					
Fisher Exact Test (d)		P=0.316	P=0.107	P=0.752	P=0.500	P=0.059
Thyroid Gland: C-Cell Adenoma						
Overall Rates (a)	10/50 (20%)	9/50 (18%)	6/48 (13%)	5/47 (11%)	6/48 (13%)	2/46 (4%)
Adjusted Rates (b)	25.3%	22.7%	17.0%	14.3%	14.1%	5.9%
Terminal Rates (c)	9/38 (24%)	8/38 (21%)	5/34 (15%)	5/35 (14%)	4/39 (10%)	2/34 (6%)
Week of First Observation	91	91	104	107	96	107
Life Table Tests (d)	P=0.018N	P=0.500N	P=0.276N	P=0.165N	P=0.185N	P=0.024N
Incidental Tumor Tests (d)	P=0.022N	P=0.541N	P=0.259N	P=0.189N	P=0.237N	P=0.027N
Cochran-Armitage Trend Test (d)	P=0.021N					
Fisher Exact Test (d)		P=0.500N	P=0.233N	P=0.160N	P=0.233N	P=0.020N
Thyroid Gland: C-Cell Carcinoma						
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/48 (2%)	4/47 (9%)	0/48 (0%)	0/46 (0%)
Adjusted Rates (b)	7.9%	9.9%	2.9%	10.5%	0.0%	0.0%
Terminal Rates (c)	3/38 (8%)	3/38 (8%)	1/34 (3%)	3/35 (9%)	0/39 (0%)	0/34 (0%)
Week of First Observation	107	94	107	92		
Life Table Tests (d)	P=0.029N	P=0.505	P=0.345N	P=0.467	P=0.116N	P=0.141N
Incidental Tumor Tests (d)	P=0.034N	P=0.512	P=0.345N	P=0.410	P=0.116N	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.032N					
Fisher Exact Test (d)		P=0.500	P=0.324N	P=0.465	P=0.129N	P=0.137N
Thyroid Gland: C-Cell Adenoma or Carcinoma						
Overall Rates (a)	12/50 (24%)	13/50 (26%)	7/48 (15%)	9/47 (19%)	6/48 (13%)	2/46 (4%)
Adjusted Rates (b)	30.5%	32.0%	19.9%	24.5%	14.1%	5.9%
Terminal Rates (c)	11/38 (29%)	11/38 (29%)	6/34 (18%)	8/35 (23%)	4/39 (10%)	2/34 (6%)
Week of First Observation	91	91	104	92	96	107
Life Table Tests (d)	P=0.002N	P=0.503	P=0.220N	P=0.377N	P=0.084N	P=0.008N
Incidental Tumor Tests (d)	P=0.003N	P=0.470	P=0.205N	P=0.445N	P=0.112N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.003N					
Fisher Exact Test (d)		P=0.500	P=0.178N	P=0.370N	P=0.113N	P=0.006N

TABLE B5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Pancreatic Islets: Islet Cell Adenoma						
Overall Rates (a)	2/50 (4%)	0/52 (0%)	1/51 (2%)	1/49 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	5.3%	0.0%	2.9%	2.9%	9.7%	0.0%
Terminal Rates (c)	2/38 (5%)	0/38 (0%)	1/35 (3%)	1/35 (3%)	3/40 (7%)	0/34 (0%)
Week of First Observation	107		107	107	106	
Life Table Tests (d)	P=0.587N	P=0.238N	P=0.529N	P=0.529N	P=0.368	P=0.263N
Incidental Tumor Tests (d)	P=0.576N	P=0.238N	P=0.529N	P=0.529N	P=0.358	P=0.263N
Cochran-Armitage Trend Test (d)	P=0.576N					
Fisher Exact Test (d)		P=0.238N	P=0.492N	P=0.508N	P=0.339	P=0.247N
Pancreatic Islets: Islet Cell Carcinoma						
Overall Rates (a)	2/50 (4%)	2/52 (4%)	1/51 (2%)	3/49 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	5.3%	5.3%	2.9%	8.1%	2.2%	0.0%
Terminal Rates (c)	2/38 (5%)	2/38 (5%)	1/35 (3%)	2/35 (6%)	0/40 (0%)	0/34 (0%)
Week of First Observation	107	107	107	105	103	
Life Table Tests (d)	P=0.136N	P=0.695	P=0.529N	P=0.475	P=0.469N	P=0.263N
Incidental Tumor Tests (d)	P=0.128N	P=0.695	P=0.529N	P=0.511	P=0.488N	P=0.263N
Cochran-Armitage Trend Test (d)	P=0.135N					
Fisher Exact Test (d)		P=0.676N	P=0.492N	P=0.490	P=0.500N	P=0.247N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma						
Overall Rates (a)	4/50 (8%)	2/52 (4%)	2/51 (4%)	4/49 (8%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	10.5%	5.3%	5.7%	10.9%	11.6%	0.0%
Terminal Rates (c)	4/38 (11%)	2/38 (5%)	2/35 (6%)	3/35 (9%)	3/40 (7%)	0/34 (0%)
Week of First Observation	107	107	107	105	103	
Life Table Tests (d)	P=0.203N	P=0.336N	P=0.375N	P=0.607	P=0.544	P=0.078N
Incidental Tumor Tests (d)	P=0.190N	P=0.336N	P=0.375N	P=0.635	P=0.525	P=0.078N
Cochran-Armitage Trend Test (d)	P=0.197N					
Fisher Exact Test (d)		P=0.320N	P=0.329N	P=0.631	P=0.500	P=0.059N
Mammary Gland: Fibroadenoma						
Overall Rates (a)	12/52 (23%)	8/52 (15%)	11/52 (21%)	17/52 (33%)	10/52 (19%)	3/52 (6%)
Adjusted Rates (b)	29.3%	17.8%	27.5%	42.9%	23.0%	7.8%
Terminal Rates (c)	10/38 (26%)	4/38 (11%)	7/35 (20%)	13/35 (37%)	8/41 (20%)	2/35 (6%)
Week of First Observation	86	84	84	77	102	93
Life Table Tests (d)	P=0.017N	P=0.235N	P=0.568N	P=0.149	P=0.330N	P=0.020N
Incidental Tumor Tests (d)	P=0.017N	P=0.254N	P=0.507N	P=0.161	P=0.462N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.014N					
Fisher Exact Test (d)		P=0.228N	P=0.500N	P=0.191	P=0.405N	P=0.012N
Mammary Gland: Adenocarcinoma						
Overall Rates (a)	1/52 (2%)	0/52 (0%)	3/52 (6%)	0/52 (0%)	1/52 (2%)	2/52 (4%)
Adjusted Rates (b)	2.6%	0.0%	7.0%	0.0%	2.4%	5.7%
Terminal Rates (c)	1/38 (3%)	0/38 (0%)	1/35 (3%)	0/35 (0%)	1/41 (2%)	2/35 (6%)
Week of First Observation	107		86		107	107
Life Table Tests (d)	P=0.370	P=0.500N	P=0.290	P=0.516N	P=0.745N	P=0.471
Incidental Tumor Tests (d)	P=0.322	P=0.500N	P=0.341	P=0.516N	P=0.745N	P=0.471
Cochran-Armitage Trend Test (d)	P=0.376					
Fisher Exact Test (d)		P=0.500N	P=0.309	P=0.500N	P=0.752	P=0.500
Mammary Gland: Fibroma or Fibroadenoma						
Overall Rates (a)	12/52 (23%)	8/52 (15%)	11/52 (21%)	17/52 (33%)	11/52 (21%)	3/52 (6%)
Adjusted Rates (b)	29.3%	17.8%	27.5%	42.9%	24.8%	7.8%
Terminal Rates (c)	10/38 (26%)	4/38 (11%)	7/35 (20%)	13/35 (37%)	8/41 (20%)	2/35 (6%)
Week of First Observation	86	84	84	77	102	93
Life Table Tests (d)	P=0.022N	P=0.235N	P=0.568N	P=0.149	P=0.416N	P=0.020N
Incidental Tumor Tests (d)	P=0.021N	P=0.254N	P=0.507N	P=0.161	P=0.552N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.018N					
Fisher Exact Test (d)		P=0.228N	P=0.500N	P=0.191	P=0.500N	P=0.012N

TABLE B5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
Mammary Gland: Fibroadenoma or Adenocarcinoma						
Overall Rates (a)	13/52 (25%)	8/52 (15%)	13/52 (25%)	17/52 (33%)	11/52 (21%)	5/52 (10%)
Adjusted Rates (b)	31.8%	17.8%	30.5%	42.9%	25.3%	13.4%
Terminal Rates (c)	11/38 (29%)	4/38 (11%)	7/35 (20%)	13/35 (37%)	9/41 (22%)	4/35 (11%)
Week of First Observation	86	84	84	77	102	93
Life Table Tests (d)	P=0.041N	P=0.172N	P=0.516	P=0.204	P=0.328N	P=0.051N
Incidental Tumor Tests (d)	P=0.046N	P=0.185N	P=0.574N	P=0.219	P=0.456N	P=0.049N
Cochran-Armitage Trend Test (d)	P=0.035N					
Fisher Exact Test (d)		P=0.164N	P=0.589	P=0.258	P=0.408N	P=0.034N
Mammary Gland: Fibroma, Fibroadenoma, or Adenocarcinoma						
Overall Rates (a)	13/52 (25%)	8/52 (15%)	13/52 (25%)	17/52 (33%)	12/52 (23%)	5/52 (10%)
Adjusted Rates (b)	31.8%	17.8%	30.5%	42.9%	27.0%	13.4%
Terminal Rates (c)	11/38 (29%)	4/38 (11%)	7/35 (20%)	13/35 (37%)	9/41 (22%)	4/35 (11%)
Week of First Observation	86	84	84	77	102	93
Life Table Tests (d)	P=0.050N	P=0.172N	P=0.516	P=0.204	P=0.411N	P=0.051N
Incidental Tumor Tests (d)	P=0.054N	P=0.185N	P=0.574N	P=0.219	P=0.543N	P=0.049N
Cochran-Armitage Trend Test (d)	P=0.042N					
Fisher Exact Test (d)		P=0.164N	P=0.589	P=0.258	P=0.500N	P=0.034N
Clitoral Gland: Adenoma or Cystadenoma						
Overall Rates (a)	0/52 (0%)	1/52 (2%)	3/52 (6%)	1/52 (2%)	0/52 (0%)	0/52 (0%)
Adjusted Rates (b)	0.0%	2.4%	8.6%	2.9%	0.0%	0.0%
Terminal Rates (c)	0/38 (0%)	0/38 (0%)	3/35 (9%)	1/35 (3%)	0/41 (0%)	0/35 (0%)
Week of First Observation		102	107	107		
Life Table Tests (d)	P=0.126N	P=0.510	P=0.107	P=0.484	(e)	(e)
Incidental Tumor Tests (d)	P=0.121N	P=0.527	P=0.107	P=0.484	(e)	(e)
Cochran-Armitage Trend Test (d)	P=0.127N					
Fisher Exact Test (d)		P=0.500	P=0.121	P=0.500	(e)	(e)
Clitoral Gland: Adenoma, Cystadenoma, or Carcinoma						
Overall Rates (a)	1/52 (0%)	1/52 (2%)	3/52 (6%)	1/52 (2%)	0/52 (0%)	1/52 (2%)
Adjusted Rates (b)	0.0%	2.4%	8.6%	2.9%	0.0%	2.9%
Terminal Rates (c)	0/38 (0%)	0/38 (0%)	3/35 (9%)	1/35 (3%)	0/41 (0%)	1/35 (3%)
Week of First Observation		102	107	107		107
Life Table Tests (d)	P=0.411N	P=0.510	P=0.107	P=0.484	(e)	P=0.484
Incidental Tumor Tests (d)	P=0.398N	P=0.527	P=0.107	P=0.484	(e)	P=0.484
Cochran-Armitage Trend Test (d)						
Fisher Exact Test (d)	P=0.406N	P=0.500	P=0.121	P=0.500	(e)	P=0.500
Uterus: Endometrial Stromal Polyp						
Overall Rates (a)	14/51 (27%)	8/51 (16%)	10/52 (19%)	13/52 (25%)	12/52 (23%)	15/52 (29%)
Adjusted Rates (b)	35.9%	20.6%	26.4%	32.6%	28.4%	36.4%
Terminal Rates (c)	13/38 (34%)	7/37 (19%)	8/35 (23%)	9/35 (26%)	11/41 (27%)	10/35 (29%)
Week of First Observation	102	91	91	94	103	80
Life Table Tests (d)	P=0.138	P=0.123N	P=0.310N	P=0.565N	P=0.317N	P=0.410
Incidental Tumor Tests (d)	P=0.129	P=0.126N	P=0.285N	P=0.463N	P=0.318N	P=0.440
Cochran-Armitage Trend Test (d)	P=0.154					
Fisher Exact Test (d)		P=0.114N	P=0.226N	P=0.476N	P=0.388N	P=0.525
Uterus: Endometrial Stromal Polyp or Sarcoma						
Overall Rates (a)	14/51 (27%)	8/51 (16%)	11/52 (21%)	13/52 (25%)	12/52 (23%)	15/52 (29%)
Adjusted Rates (b)	35.9%	20.6%	29.1%	32.6%	28.4%	36.4%
Terminal Rates (c)	13/38 (34%)	7/37 (19%)	9/35 (26%)	9/35 (26%)	11/41 (27%)	10/35 (29%)
Week of First Observation	102	91	91	94	103	80
Life Table Tests (d)	P=0.162	P=0.123N	P=0.402N	P=0.565N	P=0.317N	P=0.410
Incidental Tumor Tests (d)	P=0.152	P=0.126N	P=0.374N	P=0.463N	P=0.318N	P=0.440
Cochran-Armitage Trend Test (d)	P=0.179					
Fisher Exact Test (d)		P=0.114N	P=0.303N	P=0.476N	P=0.388N	P=0.525

TABLE B5. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
All Sites: Benign Tumors						
Overall Rates (a)	40/52 (77%)	37/52 (71%)	44/52 (85%)	40/52 (77%)	43/52 (83%)	36/52 (69%)
Adjusted Rates (b)	86.8%	78.4%	93.5%	86.8%	87.7%	77.9%
Terminal Rates (c)	32/38 (84%)	28/38 (74%)	32/35 (91%)	29/35 (83%)	35/41 (85%)	25/35 (71%)
Week of First Observation	81	84	82	77	89	69
Life Table Tests (d)	P=0.305N	P=0.341N	P=0.134	P=0.417	P=0.550N	P=0.471N
Incidental Tumor Tests (d)	P=0.298N	P=0.345N	P=0.180	P=0.542	P=0.208	P=0.374N
Cochran-Armitage Trend Test (d)	P=0.211N					
Fisher Exact Test (d)		P=0.328N	P=0.228	P=0.592N	P=0.313	P=0.254N
All Sites: Malignant Tumors						
Overall Rates (a)	19/52 (37%)	18/52 (35%)	20/52 (38%)	26/52 (50%)	24/52 (46%)	25/52 (48%)
Adjusted Rates (b)	41.6%	39.2%	42.7%	53.4%	49.6%	57.2%
Terminal Rates (c)	12/38 (32%)	11/38 (29%)	9/35 (26%)	13/35 (37%)	17/41 (41%)	17/35 (49%)
Week of First Observation	78	66	82	77	49	69
Life Table Tests (d)	P=0.099	P=0.489N	P=0.428	P=0.136	P=0.346	P=0.135
Incidental Tumor Tests (d)	P=0.081	P=0.486N	P=0.566	P=0.148	P=0.286	P=0.159
Cochran-Armitage Trend Test (d)	P=0.078					
Fisher Exact Test (d)		P=0.500N	P=0.500	P=0.117	P=0.213	P=0.161
All Sites: All Tumors						
Overall Rates (a)	48/52 (92%)	48/52 (92%)	49/52 (94%)	47/52 (90%)	50/52 (96%)	49/52 (94%)
Adjusted Rates (b)	94.1%	92.3%	98.0%	92.1%	96.2%	100.0%
Terminal Rates (c)	35/38 (92%)	34/38 (89%)	34/35 (97%)	31/35 (89%)	39/41 (95%)	35/35 (100%)
Week of First Observation	78	66	82	77	49	69
Life Table Tests (d)	P=0.366	P=0.544N	P=0.289	P=0.496	P=0.430N	P=0.280
Incidental Tumor Tests (d)	P=0.247	P=0.631N	P=0.493	P=0.469N	P=0.418	P=0.357
Cochran-Armitage Trend Test (d)	P=0.330					
Fisher Exact Test (d)		P=0.642N	P=0.500	P=0.500N	P=0.339	P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups.

TABLE B6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX

	Control	50 ppm	100 ppm
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/52 (2%)	3/52 (6%)	3/52 (6%)
Adjusted Rates (b)	2.3%	6.8%	7.7%
Terminal Rates (c)	1/44 (2%)	3/44 (7%)	3/39 (8%)
Week of First Observation	105	105	105
Life Table Tests (d)	P=0.197	P=0.305	P=0.263
Incidental Tumor Tests (d)	P=0.197	P=0.305	P=0.263
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.309	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/52 (6%)	3/52 (6%)	4/52 (8%)
Adjusted Rates (b)	6.8%	6.8%	10.3%
Terminal Rates (c)	3/44 (7%)	3/44 (7%)	4/39 (10%)
Week of First Observation	105	105	105
Life Table Tests (d)	P=0.358	P=0.663	P=0.434
Incidental Tumor Tests (d)	P=0.358	P=0.663	P=0.434
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/52 (12%)	9/52 (17%)	14/52 (27%)
Adjusted Rates (b)	12.8%	18.8%	34.9%
Terminal Rates (c)	4/44 (9%)	6/44 (14%)	13/39 (33%)
Week of First Observation	80	95	98
Life Table Tests (d)	P=0.018	P=0.314	P=0.024
Incidental Tumor Tests (d)	P=0.039	P=0.287	P=0.042
Cochran-Armitage Trend Test (d)	P=0.029		
Fisher Exact Test (d)		P=0.289	P=0.040
Liver: Neoplastic Nodule			
Overall Rates (a)	2/52 (4%)	23/52 (44%)	30/52 (58%)
Adjusted Rates (b)	4.5%	49.8%	69.4%
Terminal Rates (c)	2/44 (5%)	21/44 (48%)	26/39 (67%)
Week of First Observation	105	95	82
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	2/52 (4%)	23/52 (44%)	31/52 (60%)
Adjusted Rates (b)	4.5%	49.8%	70.0%
Terminal Rates (c)	2/44 (5%)	21/44 (48%)	26/39 (67%)
Week of First Observation	105	95	82
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pituitary Gland: Adenoma			
Overall Rates (a)	31/52 (60%)	23/52 (44%)	22/52 (42%)
Adjusted Rates (b)	65.9%	48.8%	50.7%
Terminal Rates (c)	28/44 (64%)	20/44 (45%)	18/39 (46%)
Week of First Observation	87	99	82
Life Table Tests (d)	P=0.136N	P=0.086N	P=0.165N
Incidental Tumor Tests (d)	P=0.042N	P=0.070N	P=0.058N
Cochran-Armitage Trend Test (d)	P=0.048N		
Fisher Exact Test (d)		P=0.085N	P=0.058N

TABLE B6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	50 ppm	100 ppm
Pituitary Gland: Carcinoma			
Overall Rates (a)	1/52 (2%)	3/52 (6%)	0/52 (0%)
Adjusted Rates (b)	2.3%	6.6%	0.0%
Terminal Rates (c)	1/44 (2%)	2/44 (5%)	0/39 (0%)
Week of First Observation	105	104	
Life Table Tests (d)	P=0.413N	P=0.313	P=0.524N
Incidental Tumor Tests (d)	P=0.354N	P=0.356	P=0.524N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	32/52 (62%)	26/52 (50%)	22/52 (42%)
Adjusted Rates (b)	68.0%	54.0%	50.7%
Terminal Rates (c)	29/44 (66%)	22/44 (50%)	18/39 (46%)
Week of First Observation	87	99	82
Life Table Tests (d)	P=0.106N	P=0.163N	P=0.124N
Incidental Tumor Tests (d)	P=0.026N	P=0.127N	P=0.039N
Cochran-Armitage Trend Test (d)	P=0.031N		
Fisher Exact Test (d)		P=0.162N	P=0.039N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	5/52 (10%)	6/52 (12%)	0/52 (0%)
Adjusted Rates (b)	11.4%	13.6%	0.0%
Terminal Rates (c)	5/44 (11%)	6/44 (14%)	0/39 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.057N	P=0.500	P=0.045N
Incidental Tumor Tests (d)	P=0.057N	P=0.500	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.500	P=0.028N
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	7/52 (13%)	6/52 (12%)	0/52 (0%)
Adjusted Rates (b)	15.9%	13.6%	0.0%
Terminal Rates (c)	7/44 (16%)	6/44 (14%)	0/39 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.015N	P=0.500N	P=0.014N
Incidental Tumor Tests (d)	P=0.015N	P=0.500N	P=0.014N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.500N	P=0.006N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/52 (6%)	2/52 (4%)	1/52 (2%)
Adjusted Rates (b)	6.8%	4.0%	2.6%
Terminal Rates (c)	3/44 (7%)	0/44 (0%)	1/39 (3%)
Week of First Observation	105	99	105
Life Table Tests (d)	P=0.257N	P=0.483N	P=0.349N
Incidental Tumor Tests (d)	P=0.178N	P=0.400N	P=0.349N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/52 (6%)	2/52 (4%)	2/52 (4%)
Adjusted Rates (b)	6.8%	4.0%	5.1%
Terminal Rates (c)	3/44 (7%)	0/44 (0%)	2/39 (5%)
Week of First Observation	105	99	105
Life Table Tests (d)	P=0.455N	P=0.483N	P=0.555N
Incidental Tumor Tests (d)	P=0.363N	P=0.400N	P=0.555N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

TABLE B6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	50 ppm	100 ppm
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/49 (10%)	3/49 (6%)	5/49 (10%)
Adjusted Rates (b)	11.4%	6.8%	12.7%
Terminal Rates (c)	5/44 (11%)	3/44 (7%)	4/38 (11%)
Week of First Observation	105	105	98
Life Table Tests (d)	P=0.486	P=0.356N	P=0.539
Incidental Tumor Tests (d)	P=0.541	P=0.356N	P=0.619
Cochran-Armitage Trend Test (d)	P=0.571		
Fisher Exact Test (d)		P=0.357N	P=0.630
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/49 (4%)	3/49 (6%)	0/49 (0%)
Adjusted Rates (b)	4.5%	6.6%	0.0%
Terminal Rates (c)	2/44 (5%)	2/44 (5%)	0/38 (0%)
Week of First Observation	105	104	
Life Table Tests (d)	P=0.236N	P=0.506	P=0.271N
Incidental Tumor Tests (d)	P=0.170N	P=0.579	P=0.271N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	6/49 (12%)	5/49 (10%)
Adjusted Rates (b)	15.9%	13.2%	12.7%
Terminal Rates (c)	7/44 (16%)	5/44 (11%)	4/38 (11%)
Week of First Observation	105	104	98
Life Table Tests (d)	P=0.417N	P=0.496N	P=0.482N
Incidental Tumor Tests (d)	P=0.324N	P=0.449N	P=0.407N
Cochran-Armitage Trend Test (d)	P=0.322N		
Fisher Exact Test (d)		P=0.500N	P=0.380N
Pancreatic Islets: Islet Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	9/52 (17%)	6/51 (12%)
Adjusted Rates (b)	8.8%	20.5%	15.4%
Terminal Rates (c)	3/44 (7%)	9/44 (20%)	6/39 (15%)
Week of First Observation	99	105	105
Life Table Tests (d)	P=0.247	P=0.121	P=0.298
Incidental Tumor Tests (d)	P=0.273	P=0.142	P=0.351
Cochran-Armitage Trend Test (d)	P=0.339		
Fisher Exact Test (d)		P=0.133	P=0.383
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	11/52 (21%)	7/51 (14%)
Adjusted Rates (b)	11.1%	25.0%	17.9%
Terminal Rates (c)	4/44 (9%)	11/44 (25%)	7/39 (18%)
Week of First Observation	99	105	105
Life Table Tests (d)	P=0.249	P=0.089	P=0.299
Incidental Tumor Tests (d)	P=0.273	P=0.105	P=0.348
Cochran-Armitage Trend Test (d)	P=0.354		
Fisher Exact Test (d)		P=0.100	P=0.394
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/52 (6%)	6/52 (12%)	3/52 (6%)
Adjusted Rates (b)	6.4%	13.1%	7.7%
Terminal Rates (c)	2/44 (5%)	5/44 (11%)	3/39 (8%)
Week of First Observation	50	75	105
Life Table Tests (d)	P=0.518	P=0.249	P=0.615
Incidental Tumor Tests (d)	P=0.289	P=0.137	P=0.445
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.244	P=0.661

TABLE B6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Control	50 ppm	100 ppm
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	3/52 (6%)	7/52 (13%)	3/52 (6%)
Adjusted Rates (b)	6.4%	15.3%	7.7%
Terminal Rates (c)	2/44 (5%)	6/44 (14%)	3/39 (8%)
Week of First Observation	50	75	105
Life Table Tests (d)	P=0.511	P=0.165	P=0.615
Incidental Tumor Tests (d)	P=0.292	P=0.083	P=0.445
Cochran-Armitage Trend Test (d)	P=0.570		
Fisher Exact Test (d)		P=0.159	P=0.661
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	12/52 (23%)	8/51 (16%)	8/52 (15%)
Adjusted Rates (b)	27.3%	18.6%	18.7%
Terminal Rates (c)	12/44 (27%)	8/43 (19%)	6/39 (15%)
Week of First Observation	105	106	82
Life Table Tests (d)	P=0.260N	P=0.241N	P=0.315N
Incidental Tumor Tests (d)	P=0.196N	P=0.241N	P=0.241N
Cochran-Armitage Trend Test (d)	P=0.186N		
Fisher Exact Test (d)		P=0.243N	P=0.228N
All Sites: Benign Tumors			
Overall Rates (a)	41/52 (79%)	36/52 (69%)	31/52 (60%)
Adjusted Rates (b)	85.4%	74.9%	70.2%
Terminal Rates (c)	37/44 (84%)	32/44 (73%)	26/39 (67%)
Week of First Observation	50	75	82
Life Table Tests (d)	P=0.128N	P=0.189N	P=0.153N
Incidental Tumor Tests (d)	P=0.055N	P=0.219N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.022N		
Fisher Exact Test (d)		P=0.186N	P=0.028N
All Sites: Malignant Tumors			
Overall Rates (a)	17/52 (33%)	24/52 (46%)	24/52 (46%)
Adjusted Rates (b)	35.4%	48.0%	52.7%
Terminal Rates (c)	13/44 (30%)	18/44 (41%)	18/39 (46%)
Week of First Observation	80	95	82
Life Table Tests (d)	P=0.057	P=0.154	P=0.071
Incidental Tumor Tests (d)	P=0.184	P=0.166	P=0.193
Cochran-Armitage Trend Test (d)	P=0.098		
Fisher Exact Test (d)		P=0.114	P=0.114
All Sites: All Tumors			
Overall Rates (a)	49/52 (94%)	47/52 (90%)	48/52 (92%)
Adjusted Rates (b)	96.1%	90.4%	96.0%
Terminal Rates (c)	42/44 (95%)	39/44 (89%)	37/39 (95%)
Week of First Observation	50	75	82
Life Table Tests (d)	P=0.232	P=0.372N	P=0.262
Incidental Tumor Tests (d)	P=0.395N	P=0.358N	P=0.419N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.358N	P=0.500N

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

TABLE B7a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Overall Historical Incidence			
TOTAL	57/2,015 (2.8%)	3/2,015 (0.1%)	59/2,015 (2.9%)
SD (c)	2.86%	0.70%	3.04%
Range (d)			
High	5/50	2/50	5/50
Low	0/50	0/88	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by Frederick Cancer Research Center are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B7b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence of Leukemia in Controls
Overall Historical Incidence	
TOTAL	375/2,021 (18.6%)
SD (c)	6.55%
Range (d)	
High	19/50
Low	3/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by Frederick Cancer Research Center are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B7c. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Adenoma (c)	Carcinoma (d)	Adenoma or Carcinoma
Overall Historical Incidence			
TOTAL	862/1,952 (44.2%)	71/1,952 (3.6%)	931/1,952 (47.7%)
SD (e)	11.56%	3.97%	11.02%
Range (f)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by Frederick Cancer Research Center are included in the historical data base.
(c) Includes all adenomas diagnosed as NOS, chromophobe, acidophil, or basophil
(d) Includes all adenocarcinomas, NOS, carcinomas, NOS, and chromophobe carcinomas
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE B7d. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Overall Historical Incidence			
TOTAL	87/2,001 (4.3%)	7/2,001 (0.3%)	94/2,001 (4.7%)
SD (c)	3.68%	0.77%	3.59%
Range (d)			
High	8/50	1/40	8/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by Frederick Cancer Research Center are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B7e. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a,b)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
TOTAL	114/1,952 (5.8%)	71/1,952 (3.6%)	182/1,952 (9.3%)
SD (c)	5.02%	2.55%	5.46%
Range (d)			
High	9/50	5/50	11/50
Low	0/86	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No 2-year studies by Frederick Cancer Research Center are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B8. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ANIMALS INITIALLY IN STUDY	52	52	52	52	52	52
ANIMALS NECROPSIED	52	52	52	52	52	52
ANIMALS EXAMINED HISTOPATH	52	52	52	52	52	52
INTEGUMENTARY SYSTEM						
None						
RESPIRATORY SYSTEM						
#Tracheal mucosa	(47)	(47)	(45)	(47)	(46)	(44)
Metaplasia, squamous		1 (2%)				
#Lung	(52)	(52)	(52)	(52)	(52)	(52)
Congestion, chronic passive			3 (6%)			3 (6%)
Inflammation, interstitial						1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)			1 (2%)		
HEMATOPOIETIC SYSTEM						
#Bone marrow	(50)	(49)	(49)	(50)	(49)	(50)
Fibrosis	1 (2%)					
Fibrosis, focal				2 (4%)		
#Spleen	(50)	(52)	(52)	(50)	(51)	(50)
Fibrosis	1 (2%)					1 (2%)
Fibrosis, focal		3 (6%)		2 (4%)	2 (4%)	
Infarct, NOS			1 (2%)	1 (2%)		
Atrophy, NOS				1 (2%)		
Depletion, lymphoid					1 (2%)	
Hematopoiesis	7 (14%)	5 (10%)	5 (10%)	7 (14%)	1 (2%)	1 (2%)
#Splenic sinusoids	(50)	(52)	(52)	(50)	(51)	(50)
Angiectasis						1 (2%)
#Mediastinal lymph node	(51)	(52)	(52)	(51)	(52)	(52)
Congestion, NOS				1 (2%)		
#Mesenteric lymph node	(51)	(52)	(52)	(51)	(52)	(52)
Inflammation, acute necrotizing						1 (2%)
Fibrosis			1 (2%)	1 (2%)		
#Thymus	(42)	(47)	(42)	(42)	(48)	(41)
Cyst, NOS		3 (6%)	4 (10%)	3 (7%)	2 (4%)	6 (15%)
Hyperplasia, epithelial	5 (12%)	5 (11%)	7 (17%)	8 (19%)	5 (10%)	13 (32%)
CIRCULATORY SYSTEM						
#Heart	(52)	(52)	(52)	(52)	(52)	(52)
Mineralization	1 (2%)					
Inflammation, chronic	44 (85%)	44 (85%)	45 (87%)	44 (85%)	49 (94%)	47 (90%)
#Left atrium	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS		1 (2%)	3 (6%)	2 (4%)		
#Cardiac valve	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, chronic						1 (2%)
*Hepatic vein	(52)	(52)	(52)	(52)	(52)	(52)
Thrombosis, NOS		1 (2%)				
#Pancreas	(50)	(52)	(51)	(49)	(50)	(50)
Periarteritis	1 (2%)		1 (2%)			
#Stomach	(50)					
Periarteritis	1 (2%)					
*Mesentery	(52)	(52)	(52)	(52)	(52)	(52)
Periarteritis		1 (2%)	1 (2%)			
#Kidney	(51)	(52)	(52)	(51)	(51)	(52)
Periarteritis				1 (2%)		
#Adrenal	(51)	(52)	(52)	(51)	(51)	(52)
Periarteritis				1 (2%)		
DIGESTIVE SYSTEM						
#Salivary gland	(51)	(51)	(51)	(51)	(52)	(52)
Abscess, NOS				1 (2%)		
#Liver	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, acute focal						1 (2%)
Inflammation, chronic			1 (2%)			
Inflammation, granulomatous			1 (2%)			
Necrosis, NOS	2 (4%)	4 (8%)	1 (2%)	7 (13%)	4 (8%)	4 (8%)
Necrosis, focal	1 (2%)		1 (2%)	4 (8%)	4 (8%)	3 (6%)
Metamorphosis, fatty	11 (21%)	13 (25%)	18 (35%)	36 (69%)	45 (87%)	43 (83%)
Pigmentation, NOS			1 (2%)			1 (2%)
Basophilic cyto change	47 (90%)	45 (87%)	45 (87%)	44 (85%)	43 (83%)	34 (65%)
Eosinophilic cyto change			1 (2%)			

TABLE B8. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
DIGESTIVE SYSTEM						
#Liver (Continued)	(52)	(52)	(52)	(52)	(52)	(52)
Hepatocytomegaly	4 (8%)	2 (4%)	3 (6%)	14 (27%)	39 (75%)	45 (87%)
Atrophy, NOS		1 (2%)	2 (4%)			
Angiectasis	3 (6%)	8 (15%)	3 (6%)	2 (4%)	2 (4%)	9 (17%)
#Liver/caudate lobe	(52)	(52)	(52)	(52)	(52)	(52)
Infarct, NOS		1 (2%)				
#Liver/centrilobular	(52)	(52)	(52)	(52)	(52)	(52)
Degeneration, NOS				1 (2%)	1 (2%)	2 (4%)
Necrosis, NOS			1 (2%)	4 (8%)		6 (12%)
Atrophy, NOS	4 (8%)	4 (8%)	7 (13%)	1 (2%)	3 (6%)	2 (4%)
#Liver/Kupffer cell	(52)	(52)	(52)	(52)	(52)	(52)
Pigmentation, NOS	1 (2%)	1 (2%)	1 (2%)			
#Bile duct	(52)	(52)	(52)	(52)	(52)	(52)
Cyst, NOS	1 (2%)					1 (2%)
Hyperplasia, NOS	23 (44%)	29 (56%)	29 (56%)	35 (67%)	37 (71%)	26 (50%)
#Pancreas	(50)	(52)	(51)	(49)	(50)	(50)
Inflammation, chronic					1 (2%)	
Fibrosis			1 (2%)			
Necrosis, fat			1 (2%)			
Eosinophilic cyto change			1 (2%)	2 (4%)		1 (2%)
#Pancreatic acinus	(50)	(52)	(51)	(49)	(50)	(50)
Atrophy, NOS	4 (8%)	1 (2%)	3 (6%)	2 (4%)	5 (10%)	3 (6%)
#Stomach	(50)	(52)	(50)	(51)	(48)	(51)
Inflammation, chronic						1 (2%)
#Gastric mucosa	(50)	(52)	(50)	(51)	(48)	(51)
Ulcer, NOS	2 (4%)	2 (4%)	3 (6%)		1 (2%)	
Erosion		2 (4%)		3 (6%)		2 (4%)
Hyperplasia, epithelial					1 (2%)	
#Gastric submucosa	(50)	(52)	(50)	(51)	(48)	(51)
Cyst, NOS	1 (2%)					
#Forestomach	(50)	(52)	(50)	(51)	(48)	(51)
Ulcer, NOS		5 (10%)	4 (8%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, acute	1 (2%)		1 (2%)	1 (2%)		
Inflammation, acute necrotizing						1 (2%)
Inflammation, chronic		1 (2%)				
Hyperplasia, epithelial	1 (2%)	5 (10%)	5 (10%)	3 (6%)	1 (2%)	1 (2%)
URINARY SYSTEM						
#Kidney	(51)	(52)	(52)	(51)	(51)	(52)
Mineralization	1 (2%)					
Hydronephrosis			1 (2%)			
Nephropathy	34 (67%)	42 (81%)	45 (87%)	47 (92%)	47 (92%)	42 (81%)
Infarct, NOS			1 (2%)			
#Kidney/cortex	(51)	(52)	(52)	(51)	(51)	(52)
Cyst, NOS			1 (2%)			
#Kidney/pelvis	(51)	(52)	(52)	(51)	(51)	(52)
Mineralization	3 (6%)	2 (4%)	1 (2%)			
Hyperplasia, epithelial		1 (2%)				
ENDOCRINE SYSTEM						
#Pituitary	(52)	(51)	(50)	(51)	(52)	(50)
Cyst, NOS			2 (4%)			2 (4%)
Hemorrhagic cyst	3 (6%)					
Hyperplasia, NOS	3 (6%)	7 (14%)	3 (6%)	5 (10%)	2 (4%)	4 (8%)
#Adrenal	(51)	(52)	(52)	(51)	(51)	(52)
Necrosis, hemorrhagic						1 (2%)
Necrosis, cortical						1 (2%)
#Adrenal cortex	(51)	(52)	(52)	(51)	(51)	(52)
Degeneration, NOS		2 (4%)	1 (2%)			
Metamorphosis, fatty	3 (6%)	2 (4%)	9 (17%)	6 (12%)	6 (12%)	4 (8%)
Cytoplasmic change, NOS	2 (4%)	5 (10%)	4 (8%)	5 (10%)	1 (2%)	
Cytoplasmic vacuolization			1 (2%)			
Hypertrophy, NOS			1 (2%)	1 (2%)		
Hyperplasia, NOS	4 (8%)	3 (6%)	4 (8%)	6 (12%)	5 (10%)	5 (10%)
#Adrenal medulla	(51)	(52)	(52)	(51)	(51)	(52)
Hyperplasia, NOS	1 (2%)	1 (2%)	2 (4%)	5 (10%)		2 (4%)
#Thyroid	(50)	(50)	(48)	(47)	(48)	(46)
Ectopia						1 (2%)
Cystic follicles		1 (2%)		1 (2%)	5 (10%)	2 (4%)
Lymphocytic inflammatory infiltr		1 (2%)				
Hyperplasia, C-cell	4 (8%)	2 (4%)	3 (6%)	1 (2%)	4 (8%)	5 (11%)

TABLE B8. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ENDOCRINE SYSTEM (Continued)						
#Parathyroid	(39)	(43)	(45)	(46)	(44)	(43)
Hyperplasia, NOS	2 (5%)	2 (5%)	1 (2%)	1 (2%)	2 (5%)	5 (12%)
Hyperplasia, focal			1 (2%)			
#Pancreatic islets	(50)	(52)	(51)	(49)	(50)	(50)
Hyperplasia, NOS	10 (20%)	8 (15%)	11 (22%)	14 (29%)	12 (24%)	8 (16%)
REPRODUCTIVE SYSTEM						
*Mammary gland	(52)	(52)	(52)	(52)	(52)	(52)
Galactocele	2 (4%)		1 (2%)		1 (2%)	1 (2%)
Cyst, NOS						1 (2%)
Cystic ducts	7 (13%)	5 (10%)	7 (13%)	8 (15%)	10 (19%)	5 (10%)
Abscess, NOS			1 (2%)	1 (2%)		
Necrosis, NOS						1 (2%)
Fibrocystic disease	12 (23%)	15 (29%)	14 (27%)	15 (29%)	10 (19%)	3 (6%)
*Preputial gland	(52)	(52)	(52)	(52)	(52)	(52)
Cyst, NOS						1 (2%)
*Clitoral gland	(52)	(52)	(52)	(52)	(52)	(52)
Cyst, NOS			1 (2%)			
Inflammation, granulomatous			1 (2%)			
*Vagina	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, chronic					1 (2%)	
#Uterus	(51)	(51)	(52)	(52)	(52)	(52)
Hydrometra	2 (4%)					1 (2%)
Cyst, NOS						1 (2%)
Angiectasis				1 (2%)		
#Cervix uteri	(51)	(51)	(52)	(52)	(52)	(52)
Hyperplasia, epithelial				1 (2%)		
#Uterus/endometrium	(51)	(51)	(52)	(52)	(52)	(52)
Cyst, NOS	1 (2%)	1 (2%)	1 (2%)			
Hyperplasia, NOS		1 (2%)	1 (2%)	1 (2%)		
Hyperplasia, cystic	6 (12%)	10 (20%)	7 (13%)	4 (8%)	6 (12%)	8 (15%)
#Ovary	(51)	(51)	(52)	(52)	(52)	(51)
Parovarian cyst	1 (2%)		1 (2%)			
NERVOUS SYSTEM						
#Brain	(52)	(52)	(51)	(52)	(52)	(52)
Hemorrhage	1 (2%)					
Malacia		1 (2%)				
Necrosis, hemorrhagic	2 (4%)	1 (2%)	1 (2%)	1 (2%)		
SPECIAL SENSE ORGANS						
*Eye/conjunctiva	(52)	(52)	(52)	(52)	(52)	(52)
Abscess, NOS				1 (2%)		
*Eye/lacrimal gland	(52)	(52)	(52)	(52)	(52)	(52)
Atrophy, NOS			1 (2%)		1 (2%)	
*Zymbal gland	(52)	(52)	(52)	(52)	(52)	(52)
Inflammation, granulomatous						1 (2%)
MUSCULOSKELETAL SYSTEM						
*Bone	(52)	(52)	(52)	(52)	(52)	(52)
Healed fracture				1 (2%)		
Fibrosis, focal					1 (2%)	
*Vertebra	(52)	(52)	(52)	(52)	(52)	(52)
Fibrous osteodystrophy					1 (2%)	
BODY CAVITIES						
*Abdominal cavity	(52)	(52)	(52)	(52)	(52)	(52)
Steatitis		1 (2%)				
Necrosis, fat	1 (2%)	1 (2%)	5 (10%)	6 (12%)	3 (6%)	1 (2%)

TABLE B8. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	0.1 ppm	1 ppm	10 ppm	25 ppm	50 ppm
ALL OTHER SYSTEMS						
Adipose tissue						
Inflammation, granulomatous				1	3	
Necrosis, NOS			1			
SPECIAL MORPHOLOGY SUMMARY						
None						

*Number of animals receiving complete necropsy exaamination; all gross lesions including masses examined microscopically.
#Number of animals examined microscopically at this site

TABLE B9. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX

	Untreated Control	50 ppm	100 ppm
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*Skin	(52)	(52)	(52)
Inflammation, acute	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(52)	(52)	(52)
Hyperplasia, alveolar epithelium	3 (6%)		3
HEMATOPOIETIC SYSTEM			
*Multiple organs	(52)	(52)	(52)
Myeloproliferative disorder		1 (2%)	
#Bone marrow	(48)	(51)	(51)
Fibrosis	1 (2%)	1 (2%)	
Hyperplasia, NOS	1 (2%)		
#Spleen	(51)	(52)	(49)
Fibrosis	1 (2%)		
Fibrosis, focal			2 (4%)
Infarct, NOS	1 (2%)		
Hyperplasia, hematopoietic			1 (2%)
Hematopoiesis	1 (2%)	3 (6%)	2 (4%)
Myelopoiesis		1 (2%)	
#Mesenteric lymph node	(51)	(52)	(52)
Fibrosis, focal		1 (2%)	
#Liver	(52)	(52)	(52)
Hematopoiesis	1 (2%)		
#Thymus	(44)	(46)	(48)
Cyst, NOS	7 (16%)	4 (9%)	3 (6%)
Hyperplasia, epithelial	9 (20%)	10 (22%)	7 (15%)
CIRCULATORY SYSTEM			
#Heart	(52)	(52)	(52)
Abscess, NOS	1 (2%)		
Inflammation, chronic	46 (88%)	46 (88%)	46 (88%)
#Left atrium	(52)	(52)	(52)
Thrombosis, NOS	1 (2%)		
#Endocardium	(52)	(52)	(52)
Hyperplasia, NOS		1 (2%)	
#Liver	(52)	(52)	(52)
Thrombosis, NOS		2 (4%)	
#Pancreas	(50)	(52)	(51)
Periarteritis		1 (2%)	
#Kidney	(52)	(52)	(52)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
*Intestinal mucosa	(52)	(52)	(52)
Ectopia			1 (2%)
*Tongue	(52)	(52)	(52)
Inflammation, granulomatous	1 (2%)	1 (2%)	
#Liver	(52)	(52)	(52)
Abscess, NOS		1 (2%)	
Inflammation, granulomatous	1 (2%)	1 (2%)	
Necrosis, NOS	1 (2%)	3 (6%)	6 (12%)
Necrosis, focal	3 (6%)	4 (8%)	10 (19%)

TABLE B9. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	50 ppm	100 ppm
DIGESTIVE SYSTEM			
#Liver (Continued)	(52)	(52)	(52)
Necrosis, hemorrhagic			1 (2%)
Metamorphosis, fatty	14 (27%)	34 (65%)	39 (75%)
Pigmentation, NOS	1 (2%)		2 (4%)
Basophilic cyto change	48 (92%)	40 (77%)	27 (52%)
Ground glass cyto change	3 (6%)	1 (2%)	
Eosinophilic cyto change	1 (2%)		
Clear cell change	5 (10%)		
Hepatocytomegaly	4 (8%)	49 (94%)	49 (94%)
Atrophy, NOS			3 (6%)
Atrophy, focal			1 (2%)
Angiectasis	6 (12%)	7 (13%)	10 (19%)
#Liver/centrilobular	(52)	(52)	(52)
Degeneration, NOS	1 (2%)		
Atrophy, NOS		1 (2%)	2 (4%)
#Bile duct	(52)	(52)	(52)
Hyperplasia, NOS	33 (63%)	43 (83%)	30 (58%)
#Pancreas	(50)	(52)	(51)
Eosinophilic cyto change		1 (2%)	1 (2%)
#Pancreatic acinus	(50)	(52)	(51)
Atrophy, NOS	4 (8%)	4 (8%)	9 (18%)
Hyperplasia, NOS	3 (6%)	1 (2%)	1 (2%)
#Peripancreatic tissue	(50)	(52)	(51)
Necrosis, fat		1 (2%)	
#Gastric mucosa	(51)	(51)	(52)
Ulcer, NOS		2 (4%)	1 (2%)
Erosion	2 (4%)		
#Forestomach	(51)	(51)	(52)
Ulcer, NOS		4 (8%)	7 (13%)
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, acute focal			1 (2%)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic			1 (2%)
Ulcer, perforated	1 (2%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)	5 (10%)	7 (13%)
URINARY SYSTEM			
#Kidney	(52)	(52)	(52)
Abscess, NOS	1 (2%)		
Nephropathy	45 (87%)	51 (98%)	52 (100%)
#Kidney/pelvis	(52)	(52)	(52)
Mineralization	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(52)	(52)	(52)
Hemorrhagic cyst		1 (2%)	
Necrosis, focal	1 (2%)		
Hyperplasia, NOS	5 (10%)	6 (12%)	3 (6%)
#Adrenal	(52)	(52)	(52)
Necrosis, focal			1 (2%)
#Adrenal cortex	(52)	(52)	(52)
Degeneration, NOS		1 (2%)	
Metamorphosis, fatty	8 (15%)	9 (17%)	14 (27%)
Cytoplasmic change, NOS	4 (8%)	7 (13%)	3 (6%)
Hyperplasia, NOS	3 (6%)	5 (10%)	5 (10%)
#Adrenal medulla	(52)	(52)	(52)
Hyperplasia, NOS	1 (2%)		

TABLE B9. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	50 ppm	100 ppm
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(49)	(49)
Cystic follicles			4 (8%)
Hyperplasia, C-cell	5 (10%)	3 (6%)	3 (6%)
Hyperplasia, follicular cell		3 (6%)	2 (4%)
#Parathyroid	(52)	(45)	(42)
Ectopia	1 (2%)	3 (7%)	
Hyperplasia, NOS	1 (2%)	4 (9%)	6 (14%)
#Pancreatic islets	(50)	(52)	(51)
Hyperplasia, NOS	12 (24%)	9 (17%)	6 (12%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(52)	(52)	(52)
Galactocele	1 (2%)	2 (4%)	
Cystic ducts	5 (10%)	7 (13%)	2 (4%)
Fibrocystic disease	16 (31%)	7 (13%)	2 (4%)
*Clitoral gland	(52)	(52)	(52)
Cystic ducts		1 (2%)	
#Uterus	(52)	(51)	(52)
Hydrometra	1 (2%)		
Angiectasis			1 (2%)
#Cervix uteri	(52)	(51)	(52)
Metaplasia, squamous	1 (2%)		
#Uterus/endometrium	(52)	(51)	(52)
Cyst, NOS			1 (2%)
Hyperplasia, cystic	3 (6%)	2 (4%)	10 (19%)
#Ovary	(52)	(52)	(52)
Cyst, NOS			2 (4%)
Parovarian cyst	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain	(52)	(52)	(52)
Hemorrhage			1 (2%)
Necrosis, hemorrhagic	1 (2%)		
*Spinal cord	(52)	(52)	(52)
Cyst, NOS		1 (2%)	
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(52)	(52)	(52)
Inflammation, chronic	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Vertebra	(52)	(52)	(52)
Fibrous osteodystrophy			1 (2%)
BODY CAVITIES			
*Abdominal cavity	(52)	(52)	(52)
Necrosis, fat	2 (4%)		1 (2%)
*Peritoneum	(52)	(52)	(52)
Inflammation, acute		1 (2%)	

TABLE B9. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE SECOND TWO-YEAR FEED STUDY OF MIREX (Continued)

	Untreated Control	50 ppm	100 ppm
ALL OTHER SYSTEMS			
*Multiple organs	(52)	(52)	(52)
Inflammation, chronic			1 (2%)
Adipose tissue			
Inflammation, granulomatous	1	1	1
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
#Number of animals examined microscopically at this site

APPENDIX C

GENETIC TOXICOLOGY OF MIREX

TABLE C1. MUTAGENICITY OF MIREX IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b,c)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100							
	0	126 ± 7.5	93 ± 11.2	145 ± 4.5	141 ± 3.6	165 ± 9.7	141 ± 8.0
	100	112 ± 4.7	86 ± 4.9	140 ± 5.8	133 ± 1.8	173 ± 3.1	118 ± 0.9
	333	124 ± 8.8	100 ± 8.2	164 ± 4.3	131 ± 23.1	172 ± 8.7	128 ± 5.6
	1,000	104 ± 5.4	99 ± 11.8	139 ± 13.6	122 ± 6.1	175 ± 8.0	128 ± 6.8
	3,333	105 ± 4.8	86 ± 5.8	141 ± 13.0	114 ± 4.3	170 ± 15.0	127 ± 5.6
	10,000	111 ± 5.7	97 ± 9.6	149 ± 16.3	133 ± 5.2	137 ± 3.5	109 ± 7.6
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,129 ± 6.8	1,334 ± 108.7	1,136 ± 4.8	2,186 ± 45.1	2,463 ± 27.0	2,193 ± 185.8
TA1535	0	3 ± 1.3	11 ± 0.9	3 ± 0.9	11 ± 2.8	5 ± 0.9	10 ± 1.7
	100	4 ± 0.7	13 ± 3.5	3 ± 1.0	11 ± 2.5	6 ± 1.0	16 ± 1.5
	333	3 ± 0.6	10 ± 4.0	3 ± 1.5	9 ± 1.5	6 ± 0.3	12 ± 2.5
	1,000	5 ± 2.3	8 ± 2.3	2 ± 0.9	7 ± 0.6	4 ± 0.9	13 ± 1.2
	3,333	4 ± 1.9	9 ± 0.9	4 ± 2.1	7 ± 1.5	2 ± 0.7	14 ± 3.1
	10,000	2 ± 0.0	9 ± 1.5	1 ± 0.7	12 ± 1.8	2 ± 0.3	13 ± 1.0
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	39 ± 2.1	1,173 ± 24.1	88 ± 7.0	158 ± 7.4	78 ± 3.2	220 ± 18.2
TA1537	0	5 ± 0.9	9 ± 0.9	5 ± 0.9	16 ± 1.5	5 ± 0.3	19 ± 2.3
	100	1 ± 0.6	5 ± 0.7	4 ± 1.5	18 ± 0.6	3 ± 1.8	12 ± 2.3
	333	3 ± 0.6	6 ± 0.9	3 ± 1.2	20 ± 1.5	3 ± 0.3	17 ± 3.0
	1,000	2 ± 0.9	8 ± 3.0	1 ± 0.9	13 ± 3.7	4 ± 0.6	17 ± 2.9
	3,333	2 ± 1.2	7 ± 2.2	3 ± 0.9	12 ± 3.5	4 ± 0.6	16 ± 3.0
	10,000	3 ± 0.3	8 ± 2.7	2 ± 0.7	10 ± 2.6	5 ± 0.3	16 ± 2.2
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	186 ± 27.0	265 ± 68.4	88 ± 9.8	386 ± 37.3	49 ± 3.5	490 ± 28.1
TA98	0	34 ± 0.5	19 ± 1.9	45 ± 3.2	34 ± 2.3	49 ± 0.5	34 ± 1.2
	100	37 ± 2.6	21 ± 1.2	60 ± 4.3	26 ± 0.3	51 ± 1.8	40 ± 1.2
	333	43 ± 2.0	19 ± 3.2	47 ± 3.1	24 ± 4.2	57 ± 4.0	24 ± 2.6
	1,000	35 ± 4.3	19 ± 2.6	58 ± 2.6	35 ± 5.5	55 ± 2.5	29 ± 5.9
	3,333	46 ± 3.8	27 ± 6.3	58 ± 1.9	32 ± 2.6	50 ± 6.9	31 ± 4.3
	10,000	42 ± 3.0	32 ± 3.8	51 ± 5.0	31 ± 3.8	61 ± 13.0	31 ± 7.1
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	286 ± 31.3	248 ± 28.2	1,522 ± 205.3	1,633 ± 99.3	1,496 ± 74.4	1,546 ± 103.7

(a) Study performed at Case Western Reserve University. The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Precipitate on plate noted in each trial at doses of 1,000 µg/plate and above.
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE C2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY MIREX (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Negative, but positive control too low								
Dimethyl sulfoxide		50	1,046	426	0.41	8.5	26.0	--
Mirex	26	50	1,048	428	0.41	8.6	26.0	101.2
	83.2	50	1,047	412	0.39	8.2	26.0	96.5
	260	50	1,049	451	0.43	9.0	26.0	105.9
Mitomycin C	0.005	50	1,050	514	0.49	10.3	26.0	121.2
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,052	409	0.39	8.2	26.0	--
Mirex	26	50	1,044	403	0.39	8.1	26.0	98.8
	83.2	50	1,044	314	0.30	6.3	26.0	76.8
	260	50	1,052	350	0.33	7.0	26.0	85.4
Mitomycin C	0.005	25	526	610	1.16	24.4	26.0	297.6
+S9 (d)								
Summary: Negative								
Dimethyl sulfoxide		50	1,047	461	0.44	9.2	26.0	--
Mirex	26	50	1,051	475	0.45	9.5	26.0	103.3
	83.2	50	1,047	491	0.47	9.8	26.0	106.5
	260	50	1,052	483	0.46	9.7	26.0	105.4
Cyclophosphamide	1	25	526	443	0.84	17.7	26.0	192.4

(a) Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE C3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY MIREX (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1					**Trial 2**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3		100	5	0.05	5
Mirex					Mirex				
26	100	4	0.04	4	26	100	8	0.08	8
83.2	100	6	0.06	6	83.2	100	8	0.08	7
260	100	5	0.05	5	260	100	8	0.08	7
	Summary: Negative					Summary: Negative			
Mitomycin C					Cyclophosphamide				
0.150	50	20	0.40	32	15	50	16	0.32	30

(a) Study performed at Columbia University. Abs = aberrations. Harvest time--12 hours. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX D

FEED AND COMPOUND CONSUMPTION BY RATS IN THE TWO-YEAR FEED STUDIES OF MIREX

TABLE D1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF MIREX

	Control		0.1 ppm			1 ppm			10 ppm			25 ppm			50 ppm		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
2	30	205	26	199	0.013	24	206	0.12	23	206	1.1	24	205	2.9	23	200	5.8
4	30	227	26	225	0.012	24	227	0.11	23	225	1.0	24	230	2.6	23	231	5.0
6	35	263	28	258	0.011	25	262	0.10	30	260	1.2	34	264	3.2	30	255	5.9
8	35	273	28	267	0.010	25	270	0.09	30	269	1.1	34	272	3.1	30	264	5.7
10	35	297	25	285	0.009	27	289	0.09	26	293	0.9	27	295	2.3	28	288	4.9
12	35	308	25	296	0.008	27	301	0.09	26	300	0.9	27	299	2.3	28	290	4.8
16	25	327	25	315	0.008	28	320	0.09	24	318	0.8	25	311	2.0	30	298	5.0
20	22	345	19	333	0.006	20	338	0.06	20	337	0.6	22	325	1.7	25	314	4.0
24	33	364	25	352	0.007	27	357	0.08	27	359	0.8	24	348	1.7	20	334	3.0
28	33	381	21	366	0.006	26	372	0.07	33	375	0.9	31	363	2.1	23	346	3.3
32	11	393	25	378	0.007	25	381	0.07	25	389	0.6	31	373	2.1	25	355	3.5
36	44	398	37	386	0.010	32	391	0.08	34	395	0.9	39	380	2.6	40	364	5.5
40	33	401	19	391	0.005	25	394	0.06	25	401	0.6	23	382	1.5	23	368	3.1
44	31	405	26	394	0.007	26	397	0.07	22	400	0.6	25	382	1.6	30	370	4.1
48	18	415	17	406	0.004	16	411	0.04	17	412	0.4	18	393	1.1	18	375	2.4
52	19	416	16	413	0.004	16	416	0.04	17	421	0.4	19	397	1.2	20	378	2.6
60	15	413	17	412	0.004	16	415	0.04	(c) 17	418	0.4	15	395	0.9	17	377	2.3
68	21	432	17	426	0.004	18	426	0.04	17	433	0.4	20	403	1.2	20	386	2.6
76	18	419	12	420	0.003	14	424	0.03	17	420	0.4	19	385	1.2	19	360	2.6
84	23	411	16	411	0.004	16	416	0.04	18	412	0.4	18	379	1.2	19	343	2.8
92	17	423	14	423	0.003	15	425	0.04	15	420	0.4	13	392	0.8	12	360	1.7
100	18	418	15	415	0.004	16	425	0.04	17	405	0.4	15	371	1.0	16	344	2.3
Mean	26.4	360.6	21.8	353.2	0.007	22.2	357.4	0.07	22.9	357.6	0.7	24.0	342.9	1.8	23.6	327.3	3.8
SD (d)	8.6		6.0		0.003	5.3		0.03	5.7		0.3	6.8		0.7	6.3		1.3
CV (e)	32.6		27.5		42.9	23.9		42.9	24.9		42.9	28.3		38.9	26.7		34.2

(a) Grams of feed removed from feed hopper per animal per day; not corrected for scatter.
(b) Estimated milligrams of mirex consumed per day per kilogram of body weight
(c) Feed consumption data not available; value presented is the mean of values reported for weeks 52 and 68
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE D2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE FIRST TWO-YEAR FEED STUDY OF MIREX

Week	Control		0.1 ppm			1 ppm			10 ppm			25 ppm			50 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
2	20	146	17	145	0.012	18	144	0.13	17	142	1.2	18	142	3.2	15	142	5.3
4	20	156	17	155	0.011	18	154	0.12	17	153	1.1	18	159	2.8	15	158	4.7
6	26	174	20	173	0.012	26	172	0.15	21	171	1.2	20	170	2.9	19	172	5.5
8	26	175	20	173	0.012	26	172	0.15	21	170	1.2	20	170	2.9	19	172	5.5
10	22	190	18	183	0.010	21	182	0.12	16	180	0.9	19	182	2.6	18	183	4.9
12	22	194	18	191	0.009	21	188	0.11	16	185	0.9	19	186	2.6	18	185	4.9
16	17	209	21	207	0.010	37	206	0.18	18	200	0.9	20	203	2.5	18	200	4.5
20	15	211	15	208	0.007	13	209	0.06	12	203	0.6	15	207	1.8	12	200	3.0
24	16	219	15	216	0.007	15	217	0.07	19	211	0.9	27	215	3.1	16	204	3.9
28	14	227	14	223	0.006	15	225	0.07	18	218	0.8	19	219	2.2	18	213	4.2
32	15	231	15	227	0.007	16	230	0.07	15	223	0.7	16	225	1.8	18	216	4.2
36	27	238	21	232	0.009	23	234	0.10	25	228	1.1	22	229	2.4	26	220	5.9
40	20	243	15	237	0.006	31	240	0.13	16	233	0.7	18	235	1.9	19	224	4.2
44	28	246	21	241	0.009	16	244	0.07	16	239	0.7	15	239	1.6	23	228	5.0
48	11	246	10	239	0.004	12	243	0.05	11	239	0.5	12	238	1.3	12	229	2.6
52	12	249	11	243	0.005	12	248	0.05	11	243	0.5	11	244	1.1	12	232	2.6
60	17	264	13	256	0.005	13	261	0.05	12	257	0.5	15	257	1.5	11	242	2.3
68	16	285	13	278	0.005	12	282	0.04	13	275	0.5	13	272	1.2	16	256	3.1
76	13	287	10	283	0.004	11	286	0.04	11	280	0.4	12	279	1.1	12	258	2.3
84	13	302	13	288	0.005	13	284	0.05	11	288	0.4	15	284	1.3	13	255	2.5
92	16	315	14	298	0.005	14	303	0.05	12	302	0.4	12	299	1.0	13	267	2.4
100	13	320	11	298	0.004	11	307	0.04	12	298	0.4	11	296	0.9	12	267	2.2
Mean	18.1	233.0	15.5	227.0	0.007	17.9	228.7	0.08	15.5	224.5	0.7	16.7	225.0	2.0	16.1	214.7	3.9
SD (c)	5.2		3.6		0.003	7.0		0.04	3.9		0.3	4.1		0.8	3.9		1.2
CV (d)	28.7		23.2		42.9	39.1		50.0	25.2		42.9	24.6		40.0	24.2		30.8

(a) Grams of feed removed from feed hopper per animal per day; not corrected for scatter.
(b) Estimated milligrams of mirex consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX E

AUDIT SUMMARY

APPENDIX E. AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of mirex in rats were audited for accuracy, consistency, and completeness. The laboratory experiments were conducted for the National Cancer Institute by the Frederick Cancer Research Center (FCRC), Frederick, Maryland. Two studies were conducted: In the first study, animal exposures to mirex began in June 1977 and ended in June 1979; the second study in female rats began in January 1978 and ended in January 1980. Both studies were completed before October 1, 1981, the date when the NTP implemented its requirement that studies be conducted in compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration. The retrospective audit was conducted at the FCRC in December 1984 and January 1985 by Dynamac Corporation. The individuals who conducted the audit are listed in the full audit report, which is on file at the NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records.
(3) Body weight (by cage) and clinical observation data for a random 10% sample of the study animals.
(4) Feed consumption data for approximately 10% of the animals.
(5) All inlife records concerning environmental conditions, palpable masses, and mortality.
(6) All postmortem records for individual animals concerning identification, disposition and condition codes, and correlation between gross observations and microscopic diagnoses.
(7) Wet tissues from a random 10% sample of the study animals to verify animal identification and to examine for untrimmed lesions.
(8) Slides and blocks of tissues from all control and high dose animals to examine for inventory and correspondence.
(9) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

The audit indicated that records were not available for environmental conditions or for the randomization procedure used for the second study. Records indicated that analyses of the chemical/vehicle mixtures for the high dose group in the second study were not done except for the final 4 months of the study. Other chemistry records showed no major discrepancies.

Clinical observations were intermittently recorded, did not include all animals, and were occasionally inconsistent regarding sequential recordings. This information was not complete or reliable enough to be interpreted as is usually done. An audit of the correlation between masses noted inlife and at necropsy showed that 43/64 observations recorded for male rats and 52/64 observations for female rats were noted at necropsy; the majority of those not recorded at necropsy included small, apparently cutaneous masses on the head, neck, legs, or tail which either regressed or could not be correlated because of inadequate description for the location of these masses on the necropsy record forms.

Wet tissues were present for all rats on study with the exception of one control male and one high dose female; animals were properly identified. Because of an apparent disproportionate number of liver tissue samples taken from the high dose groups, additional and comparative liver sections were made for the male and female control groups and the high dose male group after the initial Pathology Working Group (PWG) review of the study. A second PWG was convened to review the liver sections. Any discrepancies noted during the subsequent review of the pathology materials were considered minor in nature and not clustered in any one group of study animals.

The audit findings were reviewed by NTP staff. Although some omissions and discrepancies were noted in the audited experiments, the materials and documents at the NTP Archives are considered adequate to support the data and results presented in this Technical Report.