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BIOASSAY OF EMETINE FOR POSSIBLE CARCINOGENICITY

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

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EMETINE

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

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CONTRIBUTORS: This report presents the results of the bioassay of emetine for possible carcinogenicity, conducted for the Carcinogenesis Testing Program, Divison of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Southern Research Institute, Birmingham, Alabama, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Drs. D. P. Griswold[1], J. D. Prejean[1], E. K. Weisburger[2], and J. H. Weisburger[2,3]. Ms. J. Belzer[1] and Mr. I. Brown[1] were responsible for the care of the laboratory animals. Data management and retrieval were performed by Ms. C. A. Dominick[1]. Histopathologic examinations were performed by Drs. S. D. Kosanke[1] and J. C. Peckham[1], and the diagnoses included in this report represent their interpretation. Reported neoplasms and treatment-related hyperplastic lesions were reviewed by Dr. J. F. Hardisty[4], who also prepared the interpretive pathology summary included in this report.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[5]. The statistical analyses were performed by Dr. J. R. Joiner[6], using methods selected for the bioassay program by Dr. J. J. Gart[7]. Chemicals used in this bioassay were analyzed by Drs. W. J. Morris[8] and R. H. Iwamoto[8], and the analytical results were reviewed by Dr. S. S. Olin[6].

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SUMMARY

A bioassay of emetine, an amebicide and anticancer drug, for possible carcinogenicity was conducted by administering the test material by intraperitoneal injection to Sprague-Dawley rats and B6C3F1 mice.

Groups of 35 rats of each sex were administered emetine at one of two doses, either 0.5 or 1 mg/kg body weight, three times per week for 52 weeks, and then observed for an additional 31 or 32 weeks. Control groups of each sex consisted of 10 untreated rats (untreated controls) and 10 rats injected with buffered saline (vehicle controls). Pooled-control groups, used for statistical evaluation, consisted of the vehicle-control rats of each sex for this study combined with 15 vehicle-control rats of each sex from a similar bioassay of another test chemical. All surviving rats were killed at 83 or 84 weeks.

Initially, groups of 35 mice of each sex were administered emetine at one of two doses, either 3.2 or 6.4 mg/kg body weight (mid- and high-dose), three times per week. Control groups of each sex consisted of 15 untreated mice (untreated controls) and 15 mice injected with buffered saline (vehicle controls). Due to high mortality rates in the initial treated groups, additional groups of 35 mice of each sex were later put on study at 1.6 mg/kg (low-dose), together with 10 untreated-control and 10 vehicle-control mice of each sex. The high-dose males were treated for 28 weeks and the mid- and high-dose females for 40 and 33 weeks, respectively. Mid- and low-dose male mice and low-dose female mice were treated for 52 weeks, and then observed for an additional 20 or 26 weeks. All surviving mice were killed at 78-83 weeks.

Emetine was toxic to male rats at the high dose, to both sexes of mice at the high and mid doses and to a lesser extent at the low dose, as shown by the low survival in these groups. Twenty-six percent of the high-dose male rats and 69% of the high-dose female rats, but none of the high- and mid-dose mice of either sex, survived to the end of the study. In the low-dose mice,

30/35 males and 21/35 females lived at least 1 year, and the median time on study was 72 weeks for males and 59 weeks for females.

No tumors occurred at a statistically significant incidence in treated rats or mice compared with controls; however, it should be noted that in this study, treatment of both species was stopped at week 52 and the studies were terminated by week 83, which is earlier than in current bioassays where animals are treated until termination of the studies at 2 years. In addition, there was poor survival among the treated mice.

It is concluded that the results of this study do not allow evaluation of the possible carcinogenicity of emetine.

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I. INTRODUCTION

Emetine (CAS 483-18-1; NCI C01605), an alkaloid derived from the root of the tropical plant Cephaelis ipecacuanha, is used to treat severe amebic intestinal infections, amebic hepatitis, and amebic involvement of the lung, brain, skin, and other tissues (Rollo, 1975). Clinical symptoms of toxicity due to emetine include nausea, vomiting, diarrhea, muscle weakness, and cardiovascular disturbance.

In experimental studies, emetine was cytotoxic to transplantable mouse osteosarcoma in vitro but not in vivo (Morasca et al., 1974). In clinical studies, emetine was effective against non-specific granuloma (Grollman, 1966), and the analogue, dehydro-emetine, was effective against leukemia, Hodgkin's disease, and rectal adenocarcinoma (Abd-Rabbo, 1966 and 1969; Wyburn-Mason, 1969). The drug has been shown to interfere with nucleic acid and protein biosynthesis in HeLa and other mammalian cells (Gilead and Becker, 1971; Grollman and Huang, 1973).

Emetine was tested in the carcinogenesis program in an attempt to evaluate the carcinogenicity of certain drugs that are used in humans over extended periods of time.

II. MATERIALS AND METHODS

A. Chemical

Emetine hydrochloride (6′,7′,10,11-tetramethoxyemetan dihydrochloride) was supplied by the Drug Development Branch, Division of Cancer Treatment (DCT), National Cancer Institute (NCI). The chemical was obtained in a single batch (Lot No. 988-0800) from Sigma Chemical Company, St. Louis, Missouri.

Analyses performed by Stanford Research Institute under contract to the Drug Development Branch, DCT, NCI, confirmed the identity and purity of this batch. Following United States Pharmacopeia (USP) assay procedures, the batch was found to contain 11.5% water, corresponding to a tetrahydrate, and approximately 1.5% cephaeline (a precursor in the synthesis). Less than 0.1% of one additional (unidentified) alkaloid was detected. These results conform to USP specifications. In addition, elemental analyses (C, H, N, Cl^-) were correct for $C_{29}H_{40}N_2O_4 \cdot 2HCl \cdot 4H_2O$, the molecular formula of emetine dihydrochloride tetrahydrate. Infrared, ultraviolet, and nuclear magnetic resonance spectra also were as expected for emetine hydrochloride, hereinafter called emetine.

According to the USP, the chemical is affected by light. Stanford Research Institute reported noticeable decomposition (by

thin-layer chromatography) of an aqueous solution (ca. 25 mg/ml) after 1 week of exposure to ordinary illumination at room temperature. Therefore, solutions were prepared immediately before injection.

The bulk chemical was stored at -20°C.

B. Dosage Preparation

Buffered saline solution (pH 6.9) was used as the vehicle for intraperitoneal injection of the chemical. The drug and the vehicle were mixed in a 10-ml glass Potter-Elvehjem tissue grinder with a Teflon pestle. Fresh solutions were prepared daily and administered immediately. The concentrations were 0.02 and 0.04% for rats and 0.016, 0.032, and 0.064% for mice.

C. Animals

Sprague-Dawley rats and B6C3F1 mice of both sexes, obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, through contracts of the DCT, NCI, were used in this bioassay. On arrival at the laboratory, all animals were quarantined for an acclimation period (rats for 5 days, mice in the original study for 18 days, mice in the restarted study for 25 days), assigned to control and treated groups, and then earmarked for individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 20-24°C, and the relative humidity was maintained at 40-60%. The room air was changed 15 times per hour and passed through incoming and exhaust fiberglass roughing filters. In addition to natural light, illumination was provided by fluorescent light for 9 hours each day. Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) and water were supplied daily and were available ad libitum.

Rats were housed five per cage and mice seven per cage in solid-bottom stainless steel cages (Hahn Roofing and Sheet Metal Co., Birmingham, Ala.). The bottoms of the rat cages were lined with Iso-Dri® hardwood chips (Carworth, Edison, N.J.), and cage tops were covered with disposable filter bonnets beginning at week 18. Mouse cages were provided with Sterolit® clay bedding (Englehard Mineral and Chemical Co., New York, N.Y.). Cages of restarted groups of mice were provided with filter bonnets at week 75. Bedding was replaced once per week; cages, water bottles, feeders, and racks were sanitized once per week.

The rats and mice were housed in separate rooms. Control animals were housed with their respective treated animals. Animals treated with emetine were maintained in the same rooms as animals of the same species being treated with the following chemicals:

RATS

Gavage Studies

cholesterol (p-(bis(2-chloroethyl)amino)phenyl)acetate (phenesterin) (CAS 3546-10-9)
estradiol bis((p-(bis(2-chloroethyl)amino)phenyl)acetate) (estradiol mustard) (CAS 22966-79-6)

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride (MAAM) (NSC 141549)
acronycine (CAS 7008-42-6)
5-azacytidine (CAS 320-67-2)
beta-2′-deoxy-6-thioguanosine monohydrate (beta-TGdR) (CAS 789-61-7)
1,4-butanediol dimethanesulfonate (busulfan) (CAS 55-98-1)
3,3′-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride [IPD] (CAS 3458-22-8)
(±)-4,4′-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione (ICRF-159) (CAS 21416-87-5)
N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide (isophosphamide) (CAS 3778-73-2)
N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride (phenoxybenzamine) (CAS 63-92-3)
N-(1-methylethyl)-4-((2-methylhydrazino)methyl)benzamide monohydrochloride (procarbazine) (CAS 366-70-1)
tris(1-aziridinyl)phosphine sulfide (thio-TEPA) (CAS 52-24-4)
2,4,6-tris(dimethylamino)-s-triazine (CAS 645-05-6)

MICE

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide (acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide (chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine (pyrimethamine) (CAS 58-14-0)
ethionamide (CAS 536-33-4)
2,6-diamino-3-(phenylazo)pyridine hydrochloride (phenazopyridine hydrochloride) (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)

N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-sulfonyldianiline (dapsone) (CAS 80-08-0)
4,4′-thiodianiline (CAS 139-65-1)
ethionamide (CAS 536-33-4)

Gavage Studies

cholesterol (p-(bis(2-chloroethyl)amino)phenyl)acetate
(phenesterin) (CAS 3546-10-9)
estradiol bis((p-(bis(2-chloroethyl)amino)phenyl)acetate)
(estradiol mustard) (CAS 22966-79-6)

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride
(MAAM) (NSC 141549)
acronycine (CAS 7008-42-6)
5-azacytidine (CAS 320-67-2)
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(CAS 789-61-7)
1,4-butanediol dimethanesulfonate (busulfan) (CAS 55-98-1)
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tris(1-aziridinyl)phosphine sulfide (thio-TEPA) (CAS 52-24-4)
2,4,6-tris(dimethylamino)-s-triazine (CAS 645-05-6)

E. Subchronic Studies

Subchronic studies were conducted to estimate the maximum tolerated doses of emetine, on the basis of which low and high doses were determined for administration in the chronic studies.

In the subchronic studies, Sprague-Dawley male rats and Swiss male mice were administered emetine by intraperitoneal injection three times per week for 45 days. Following treatment, all animals were observed for an additional 45 days before termination of the study. Five animals of each species were used at each dose, and 10 animals of each species were used as untreated or vehicle (saline) controls.

In rats, administration of emetine at 0.1, 0.25, 0.5, and 1.0 mg/kg body weight resulted in no deaths and in no weight depression that exceeded the 15% guideline. At 2.0 mg/kg, the mean body weight was depressed and two animals died, one in week 7 and one in week 8. No lesions were observed in any of the animals. The low and high doses for rats were set at 0.5 and 1 mg/kg for the chronic studies.

In mice, the subchronic study was initially conducted at doses of 0.17, 0.43, 0.85, 1.7, and 3.4 mg/kg. No deaths attributable to drug toxicity and no weight depression exceeding the 15% guideline resulted. A second study was then performed using doses of 6.4, 12.8, and 25.6 mg/kg. Four of the five animals receiving 12.8 mg/kg died prior to week 6, and 4/5 animals receiving 25.6 mg/kg died prior to week 4; however, there were no deaths at 6.4 mg/kg. Weight depression did not exceed the 15% guideline in animals receiving 6.4 mg/kg, and no lesions were

seen in any of the animals at necropsy. The low and high doses for mice were set at 3.2 and 6.4 mg/kg for the chronic studies.

F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1, 2, and 3.

Since the numbers of rats in the matched vehicle-control groups were small, pooled vehicle-control groups of rats also were used for statistical comparisons. Vehicle-control rats from the current injection studies on emetine were combined with vehicle-control rats from injection studies performed on 5-azacytidine (CAS 320-67-2). The pooled controls for statistical tests using rats consisted of 25 males and 25 females. The study on 5-azacytidine in rats was also conducted at Southern Research Institute and overlapped the emetine study by at least 17 months. The vehicle-control groups for 5-azacytidine were of the same strain and from the same suppliers, and they were examined by the same pathologists.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, and animals that were moribund were killed and necropsied. Rats and mice were weighed individually every week for the first 2 months

Table 1. Design of Chronic Studies of Emetine in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Emetine Dose[b] (mg/kg)	Time on Study: Treated[c] (weeks)	Time on Study: Untreated (weeks)
Male				
Untreated-Control	10	0		84
Vehicle-Control	10	0[d]	52	32
Low-Dose	35	0.5	52	32
High-Dose	35	1	52	31
Female				
Untreated-Control	10	0		84
Vehicle-Control	10	0[d]	52	32
Low-Dose	35	0.5	52	32
High-Dose	35	1	52	32

[a]Male rats were 34 days of age and female rats were 41 days of age when placed on study.

[b]Emetine was administered intraperitoneally in buffered saline three times per week at a volume of 0.25 ml/100 g body weight. Doses were based on individual weights.

[c]All rats were placed on study on the same day.

[d]Vehicle-control groups received buffered saline solution at the same volume as the treated groups.

Table 2. Design of Chronic Studies of Emetine in Male Mice

Sex and Treatment Group	Initial No. of Animals[a]	Emetine Dose[b] (mg/kg)	Time on Study: Treated (weeks)	Time on Study: Untreated (weeks)
Low-Dose Untreated-Control[c]	10	0		80
Low-Dose Vehicle-Control[c]	10	0[d]	52	26
Low-Dose[c]	35	1.6	52	26
Mid- and High-Dose Untreated-Control	15	0		83
Mid- and High-Dose Vehicle-Control	15	0[d]	52	30
Mid-Dose	35	3.2	52	20[e]
High-Dose	35	6.4	28[f]	

[a]High- and mid-dose animals and their controls were 48 days of age when placed on study; low-dose animals and their controls were 58 days of age.

[b]Emetine was administered intraperitoneally in buffered saline three times per week at a volume of 0.1 ml/10 g body weight. Doses were based on the mean weights of the animals in each cage.

[c]Due to the high mortality of the treated animals, one additional low-dose group and two low-dose control groups were started 32 weeks after the original start of the study. The original low-dose group became the mid-dose group.

[d]Vehicle-control groups received buffered saline solution at the same volume as the treated groups.

[e]All mid-dose animals died or were killed by week 72.

[f]All high-dose animals died or were killed by week 28.

Table 3. Design of Chronic Studies of Emetine in Female Mice

Sex and Treatment Group	Initial No. of Animals[a]	Emetine Dose[b] (mg/kg)	Time on Study	
			Treated (weeks)	Untreated (weeks)
Low-Dose Untreated-Control[c]	10	0		80
Low-Dose Vehicle-Control[c]	10	0[d]	52	27
Low-Dose[c]	35	1.6	52	26
Mid- and High-Dose Untreated-Control	15	0		83
Mid- and High-Dose Vehicle-Control	15	0[d]	52	31
Mid-Dose	35	3.2	40[e]	
High-Dose	35	6.4	33[f]	

[a]High- and mid-dose animals and their controls were 49 days of age when placed on study; low-dose animals and their controls were 58 days of age.

[b]Emetine was administered intraperitoneally in buffered saline three times per week at a volume of 0.1 ml/10 g body weight. Doses were based on the mean weights of the animals in each cage.

[c]Due to the high mortality of the treated animals, one additional low-dose group and two low-dose control groups were started 32 weeks after the original start of the study. The original low-dose group became the mid-dose group.

[d]Vehicle-control groups received buffered saline solution at the same volume as the treated groups.

[e]All mid-dose animals died or were killed by week 40.

[f]All high-dose animals died or were killed by week 33.

and every 2 weeks thereafter. Palpation for masses was carried out at each weighing.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, muscle, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, testis or ovary, prostate or uterus, brain, and sensory organs. Peripheral blood smears from each animal were prepared. Occasionally, additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily

represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

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

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for

a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are

compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

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

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which

the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control

group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

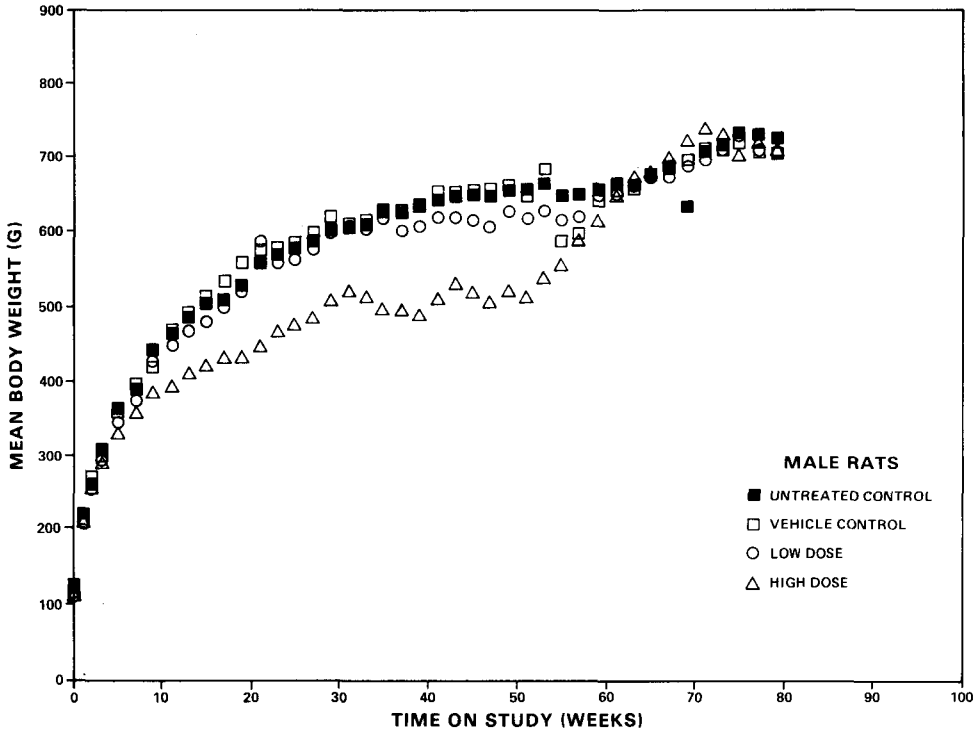
A. Body Weights and Clinical Signs (Rats)

Body weights of the low-dose male rats were comparable to those of both the untreated and vehicle controls (figure 1). The weights of the high-dose males were lower than those of the controls during the period in which emetine was administered, but were similar after treatment was discontinued. The high-dose female rats had lower body weights than those of both the control groups, while the body weights of the low-dose female rats were lower than those of the untreated controls, but similar to those of the vehicle controls. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation.

No other clinical signs clearly associated with the administration of emetine were recorded.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered emetine by intraperitoneal injection at the doses used in this experiment, together with those of the matched controls, are shown in figure 2.



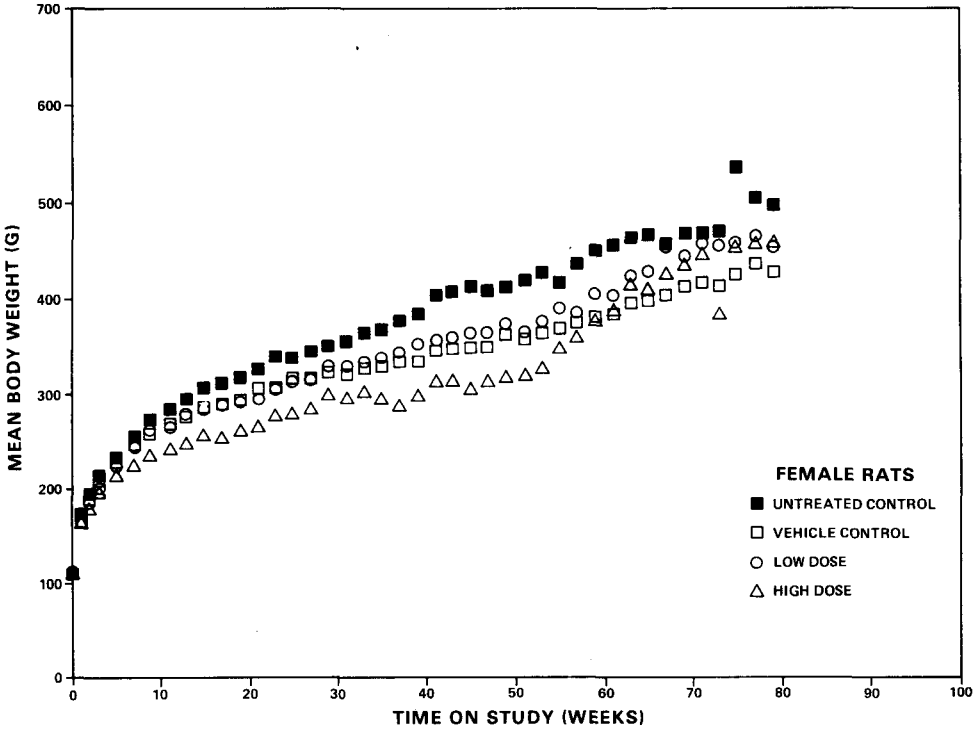


Figure 1. Growth Curves For Rats Treated With Emetine

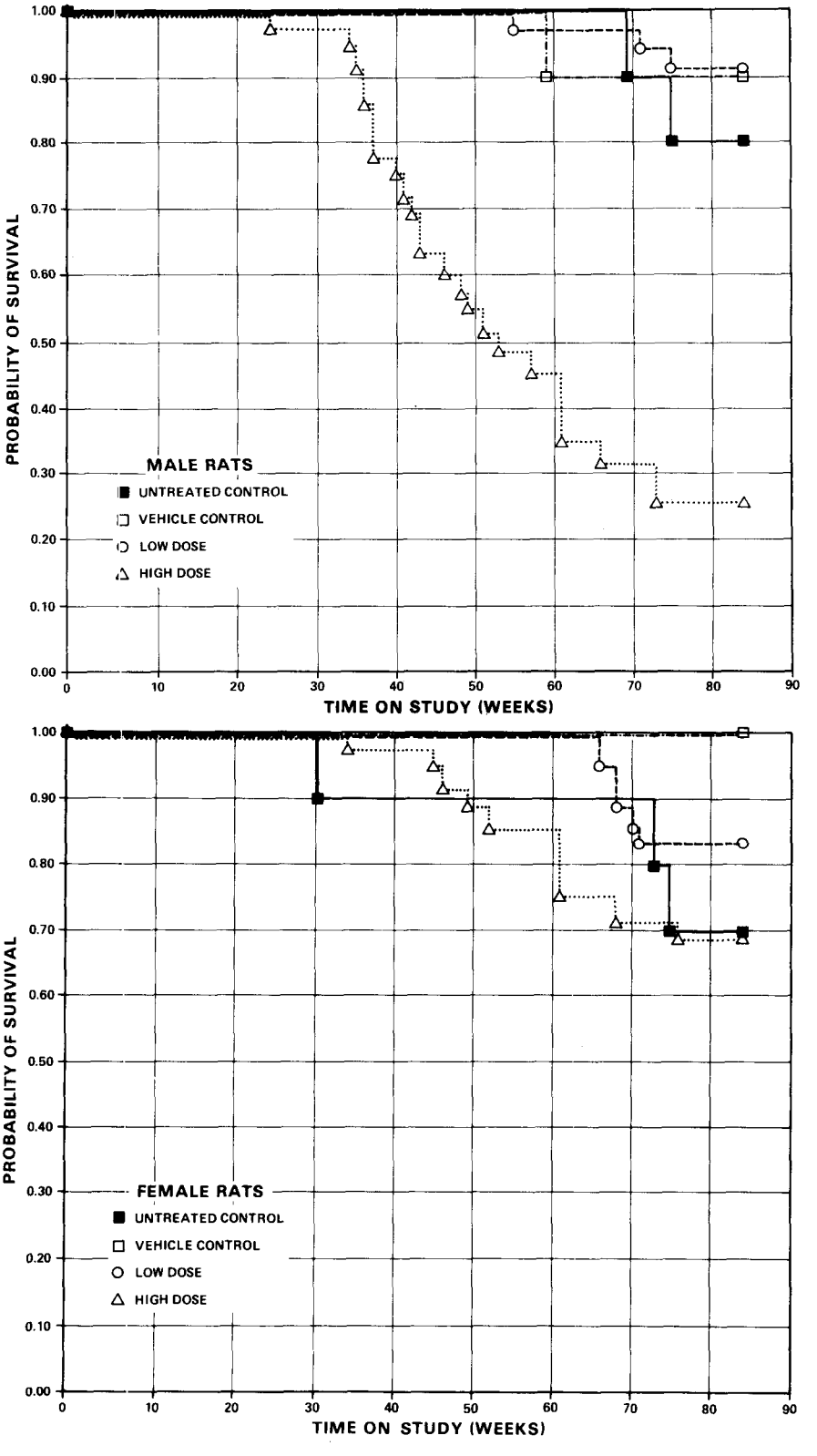


Figure 2. Survival Curves for Rats Treated With Emetine

In male rats, the Tarone test result for positive dose-related trend in mortality is significant ($P < 0.001$), and an indicated departure from linear trend is observed ($P < 0.001$), due to the steep increase in mortality in the high-dose rats, of which only 26% lived to the end of the study, with a median time on study of 53 weeks. Of the high-dose male rats, 18/35 lived at least 52 weeks on study, and no tumor was observed before this time. At least 80% of the low-dose, vehicle-control, and untreated-control groups survived to the end of the study.

In female rats, the Tarone test result is not significant; 69% of the high-dose group, 83% of the low-dose group, all of the vehicle-control group, and 70% of the untreated-control group survived to termination of the study, providing sufficient numbers of treated female rats for development of late-appearing tumors.

C. Pathology (Rats)

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

A variety of neoplasms were seen both in control and treated rats. Neoplasms were seen more frequently in the females than in the males. The most frequently observed neoplasms in the female

rats were chromophobe adenomas of the pituitary gland, cortical adenomas of the adrenal gland, and fibroadenomas of the mammary gland. The neoplasms of the pituitary and adrenal glands occurred with approximately equal frequency in treated and control rats. The incidence of fibroadenomas of the mammary gland was higher in the treated female rats than in the controls. These tumors were characterized by local proliferations of well-differentiated fibrous tissue surrounding proliferating mammary acinar and ductular epithelium. Much structural variation was present in these neoplasms. In some of the neoplasms, the connective tissue stroma was predominant, and in others, there was a marked epithelial overgrowth. The histologic appearance of the neoplasms in both the treated and control female rats was similar to fibroadenomas known to occur spontaneously in female Sprague-Dawley rats. Although the incidence of the neoplasm was higher in the treated rats than in the controls, it was comparable to published reports of spontaneously occurring mammary gland fibroadenomas in this strain of rat (Davis et al., 1959; Prejean et al., 1973; Thompson et al., 1961).

A variety of inflammatory, degenerative, and proliferative lesions commonly seen in aged Sprague-Dawley rats were observed with approximately equal frequency in treated and control animals. Although there was a higher incidence of spontaneous

deaths in the treated groups, there were no consistent neoplastic or nonneoplastic lesions in the animals that died spontaneously.

There were instances in this study where neoplastic lesions occurred only in treated animals, or with increased frequency when compared with the control group. The nature and incidence of these lesions were similar to those known to occur spontaneously in aged Sprague-Dawley rats. The histopathologic evaluation of the study indicated that emetine administered for the time period and at the doses used in this study did not induce neoplastic lesions in the Sprague-Dawley rat.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that were observed in at least 5% of a treated group. The untreated controls are not included in these tables and analyses, since the experimental conditions of the vehicle controls more closely resemble those of the treated animals.

In both sexes, the results of the Cochran-Armitage test for positive dose-related trend and the Fisher exact test for direct comparison of incidences between each of the control groups and each of the treated groups are not significant.

In female rats the Cochran-Armitage test and the incidence of cortical adenoma of the adrenal gland using pooled controls indicate a significant trend in the negative direction, but this negative trend is not substantiated by the Fisher exact test. Furthermore, the life-table-adjusted test for the incidence of cortical adenoma does not show a significant negative trend.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included, indicating the absence of positive significant results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by emetine, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

The high-dose male and female mice gained little weight, and most of these animals died by week 33 (figures 3 and 4). The mean body weights of the male mid-dose mice were lower than those of both the control groups, while those of the female mid-dose mice were comparable to those of the vehicle controls during the 40 weeks these mice survived. Mean body weights of the low-dose groups of both sexes were comparable to those of both the control groups.

Emetine was sufficiently toxic at the mid dose and high dose to cause a shortened life span. No clinical signs of toxicity were reported for the low-dose groups.

To control respiratory disease, the initial groups of mice were treated with oxytetracycline in the drinking water at doses of 0.6 mg/ml for 5 days during week 55, followed by treatment for 5 days at 0.3 mg/ml. The restarted groups were not treated with oxytetracycline.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered emetine by

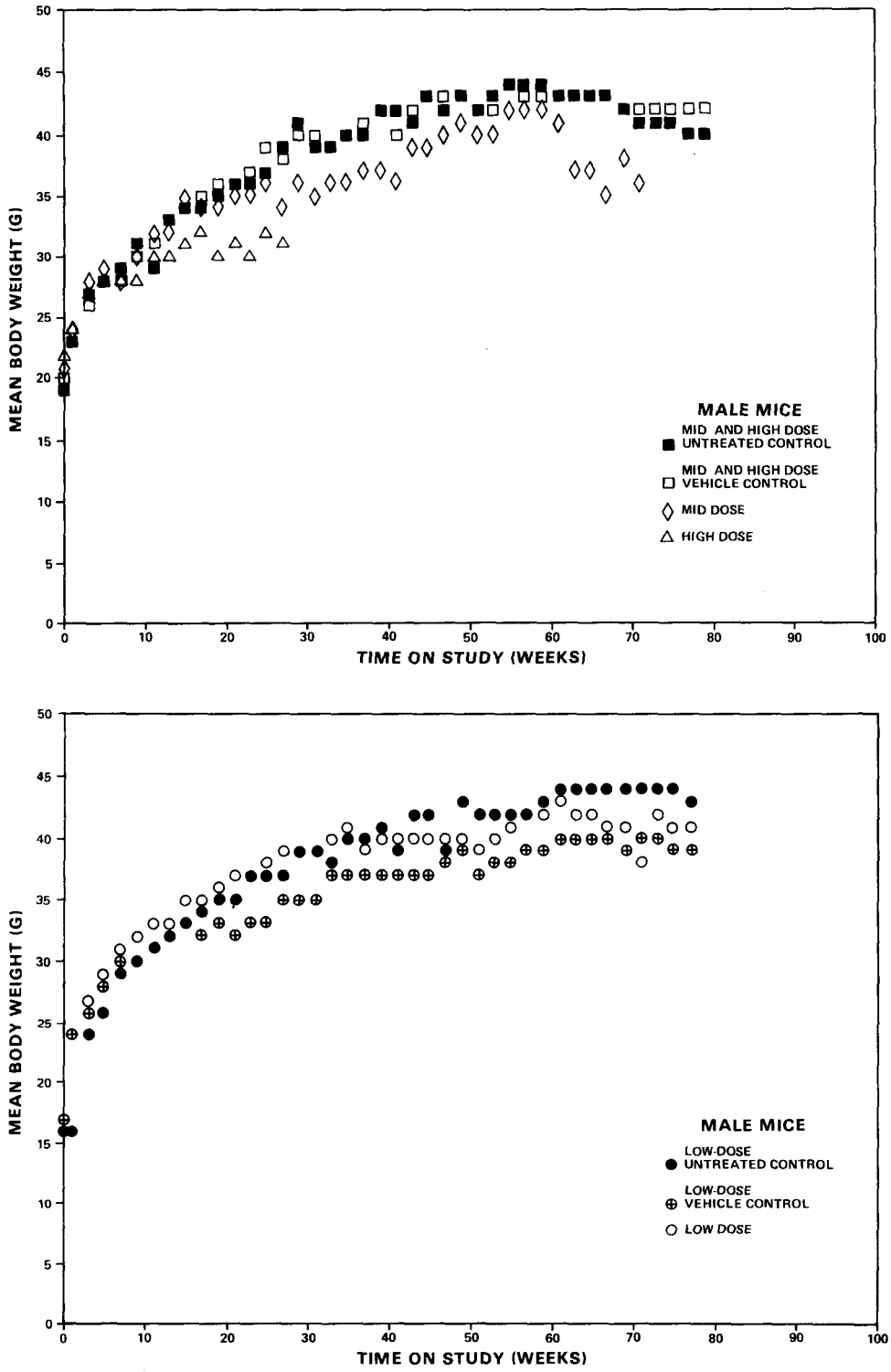


Figure 3. Growth Curves For Male Mice Treated With Emetine

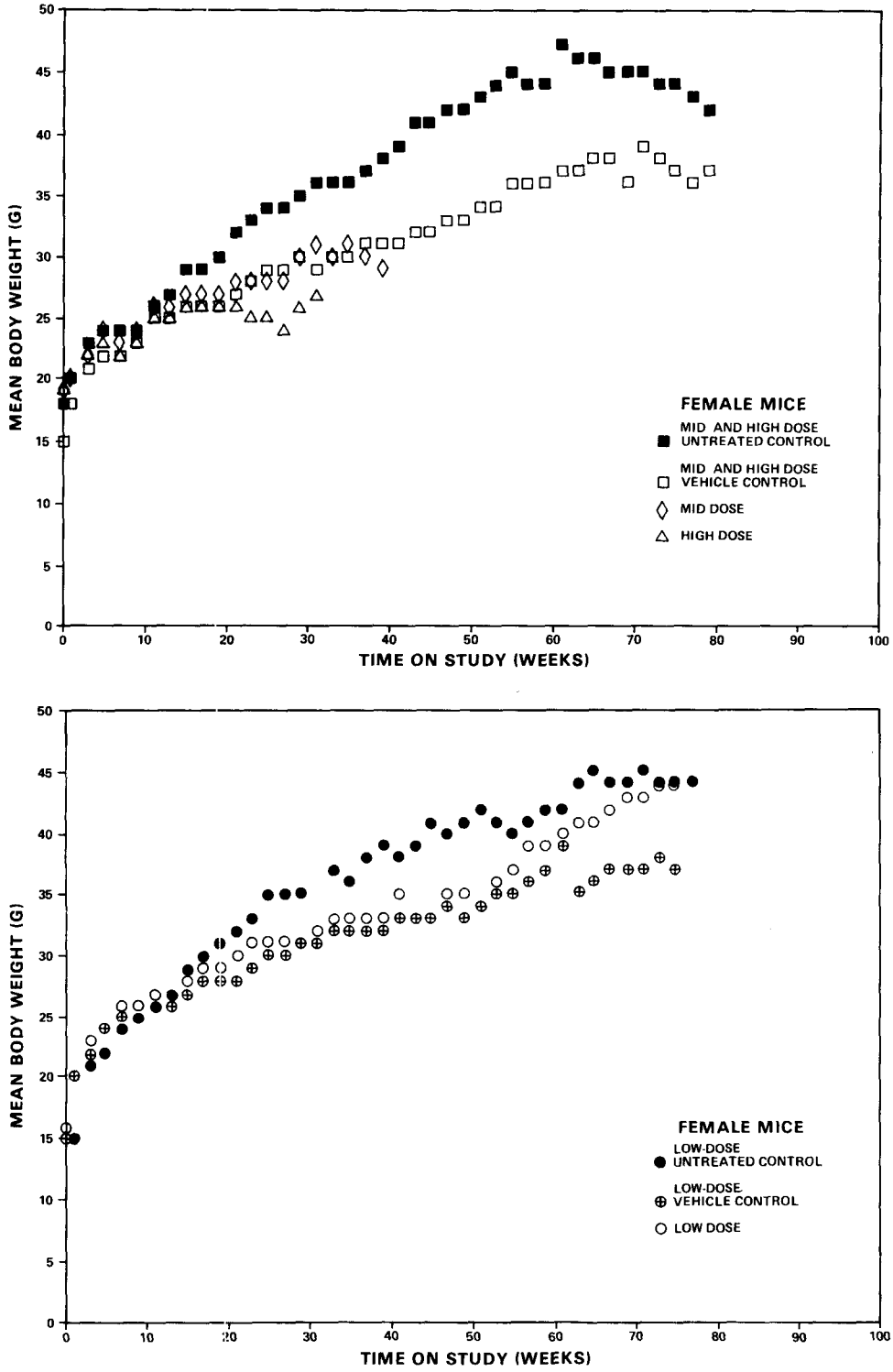


Figure 4. Growth Curves For Female Mice Treated With Emetine

intraperitoneal injection at the doses used in this experiment, together with those of the matched controls, are shown in figures 5 and 6.

In both sexes, the Tarone test results for positive dose-related trend in mortality are significant ($P < 0.001$), and an indicated departure from linear trend is observed ($P < 0.001$), due to the steep increase in mortality in the high- and mid-dose mice. In male mice, none of the high- and mid-dose groups, but 41% of the low-dose group and at least 78% of the controls, lived to the end of the study. The median times on study for the high-, mid-, and low-dose male mice were 21 weeks, 30 weeks, and 72 weeks, respectively. Only 1/35 high-dose and 2/35 mid-dose male mice lived beyond week 52 on study; no tumor was observed in these two groups of mice. Thirty of 35 low-dose male mice survived beyond week 52, but one tumor (hepatocellular carcinoma) was found as early as week 50 on study. Time-adjusted analyses were also performed, eliminating animals that died before week 52 on study. Since one hepatocellular carcinoma occurred at week 50, the time-adjusted analysis of this particular incidence is based on animals that lived at least as long as week 50 on study.

In female mice, none of the high- and mid-dose groups, but 31% of the low-dose group, at least 60% of the vehicle controls, and at least 80% of the untreated controls lived to the end of the

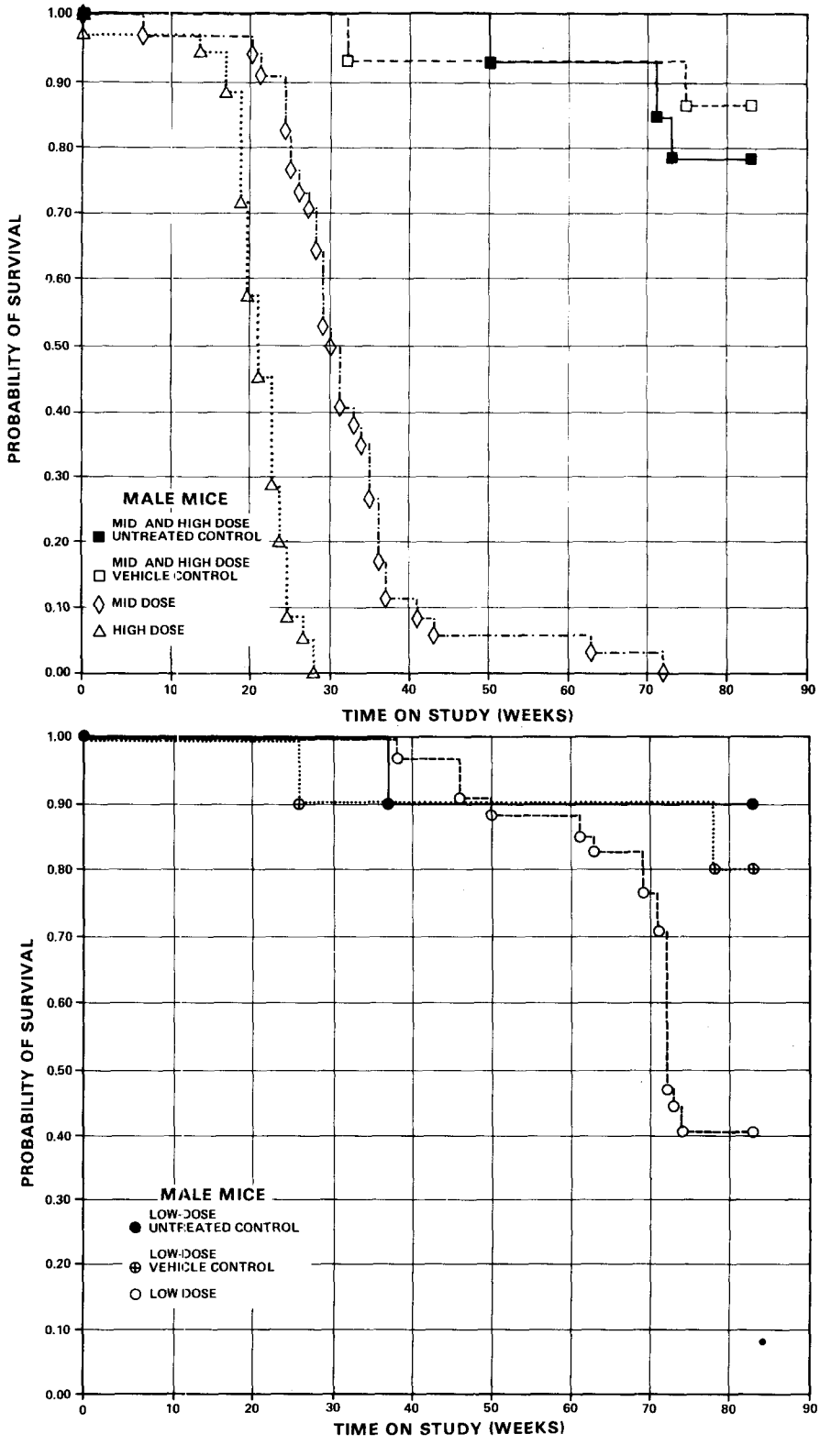


Figure 5. Survival Curves For Male Mice Treated With Emetine

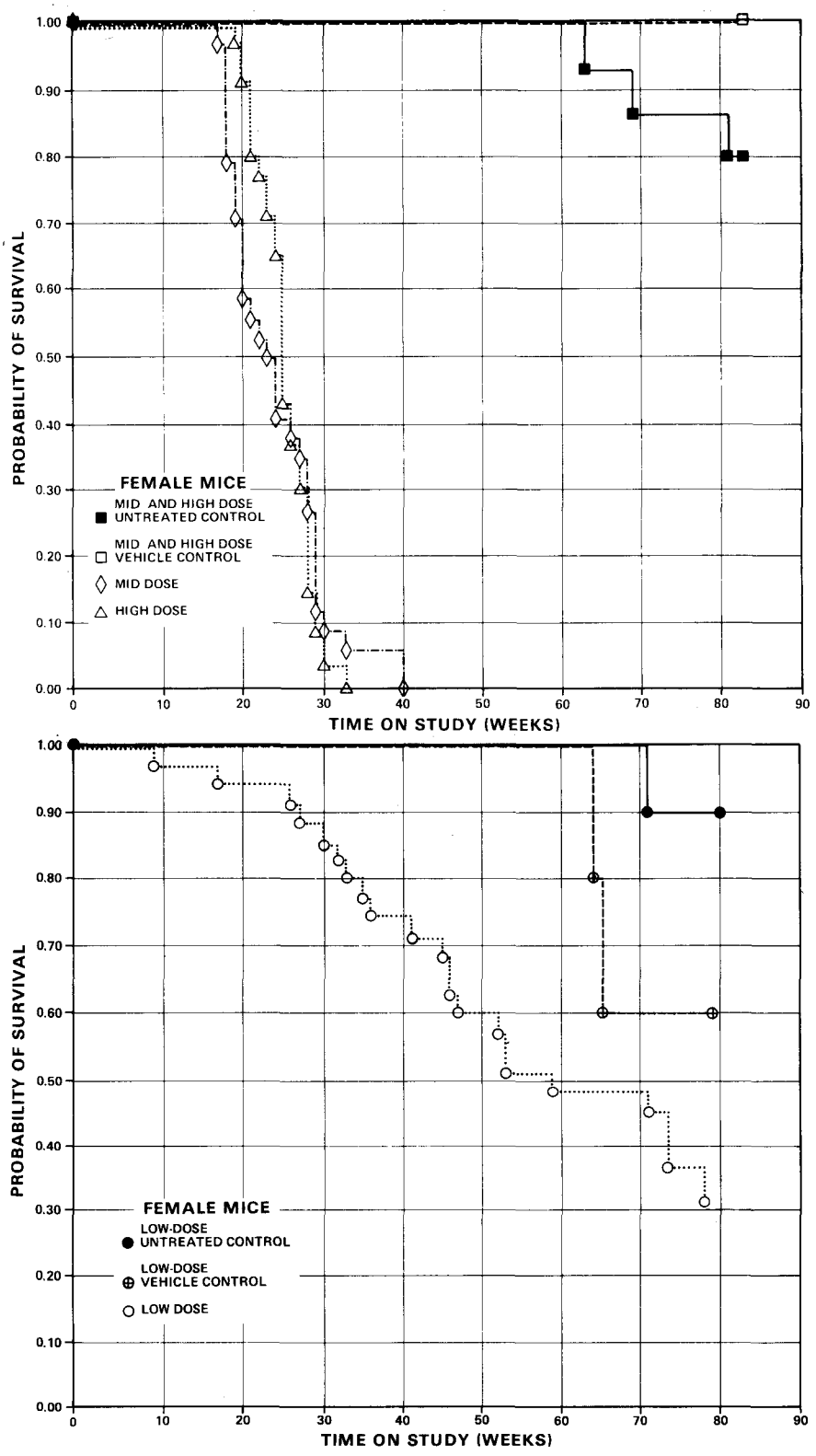


Figure 6. Survival Curves For Female Mice Treated With Emetine

study. The median times on study of the high-, mid-, and low-dose female mice were 25 weeks, 23 weeks, and 59 weeks, respectively. All of the high- and mid-dose female mice died before week 52 on study. No tumor was observed in the mid-dose group, but one alveolar/bronchiolar adenoma was found in the high-dose group as early as week 21. Of the low-dose female mice, 21/35 lived to at least week 52; no tumor was observed before that time.

The early deaths of the treated mice of both sexes may have affected the incidences of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1-B4; findings on nonneoplastic lesions are summarized in Appendix D, tables D1-D4.

A variety of neoplasms occurred with approximately equal frequency in control and treated mice. There was a low incidence of neoplasia in both control and treated mice. The extremely low incidence of neoplasia in the mid- and high-dose mice was probably due to the high number of early deaths that occurred in these groups.

Several inflammatory and degenerative lesions occurred with approximately equal frequency in the control and treated mice. The treated groups had a higher incidence of inflammatory lesions in the respiratory system, the digestive system, and the abdominal cavity when compared with the control groups. These inflammatory lesions appeared to be related to emetine at these doses and associated with an increase in mortality.

The histopathologic evaluation of the lesions indicated that emetine administered for the time period and at the doses used in this study had a toxic effect, since the higher doses caused a shortened life span.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that were observed in at least 5% of a treated group. The untreated controls are not included in these tables and analyses, since the experimental conditions of the vehicle controls more closely resemble those of the treated groups. There is no table or analysis for female mice, because the proportions of lesions in the treated groups are less than 5%. In fact, only three tumors were observed among all treated female mice: two in the low-dose and one in the high-dose group.

Since there was extremely high mortality in the treated male mice, time-adjusted analyses were performed, eliminating animals that died before week 52 on study. One hepatocellular carcinoma was found as early as week 50 in the low-dose group; thus, the time-adjusted analysis of the incidence of this tumor of the liver is based only on animals that lived at least as long as week 50 on study. These time-adjusted analyses of the male mice are shown in table F2 in Appendix F.

The Cochran-Armitage test is not applied here, because the survivals of the various treated and control groups are not comparable. The Fisher exact test for direct comparison of the incidences in each of the control groups with those in each of the treated groups are not significant, either before or after the time-adjustment. In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included, indicating the absence of positive significant results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by emetine, which could not be detected under the conditions of this test.

V. DISCUSSION

In this bioassay, emetine was toxic to male rats at the high dose, to both sexes of mice at the high and mid doses, and to a lesser extent at the low dose, as shown by the low survival in these groups. This study was terminated at week 84 in rats and week 83 in mice. Twenty-six percent of the high-dose male rats and 69% of the high-dose female rats survived to the end of the study. In mice, none of the high- and mid-dose animals of either sex survived to the end of the study. At the low-dose, 30/35 males and 21/35 females lived for at least 1 year, and the median time on study was 72 weeks for the males and 59 weeks for the females.

A variety of neoplasms were observed in both control and treated rats, but only the incidence of fibroadenoma of the mammary gland in the females was higher in the treated rats than in the controls. However, the incidence was not statistically significant.

The incidences of neoplasms in treated mice of each sex were low and were similar to those of both untreated and vehicle controls.

As early as 1912, the use of emetine in the chemotherapy of amebiasis was recorded, and reports of its antitumor activity appeared as early as 1918 and 1919 (Grollman and Jarkovsky,

1975). The results of a 24-week test for the carcinogenicity of emetine in mice, evaluated by measuring the induction of pulmonary tumors, was negative (Stoner et al., 1973).

It should be noted that in this study, treatment of both species was stopped at week 52 and the studies were terminated by week 83, which is earlier than in current bioassays where animals are treated until termination of the studies at 2 years. In addition, there was poor survival among the treated mice.

It is concluded that the results of this study do not allow evaluation of the possible carcinogenicity of emetine.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH EMETINE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH EMETINE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	35	35
ANIMALS NECROPSIED	10	10	35	27
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	35	27
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(10)	(35)	(27)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
*SUBCUT TISSUE	(10)	(10)	(35)	(27)
FIBROMA			2 (6%)	
LIPOMA			1 (3%)	
LEIOMYOSARCOMA			1 (3%)	
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
NONE				
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(35)	(27)
HEPATOCELLULAR ADENOMA			2 (6%)	
#STOMACH	(10)	(10)	(35)	(27)
FIBROSARCOMA				1 (4%)
URINARY SYSTEM				
NONE				

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(10)	(10)	(32)	(22)
CHROMOPHOBE ADENOMA	1 (10%)	1 (10%)	3 (9%)	1 (5%)
CHROMOPHOBE CARCINOMA	2 (20%)	1 (10%)	1 (3%)	1 (5%)
#ADRENAL	(9)	(10)	(35)	(27)
CORTICAL ADENOMA			1 (3%)	
PHEOCHROMOCYTOMA		1 (10%)	1 (3%)	
#PARATHYROID	(8)	(4)	(10)	(7)
ADENOMA, NOS				1 (14%)
#PANCREATIC ISLETS	(10)	(9)	(34)	(26)
ISLET-CELL ADENOMA			2 (6%)	1 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(35)	(27)
FIBROADENOMA				1 (4%)
#TESTIS	(9)	(10)	(34)	(27)
INTERSTITIAL-CELL TUMOR			3 (9%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	35	35
NATURAL DEATH@	2	1	1	15
MORIBUND SACRIFICE			2	11
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	8	9	31	9
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	3	13	5
TOTAL PRIMARY TUMORS	3	3	18	6
TOTAL ANIMALS WITH BENIGN TUMORS	1	2	13	4
TOTAL BENIGN TUMORS	1	2	16	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	1	2	2
TOTAL MALIGNANT TUMORS	2	1	2	2
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH EMETINE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	35	35
ANIMALS NECROPSIED	10	10	35	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	35	35
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(10)	(10)	(35)	(35)
FIBROSARCOMA			1 (3%)	
LIPOMA			1 (3%)	
LIPOSARCOMA			1 (3%)	
RESPIRATORY SYSTEM				
#LUNG	(10)	(9)	(34)	(35)
ADENOCARCINOMA, NOS, METASTATIC	1 (10%)			
SARCOMA, NOS, METASTATIC				1 (3%)
HEMATOPOIETIC SYSTEM				
NONE				
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(10)	(10)	(35)	(33)
CHROMOPHOBE ADENOMA	3 (30%)	3 (30%)	11 (31%)	8 (24%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CHROMOPHOBE CARCINOMA	1 (10%)	1 (10%)	1 (3%)	1 (3%)
ACIDOPHIL ADENOMA			1 (3%)	
#ADRENAL	(10)	(10)	(35)	(35)
CORTICAL ADENOMA	1 (10%)	3 (30%)	9 (26%)	2 (6%)
PHEOCHROMOCYTOMA			1 (3%)	
#THYROID	(10)	(7)	(28)	(24)
C-CELL ADENOMA			1 (4%)	1 (4%)
#PANCREATIC ISLETS	(10)	(10)	(35)	(34)
ISLET-CELL ADENOMA			1 (3%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(35)	(35)
ADENOMA, NOS			1 (3%)	
ADENOCARCINOMA, NOS	1 (10%)		1 (3%)	2 (6%)
PAPILLARY ADENOMA			1 (3%)	
FIBROMA	1 (10%)			1 (3%)
FIBROADENOMA	1 (10%)	2 (20%)	14 (40%)	10 (29%)
#UTERUS	(10)	(10)	(35)	(35)
SQUAMOUS CELL CARCINOMA			1 (3%)	
SARCOMA, NOS				1 (3%)
LEIOMYOMA				1 (3%)
LEIOMYOSARCOMA			1 (3%)	1 (3%)
ENDOMETRIAL STROMAL POLYP	1 (10%)		3 (9%)	1 (3%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MESENTERY	(10)	(10)	(35)	(35)
LIPOMA				2 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	35	35
NATURAL DEATH@	1		1	1
MORIBUND SACRIFICE	2		5	10
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	7	10	29	24
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	6	26	22
TOTAL PRIMARY TUMORS	9	9	50	31
TOTAL ANIMALS WITH BENIGN TUMORS	5	6	22	20
TOTAL BENIGN TUMORS	7	8	44	26
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	1	5	5
TOTAL MALIGNANT TUMORS	2	1	6	5
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			1
TOTAL SECONDARY TUMORS	1			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH EMETINE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH EMETINE (CONTROL GROUPS)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	15	10	15	10
ANIMALS MISSING	1			
ANIMALS NECROPSIED	14	10	14	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	10	14	10
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(14)	(9)	(14)	(10)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (7%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(14)	(10)	(14)	(10)
MONOCYTIC LEUKEMIA				1 (10%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(14)	(10)	(14)	(10)
HEPATOCELLULAR ADENOMA	2 (14%)		1 (7%)	
HEPATOCELLULAR CARCINOMA	1 (7%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	10	15	10
NATURAL DEATH@	2	1	2	1
MORIBUND SACRIFICE	1			1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	11	9	13	8
ANIMAL MISSING	1			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	3		2	1
TOTAL PRIMARY TUMORS	3		2	1
TOTAL ANIMALS WITH BENIGN TUMORS	2		2	
TOTAL BENIGN TUMORS	2		2	
TOTAL ANIMALS WITH MALIGNANT TUMORS	1			1
TOTAL MALIGNANT TUMORS	1			1
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH EMETINE (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	35	30	30
ANIMALS EXAMINED HISTOPATHOLOGICALLY	35	29	30
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(35)	(28)	(29)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (6%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (3%)		
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(35)	(27)	(30)
HEPATOCELLULAR CARCINOMA	3 (9%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(25)	(19)	(16)
PAPILLARY CYSTADENOMA, NOS	1 (4%)		

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

TABLE B2. MALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DO
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH@	7	24	18
MORIBUND SACRIFICE	13	10	17
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1	1	
TERMINAL SACRIFICE	14		
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. MALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7		
TOTAL PRIMARY TUMORS	7		
TOTAL ANIMALS WITH BENIGN TUMORS	3		
TOTAL BENIGN TUMORS	3		
TOTAL ANIMALS WITH MALIGNANT TUMORS	4		
TOTAL MALIGNANT TUMORS	4		
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH EMETINE (CONTROL GROUPS)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	15	10	15	10
ANIMALS NECROPSIED	15	10	15	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	10	15	10
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(15)	(10)	(15)	(10)
LYMPHOCYTIC LEUKEMIA		1 (10%)		
#MESENTERIC L. NODE	(6)	(8)	(6)	(8)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (13%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				

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

TABLE B3. FEMALE MICE: NEOPLASMS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
REPRODUCTIVE SYSTEM				
#UTERUS	(15)	(9)	(15)	(10)
ENDOMETRIAL STROMAL POLYP	1 (7%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	10	15	10
NATURAL DEATH@	3			2
MORIBUND SACRIFICE		1		2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	12	9	15	6
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B3. FEMALE MICE: NEOPLASMS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	2		
TOTAL PRIMARY TUMORS	1	2		
TOTAL ANIMALS WITH BENIGN TUMORS	1			
TOTAL BENIGN TUMORS	1			
TOTAL ANIMALS WITH MALIGNANT TUMORS		2		
TOTAL MALIGNANT TUMORS		2		
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH EMETINE (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS MISSING		1	
ANIMALS NECROPSIED	34	26	27
ANIMALS EXAMINED HISTOPATHOLOGICALLY	34	26	27
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(33)	(26)	(27)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (4%)
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(31)	(12)	(16)
ADENOMA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
NONE			

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

TABLE B4. FEMALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(34)	(26)	(27)
LIPOMA	1 (3%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH@	5	19	23
MORIBUND SACRIFICE	19	15	12
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11		
ANIMAL MISSING		1	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B4. FEMALE MICE: NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2		1
TOTAL PRIMARY TUMORS	2		1
TOTAL ANIMALS WITH BENIGN TUMORS	2		1
TOTAL BENIGN TUMORS	2		1
TOTAL ANIMALS WITH MALIGNANT TUMORS			
TOTAL MALIGNANT TUMORS			
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH EMETINE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	35	35
ANIMALS NECROPSIED	10	10	35	27
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	35	27
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(10)	(35)	(27)
EPIDERMAL INCLUSION CYST			2 (6%)	
RESPIRATORY SYSTEM				
#TRACHEA	(10)	(10)	(34)	(26)
INFLAMMATION, NOS	3 (30%)	5 (50%)	6 (18%)	
LYMPHOCYTIC INFILTRATE	1 (10%)			
INFLAMMATION, SUPPURATIVE			1 (3%)	1 (4%)
INFLAMMATION, ACUTE/CHRONIC			3 (9%)	
INFLAMMATION, CHRONIC				1 (4%)
#LUNG/BRONCHUS	(10)	(10)	(35)	(27)
BRONCHIECTASIS	1 (10%)			
INFLAMMATION, NOS			2 (6%)	
INFLAMMATION, ACUTE/CHRONIC			1 (3%)	
INFLAMMATION, CHRONIC		1 (10%)	1 (3%)	
#LUNG/BRONCHIOLE	(10)	(10)	(35)	(27)
INFLAMMATION, SUPPURATIVE	1 (10%)			
PERIVASCULAR CUFFING			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#LUNG	(10)	(10)	(35)	(27)
EMPHYSEMA, NOS				1 (4%)
ABSCESS, NOS	1 (10%)			
PNEUMONIA INTERSTITIAL CHRONIC		1 (10%)		1 (4%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(10)	(10)	(35)	(27)
ATROPHY, NOS			12 (34%)	5 (19%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#HEART	(10)	(10)	(35)	(27)
CALCIFICATION, NOS				2 (7%)
#MYOCARDIUM	(10)	(10)	(35)	(27)
INFLAMMATION, NOS				2 (7%)
INFLAMMATION, INTERSTITIAL				1 (4%)
DIGESTIVE SYSTEM				
#LIVER	(10)	(10)	(35)	(27)
INFLAMMATION, SUPPURATIVE			1 (3%)	
NECROSIS, COAGULATIVE				1 (4%)
#PANCREAS	(10)	(9)	(34)	(26)
INFLAMMATION, CHRONIC			1 (3%)	
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(35)	(27)
PYELONEPHRITIS, NOS				1 (4%)
ABSCESS, NOS	1 (10%)			
INFLAMMATION, CHRONIC	4 (40%)	1 (10%)	10 (29%)	2 (7%)
NEPHROSIS, NOS				4 (15%)
#KIDNEY/GLOMERULUS	(10)	(10)	(35)	(27)
INFLAMMATION, NOS			1 (3%)	
FIBROSIS			5 (14%)	
#URINARY BLADDER	(9)	(9)	(26)	(24)
HYPERPLASIA, EPITHELIAL				3 (13%)
ENDOCRINE SYSTEM				
#ADRENAL	(9)	(10)	(35)	(27)
ABSCESS, NOS	1 (11%)			
REPRODUCTIVE SYSTEM				
#PROSTATE	(9)	(10)	(33)	(26)
INFLAMMATION, SUPPURATIVE	1 (11%)			3 (12%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE SUPPURATIVE				1 (4%)
INFLAMMATION, CHRONIC				1 (4%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (11%)			2 (8%)
*SEMINAL VESICLE	(10)	(10)	(35)	(27)
INFLAMMATION, ACUTE/CHRONIC				1 (4%)
NERVOUS SYSTEM				
*CEREBELLUM	(10)	(10)	(35)	(25)
GLIOSIS			1 (3%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*JOINT	(10)	(10)	(35)	(27)
INFLAMMATION, SUPPURATIVE	1 (10%)			
*SKELETAL MUSCLE	(10)	(10)	(35)	(27)
FIBROSIS	1 (10%)			
ATROPHY, FOCAL	1 (10%)			
BODY CAVITIES				
*PERITONEUM	(10)	(10)	(35)	(27)
INFLAMMATION, CHRONIC				1 (4%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	2	4	8
AUTOLYSIS/NO NECROPSY				8

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH EMETINE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	35	35
ANIMALS NECROPSIED	10	10	35	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	35	35
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(10)	(10)	(35)	(35)
EDEMA, NOS				1 (3%)
RESPIRATORY SYSTEM				
#TRACHEA	(10)	(10)	(34)	(32)
INFLAMMATION, NOS	1 (10%)	3 (30%)	11 (32%)	
INFLAMMATION, SUPPURATIVE			1 (3%)	
INFLAMMATION, ACUTE/CHRONIC			5 (15%)	5 (16%)
HYPERPLASIA, PLASMA CELL			1 (3%)	
#LUNG/BRONCHUS	(10)	(9)	(34)	(35)
BRONCHIECTASIS			1 (3%)	
INFLAMMATION, NOS			1 (3%)	
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)	
#LUNG	(10)	(9)	(34)	(35)
EMPHYSEMA, NOS				1 (3%)
BRONCHOPNEUMONIA SUPPURATIVE				1 (3%)
BRONCHOPNEUMONIA CHRONIC SUPPURA				1 (3%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(10)	(10)	(35)	(35)
ATROPHY, NOS			1 (3%)	8 (23%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(35)	(35)
INFLAMMATION, INTERSTITIAL			1 (3%)	1 (3%)
INFLAMMATION, CHRONIC			4 (11%)	
#KIDNEY/GLOMERULUS	(10)	(10)	(35)	(35)
FIBROSIS			1 (3%)	
#KIDNEY/TUBULE	(10)	(10)	(35)	(35)
MINERALIZATION				1 (3%)
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(35)	(35)
HYPERPLASIA, CYSTIC				1 (3%)
#UTERUS	(10)	(10)	(35)	(35)
PYOMETRA	1 (10%)	1 (10%)	2 (6%)	
#UTERUS/ENDOMETRIUM	(10)	(10)	(35)	(35)
INFLAMMATION, SUPPURATIVE	1 (10%)			2 (6%)
#OVARY	(10)	(3)	(32)	(27)
CYST, NOS				1 (4%)
ABSCESS, NOS			1 (3%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR/CARTILAGE	(10)	(10)	(35)	(35)
HYPERPLASIA, NOS				1 (3%)
METAPLASIA, OSSEOUS				1 (3%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(10)	(10)	(35)	(35)
MINERALIZATION				1 (3%)
BODY CAVITIES				
*PERITONEUM	(10)	(10)	(35)	(35)
INFLAMMATION, CHRONIC SUPPURATIV				1 (3%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	2	3	2

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

APPENDIX D

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

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH EMETINE (CONTROL GROUPS)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	15	10	15	10
ANIMALS MISSING	1			
ANIMALS NECROPSIED	14	10	14	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	10	14	10
INTEGUMENTARY SYSTEM				
*SKIN	(14)	(10)	(14)	(10)
INFLAMMATION, NOS	2 (14%)			
*SUBCUT TISSUE	(14)	(10)	(14)	(10)
LIPOGRANULOMA				1 (10%)
RESPIRATORY SYSTEM				
#TRACHEA	(13)	(8)	(13)	(9)
INFLAMMATION, SUPPURATIVE				1 (11%)
#LUNG	(14)	(9)	(14)	(10)
EDEMA, NOS	1 (7%)			
INFLAMMATION, INTERSTITIAL	1 (7%)			1 (10%)
BRONCHOPNEUMONIA SUPPURATIVE	1 (7%)			
BRONCHOPNEUMONIA CHRONIC SUPPURA				1 (10%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(14)	(9)	(14)	(10)
HEMATOPOIESIS			2 (14%)	1 (10%)
#MESENTERIC L. NODE	(7)	(4)	(11)	(9)
INFLAMMATION, SUPPURATIVE			1 (9%)	
INFLAMMATION, NECROTIZING			1 (9%)	
HYPERPLASIA, HEMATOPOIETIC	1 (14%)			
HYPERPLASIA, LYMPHOID			2 (18%)	3 (33%)
#THYMUS	(8)	(1)	(10)	
ATROPHY, NOS	1 (13%)			
CIRCULATORY SYSTEM				
#HEART	(14)	(10)	(14)	(10)
PERIARTERITIS			1 (7%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
DIGESTIVE SYSTEM				
*LIVER	(14)	(10)	(14)	(10)
INFLAMMATION, CHRONIC			1 (7%)	
HYPERPLASTIC NODULE	1 (7%)	1 (10%)	3 (21%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
*THYROID	(13)	(4)	(10)	(9)
PERIARTERITIS	1 (8%)			
REPRODUCTIVE SYSTEM				
*SEMINAL VESICLE	(14)	(10)	(14)	(10)
HYPERPLASIA, CYSTIC	1 (7%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(14)	(10)	(14)	(10)
CYTOMEGALY				1 (10%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	7	9	7	4
ANIMAL MISSING/NO NECROPSY	1			
AUTOLYSIS/NO NECROPSY			1	

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH EMETINE (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	35	30	30
ANIMALS EXAMINED HISTOPATHOLOGICALLY	35	29	30
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(35)	(28)	(28)
INFLAMMATION, SUPPURATIVE	11 (31%)		
INFLAMMATION, ACUTE/CHRONIC	1 (3%)		
#LUNG/BRONCHUS	(35)	(28)	(29)
BRONCHIECTASIS	12 (34%)		
INFLAMMATION, NOS	2 (6%)		
INFLAMMATION, SUPPURATIVE	10 (29%)		
#LUNG/BRONCHIOLE	(35)	(28)	(29)
INFLAMMATION, FOCAL	1 (3%)		
INFLAMMATION, SUPPURATIVE	2 (6%)		
#LUNG	(35)	(28)	(29)
EDEMA, NOS	1 (3%)		
HEMORRHAGE	1 (3%)		
BRONCHOPNEUMONIA, NOS	10 (29%)		
INFLAMMATION, INTERSTITIAL	1 (3%)		
INFLAMMATION, SUPPURATIVE	1 (3%)		
BRONCHOPNEUMONIA SUPPURATIVE	5 (14%)		
BRONCHOPNEUMONIA, ACUTE	1 (3%)		
INFLAMMATION, ACUTE HEMORRHAGIC	1 (3%)		
INFLAMMATION, ACUTE/CHRONIC	1 (3%)		
BRONCHOPNEUMONIA CHRONIC SUPPURA	3 (9%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(34)	(22)	(25)
HEMATOPOIESIS	5 (15%)		

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

TABLE D2. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
#MANDIBULAR L. NODE	(32)	(22)	(19)
ATROPHY, NOS	1 (3%)		
#MEDIASTINAL L.NODE	(32)	(22)	(19)
PLASMACYTOSIS	1 (3%)		
#MESENTERIC L. NODE	(32)	(22)	(19)
INFLAMMATION, NECROTIZING	1 (3%)		
INFLAMMATION, CHRONIC			1 (5%)
#THYMUS	(6)	(1)	
ATROPHY, NOS	6 (100%)		
CIRCULATORY SYSTEM			
#HEART	(35)	(27)	(29)
DEGENERATION, NOS	2 (6%)		
NECROSIS, NOS	2 (6%)		
#HEART/ATRIUM	(35)	(27)	(29)
THROMBOSIS, NOS	1 (3%)		
#MYOCARDIUM	(35)	(27)	(29)
INFLAMMATION, NOS	1 (3%)		
INFLAMMATION, INTERSTITIAL	2 (6%)		
INFLAMMATION, SUPPURATIVE	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(35)	(27)	(30)
INFLAMMATION, SUPPURATIVE	1 (3%)		
NECROSIS, FOCAL		1 (4%)	
NECROSIS, COAGULATIVE		3 (11%)	1 (3%)
BASOPHILIC CYTO CHANGE	2 (6%)		
FOCAL CELLULAR CHANGE	1 (3%)		
#PANCREAS	(33)	(26)	(29)
INFLAMMATION, CHRONIC	1 (3%)	1 (4%)	
#PANCREATIC ACINUS	(33)	(26)	(29)
ATROPHY, NOS		1 (4%)	
#ESOPHAGUS	(34)	(24)	(24)
ULCER, NOS	1 (3%)		1 (4%)

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

TABLE D2. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (3%)		
ULCER, CHRONIC		2 (8%)	1 (4%)
#SMALL INTESTINE	(26)	(27)	(15)
HEMORRHAGE			1 (7%)
#DUODENUM	(26)	(27)	(15)
HEMORRHAGE			1 (7%)
#ILEUM	(26)	(27)	(15)
INFLAMMATION, HEMORRHAGIC			1 (7%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#PROSTATE	(21)	(22)	(15)
ULCER, NOS	1 (5%)		
INFLAMMATION, SUPPURATIVE	1 (5%)		
*SEMINAL VESICLE	(35)	(30)	(30)
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(35)	(28)	(29)
INFLAMMATION, SUPPURATIVE	1 (3%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D2. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(35)	(30)	(30)
INFLAMMATION, SUPPURATIVE	2 (6%)		
INFLAMMATION, CHRONIC	2 (6%)		
INFLAMMATION, CHRONIC NECROTIZIN			1 (3%)
FIBROSIS	2 (6%)		
HEMOSIDEROSIS	1 (3%)		
*VISCERAL PERITONEUM	(35)	(30)	(30)
INFLAMMATION, HEMORRHAGIC		1 (3%)	2 (7%)
INFLAMMATION, CHRONIC		16 (53%)	12 (40%)
INFLAMMATION, CHRONIC NECROTIZIN			2 (7%)
*PLEURA	(35)	(30)	(30)
INFLAMMATION, SUPPURATIVE		1 (3%)	
INFLAMMATION, CHRONIC NECROTIZIN		1 (3%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	12	12
NECROPSY PERF/NO HISTO PERFORMED		1	
NO NECROPSY PERFORMED		1	1
AUTOLYSIS/NO NECROPSY		4	4

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

TABLE D3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH EMETINE (CONTROL GROUPS)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	15	10	15	10
ANIMALS NECROPSIED	15	10	15	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	10	15	10
INTEGUMENTARY SYSTEM				
*SKIN	(15)	(10)	(15)	(10)
INFLAMMATION, NOS	1 (7%)			
INFLAMMATION, SUPPURATIVE	1 (7%)			
RESPIRATORY SYSTEM				
#TRACHEA	(14)	(7)	(14)	(9)
INFLAMMATION, SUPPURATIVE				2 (22%)
#LUNG/BRONCHUS	(15)	(10)	(14)	(9)
INFLAMMATION, CHRONIC SUPPURATIV				1 (11%)
#LUNG	(15)	(10)	(14)	(9)
CONGESTION, NOS	1 (7%)			
EDEMA, NOS	2 (13%)			
HEMORRHAGE	1 (7%)			
BRONCHOPNEUMONIA CHRONIC SUPPURA				4 (44%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(13)	(10)	(15)	(10)
HEMATOPOIESIS			3 (20%)	4 (40%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(15)	(10)	(15)	(9)
INFLAMMATION, ACUTE	1 (7%)			
DIGESTIVE SYSTEM				
#LIVER	(14)	(10)	(15)	(10)
INFLAMMATION, SUPPURATIVE				1 (10%)

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

TABLE D3. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
#STOMACH	(14)	(8)	(15)	(10)
INFLAMMATION, SUPPURATIVE	1 (7%)			
HYPERPLASIA, NOS	1 (7%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(15)	(10)	(15)	(10)
HYPERPLASIA, CYSTIC	1 (7%)			
#UTERUS	(15)	(9)	(15)	(10)
INFLAMMATION, SUPPURATIVE	1 (7%)			
PYOMETRA	3 (20%)			
#UTERUS/ENDOMETRIUM	(15)	(9)	(15)	(10)
HYPERPLASIA, CYSTIC	10 (67%)	8 (89%)	14 (93%)	8 (80%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR	(15)	(10)	(15)	(10)
THROMBOSIS, NOS	1 (7%)			
HEMORRHAGE	1 (7%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(15)	(10)	(15)	(10)
INFLAMMATION, SUPPURATIVE	1 (7%)			

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

TABLE D3. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MID & HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID & HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
*PLEURA	(15)	(10)	(15)	(10)
INFLAMMATION, SUPPURATIVE	1 (7%)			
*EPICARDIUM	(15)	(10)	(15)	(10)
INFLAMMATION, SUPPURATIVE	1 (7%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	2	1	

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

TABLE D4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH EMETINE (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS MISSING		1	
ANIMALS NECROPSIED	34	26	27
ANIMALS EXAMINED HISTOPATHOLOGICALLY	34	26	27
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(34)	(19)	(27)
INFLAMMATION, SUPPURATIVE	1 (3%)		
#LUNG	(33)	(26)	(27)
INFLAMMATION, INTERSTITIAL	2 (6%)		
BRONCHOPNEUMONIA SUPPURATIVE	1 (3%)		
BRONCHOPNEUMONIA CHRONIC SUPPURA	9 (27%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(32)	(21)	(25)
ATROPHY, NOS	1 (3%)		
#SPLEEN	(34)	(20)	(26)
INFLAMMATION, NECROTIZING	1 (3%)		
HEMATOPOIESIS	4 (12%)	2 (10%)	3 (12%)
#MESENTERIC L. NODE	(26)	(20)	(23)
INFLAMMATION, NECROTIZING	1 (4%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (4%)		
HYPERPLASIA, LYMPHOID			1 (4%)
#INGUINAL LYMPH NODE	(26)	(20)	(23)
HYPERPLASIA, LYMPHOID		1 (5%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE D4. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(33)	(24)	(27)
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, NECROTIZING	1 (3%)		1 (4%)
NECROSIS, FOCAL		1 (4%)	
NECROSIS, COAGULATIVE		1 (4%)	3 (11%)
HEMATOPOIESIS	1 (3%)		
#HEPATIC CAPSULE	(33)	(24)	(27)
CALCIFICATION, DYSTROPHIC	1 (3%)		
#ESOPHAGUS	(29)	(20)	(24)
ULCER, NOS		6 (30%)	3 (13%)
INFLAMMATION, SUPPURATIVE	1 (3%)		
ULCER, CHRONIC		4 (20%)	
#STOMACH	(33)	(18)	(17)
ULCER, NOS	1 (3%)		
URINARY SYSTEM			
#URINARY BLADDER	(26)	(21)	(18)
INFLAMMATION, SUPPURATIVE			1 (6%)
ULCER, CHRONIC		1 (5%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(29)	(22)	(25)
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, ACUTE/CHRONIC	1 (3%)		
HYPERPLASIA, CYSTIC	21 (72%)		
#OVARY	(21)	(19)	(24)
CYST, NOS		1 (5%)	
NERVOUS SYSTEM			
NONE			

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

TABLE D4. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(34)	(26)	(27)
INFLAMMATION, CHRONIC	13 (38%)	1 (4%)	
*VISCERAL PERITONEUM	(34)	(26)	(27)
INFLAMMATION, SUPPURATIVE			1 (4%)
INFLAMMATION, HEMORRHAGIC			1 (4%)
INFLAMMATION, CHRONIC		24 (92%)	14 (52%)
INFLAMMATION, CHRONIC NECROTIZIN			1 (4%)
*PLEURA	(34)	(26)	(27)
INFLAMMATION, SUPPURATIVE		4 (15%)	2 (7%)
INFLAMMATION, CHRONIC		2 (8%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2		6
ANIMAL MISSING/NO NECROPSY		1	
NO NECROPSY PERFORMED	1		
AUTOLYSIS/NO NECROPSY		8	8

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS TREATED WITH EMETINE

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Treated with Emetine[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma[b]	0/25 (0)	0/10 (0)	2/35 (6)	0/27 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.218	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.093	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	75	--
Liver: Hepatocellular Adenoma[b]	0/25 (0)	0/10 (0)	2/35 (6)	0/27 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.218	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.093	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	84	--

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Treated with Emetine[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma[b]	2/25 (8)	1/10 (10)	1/32 (3)	1/22 (5)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.391	0.568
Lower Limit			0.007	0.010
Upper Limit			7.098	10.110
Relative Risk (Vehicle Control)[f]			0.313	0.455
Lower Limit			0.004	0.006
Upper Limit			23.802	34.087
Weeks to First Observed Tumor	--	84	84	80
Pituitary: Chromophobe Adenoma or Carcinoma[b]	3/25 (12)	2/10 (20)	4/32 (13)	2/22 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.042	0.758
Lower Limit			0.195	0.069
Upper Limit			6.533	5.976
Relative Risk (Vehicle Control)[f]			0.625	0.455
Lower Limit			0.114	0.040
Upper Limit			6.349	5.664
Weeks to First Observed Tumor	--	84	84	80

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Treated with Emetine[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Parathyroid:				
Adenoma, NOS[b]	0/9 (0)	0/4 (0)	0/10 (0)	1/7 (14)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			--	Infinite
Lower Limit			--	0.076
Upper Limit			--	Infinite
Relative Risk (Vehicle Control)[f]			--	Infinite
Lower Limit			--	0.039
Upper Limit			--	Infinite
Weeks to First Observed Tumor	--	--	--	83
Pancreatic Islets:				
Islet-cell Adenoma[b]	0/24 (0)	0/9 (0)	2/34 (6)	1/26 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.215	0.051
Upper Limit			Infinite	Infinite
Relative Risk (Vehicle Control)[f]			Infinite	Infinite
Lower Limit			0.088	0.020
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	84	83

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Treated with Emetine[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor[b]	0/25 (0)	0/10 (0)	3/34 (9)	0/27 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.029			
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.453	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.197	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	84	--

[a]Treated groups received doses of 0.5 or 1 mg/kg body weight by intraperitoneal injection.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Treated with Emetine[a]

(continued)

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Treated with Emetine[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma[b]	2/25 (8)	1/10 (10)	1/35 (3)	1/33 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.357	0.379
Lower Limit			0.006	0.007
Upper Limit			6.515	6.894
Relative Risk (Vehicle Control)[f]			0.286	0.303
Lower Limit			0.004	0.004
Upper Limit			21.825	23.104
Weeks to First Observed Tumor	--	84	84	84
Pituitary: Chromophobe Adenoma or Carcinoma[b]	9/25 (36)	4/10 (40)	12/35 (34)	9/33 (27)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.952	0.758
Lower Limit			0.445	0.320
Upper Limit			2.174	1.844
Relative Risk (Vehicle Control)[f]			0.857	0.682
Lower Limit			0.369	0.270
Upper Limit			3.071	2.563
Weeks to First Observed Tumor	--	84	84	61

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Treated with Emetine[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Adrenal: Cortical Adenoma[b]	3/25 (12)	3/10 (30)	9/35 (26)	2/35 (6)
P Values[c,d]	N.S.	P = 0.018(N)	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.026			
Relative Risk (Pooled Control)[f]			2.143	0.476
Lower Limit			0.608	0.043
Upper Limit			11.255	3.876
Relative Risk (Vehicle Control)[f]			0.857	0.190
Lower Limit			0.291	0.020
Upper Limit			4.323	1.494
Weeks to First Observed Tumor	--	84	66	84
Mammary Gland: Adenocarcinoma, NOS[b]	0/25 (0)	0/10 (0)	1/35 (3)	2/35 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.039	0.218
Upper Limit			Infinite	Infinite
Relative Risk (Vehicle Contol)[f]			Infinite	Infinite
Lower Limit			0.017	0.093
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	84	61

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Treated with Emetine[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	5/25 (20)	2/10 (20)	14/35 (40)	10/35 (29)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.000	1.429
Lower Limit			0.802	0.516
Upper Limit			6.183	4.720
Relative Risk (Vehicle Control)[f]			2.000	1.429
Lower Limit			0.604	0.398
Upper Limit			16.343	12.223
Weeks to First Observed Tumor	--	84	66	52
Uterus: Endometrial Stromal Polyp[b]	0/25 (0)	0/10 (0)	3/35 (9)	1/35 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.443	0.039
Upper Limit			Infinite	Infinite
Relative Risk (Vehicle Control)[f]			Infinite	Infinite
Lower Limit			0.191	0.017
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	84	83

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Treated with Emetine[a]

(continued)

[a]Treated groups received doses of 0.5 or 1 mg/kg body weight by intraperitoneal injection.

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

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE TREATED WITH EMETINE

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Treated with Emetine[a]

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	1/24 (4)	2/35 (6)	0/28 (0)	0/29 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		1.371	0.000	0.000
Lower Limit		0.076	0.000	0.000
Upper Limit		78.550	15.768	15.243
Weeks to First Observed Tumor	82	72	--	--
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	1/24 (4)	3/35 (9)	0/28 (0)	0/29 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		2.057	0.000	0.000
Lower Limit		0.180	0.000	0.000
Upper Limit		104.742	15.768	15.243
Weeks to First Observed Tumor	82	72	--	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Treated with Emetine[a]

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	1/24 (4)	3/35 (9)	0/27 (0)	0/30 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		2.057	0.000	0.000
Lower Limit		0.180	0.000	0.000
Upper Limit		104.742	16.331	14.750
Weeks to First Observed Tumor	75	50	--	--

[a]Treated groups received doses of 1.6, 3.2, or 6.4 mg/kg body weights by intraperitoneal injection.

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

[c]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]Since survivals were not comparable no trend tests were made.

[e]The 95% confidence interval of the relative risk between each treated group and the matched control group.

Table F2. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Treated with Emetine[a]

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (52)[b]	1/23 (4)	2/30 (7)	0/2 (0)	0/1 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		1.533	0.000	0.000
Lower Limit		0.085	0.000	0.000
Upper Limit		87.354	119.310	89.856
Weeks to First Observed Tumor	82	72	--	--
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (52)[b]	1/23 (4)	3/30 (10)	0/2 (0)	0/1 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		2.300	0.000	0.000
Lower Limit		0.200	0.000	0.000
Upper Limit		116.430	119.310	89.856
Weeks to First Observed Tumor	82	72	--	--

Table F2. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Treated with Emetine[a]

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma (50)[b]	1/23 (4)	3/31 (10)	0/2 (0)	0/1 (0)
P Values[c,d]	--	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[e]		2.226	0.000	0.000
Lower Limit		0.196	0.000	0.000
Upper Limit		112.848	119.310	89.856
Weeks to First Observed Tumor	75	50	--	--

[a]Treated groups received doses of 1.6, 3.2, or 6.4 mg/kg body weight by intraperitoneal injection.

[b]Number of tumor-bearing animals/number of animals examined at site (percent), based upon animals that lived at least as long as the number of weeks on study shown in parentheses after the morphology.

[c]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]Since survivals were not comparable no trend tests were made.

[e]The 95% confidence interval of the relative risk between each treated group and the matched control group.

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

November 28, 1977

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in organic chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which Emetine was reviewed.

It was noted that the drug was tested as part of a program to study the potential carcinogenicity of cancer chemotherapeutic agents. The experimental protocol deviated from the standard bioassay, since it was meant to mimic the clinical exposure situation. The primary reviewer said that the high dose levels initially tested were excessive, as evidence by the growth curves and mortality incidences. Although the NCI staff concluded that the study was inadequate to evaluate the carcinogenicity of Emetine, the Subgroup reviewer said that the survival was sufficient at low dosages to assess the drug when used as a chemotherapeutic agent in adults. He concluded that Emetine poses no carcinogenic hazard when used as an adult chemotherapeutic agent. He added that the study was inadequate as a carcinogenicity screen if the drug were to be used in children.

The secondary reviewer said that he agreed with the conclusions stated in the report. His assessment was based on the high mortality resulting in inadequate numbers of animals in each group. A discussion ensued as to the weight that should be given to a negative study that contained less than the desired number of animals. It was suggested by one Subgroup member that a probabilistic model be constructed that could be used for interpreting negative studies.

A motion was made as follows: "As part of a program of research on the potential carcinogenicity of drugs used in cancer chemotherapy, Emetine was tested in rats and mice. Survival of the mice was poor. The bioassay is inadequate to answer the question of carcinogenicity in the absolute sense, but the data obtained do not seem to indicate (Emetine to be) an appreciable risk when used in chemotherapy in adults. If (its) independent use is contemplated, more adequate data need to be developed for a definitive conclusion to be drawn." The motion was seconded and approved by all present except Mr. Garfinkel, who opposed it.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Lawrence Garfinkel, American Cancer Society
Henry C. Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
John H. Weisburger, American Health Foundation

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

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