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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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Bethesda, Maryland 20205

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

CONTRIBUTORS: This bioassay of lead dimethyldithiocarbamate was conducted by the NCI Frederick Cancer Research Center (FCRC) (1), Frederick, Maryland, operated for NCI (2) by Litton Bionetics, Inc.

The manager of the bioassay at FCRC was Dr. B. Ulland, the toxicologist was Dr. E. Gordon, and Drs. R. Cardy and B. Creasia compiled the data. Ms. S. Toms was responsible for management of data, Mr. D. Cameron for management of histopathology, Mr. L. Callahan for management of the computer branch, and Mr. R. Cypher for management of the facilities. Mr. A. Butler performed the

computer services. Drs. Ulland, Gordon, and R. L. Schueler determined the doses to be administered. Histopathologic evaluations for rats were performed by Dr. J. F. Hardisty (3), and the histopathologic evaluations for mice were performed by Dr. C. E. Gilmore (3). The diagnoses included in this report represent the interpretations of Drs. Hardisty and Gilmore.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6). The chemicals used in this bioassay were analyzed at Frederick Cancer Research Center by Dr. W. Zielinsky (1). The chemical analyses were reviewed and approved by Dr. Lijinsky (1).

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Owen, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of technical-grade lead dimethyldithiocarbamate for possible carcinogenicity was conducted by administering the test chemical in feed to F344 (Fischer) rats and B6C3F1 mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered lead dimethyldithiocarbamate at one of two doses, either 25 or 50 ppm, for 104 or 105 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of the period of administration of the test chemical.

Mean body weights of the dosed male rats and female mice were slightly lower than those of the corresponding controls; mean body weights of the dosed female rats and male mice were essentially the same as those of the corresponding controls. Survival rates in both species were unaffected by administration of the test chemical. The lack of toxicity in both species suggests that a maximum tolerated dose level may not have been used. Therefore, the studies may not have been conducted using maximum sensitivity for the assessment of the possible carcinogenicity of lead dimethyldithiocarbamate.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups.

It is concluded that under the conditions of this bioassay, lead dimethyldithiocarbamate was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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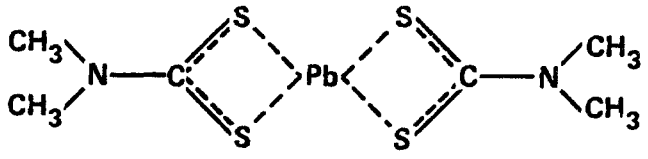
I. INTRODUCTION



Lead dimethyldithiocarbamate

The lead salt of bis(dimethyldithiocarbamic) acid (CAS 19010-66-3; NCI C02891) is used commercially as a rubber accelerator in applications involving natural rubber, and styrene-butadiene, isobutylene-isoprene, isoprene, and butadiene rubber (Del Gatto, 1968). Dithiocarbamate accelerators are known as ultra accelerators due to their speed of reaction. They are used primarily in latexes and rubber cements (Rogers, 1974; Shaver, 1965).

Production figures on lead dimethyldithiocarbamate are not reported (USITC, 1977); this may indicate that production levels do not exceed 1,000 pounds or $1,000 of sales.

Lead dimethyldithiocarbamate was selected by the Carcinogenesis Testing Program as a result of the preliminary investigations by Innes et al. (1969), which gave inconclusive results.

II. MATERIALS AND METHODS

A. Chemical

Ledate (lead dimethyldithiocarbamate; $C_6H_{12}N_2S_4Pb$) was obtained as technical-grade, nonformulated material from R. T. Vanderbilt Co. This material is a fine, gray-white powder, which has been used as a rubber accelerator. On the basis of lead analysis by atomic absorption spectrometry (experimental: 45.2%; theoretical: 46.3%), the material was 98% pure ledate. Elemental analysis was consistent with the molecular formula for this material (experimental: 16.6% carbon, 2.8% hydrogen, 6.6% nitrogen; theoretical: 16.1% carbon, 2.7% hydrogen, 6.3% nitrogen). Atomic absorption analysis also showed traces of copper; while neutron activation analysis showed trace metal levels of 240 ppm iron, 34 ppm antimony, less than 10 ppm arsenic, and less than 5 ppm chromium, silver, scandium, rubidium, and lanthanum, as well as 3% sodium.

B. Dietary Preparation

Test diets containing lead dimethyldithiocarbamate were prepared

every 1 to 1-1/2 weeks in 6- to 12-kg batches at appropriate doses. A known weight of the chemical was first mixed with an equal weight of the autoclaved Wayne® Sterilizable Lab Blox Meal (Allied Mills, Inc., Chicago, Ill.) using a mortar and pestle.

The mixing was continued with second and third additions of feed, and final mixing was performed with the remaining quantity of feed for a minimum of 15 minutes in a Patterson-Kelly twin-shell blender. The diets were routinely stored at 5°C until used.

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, NCI from the NCI Frederick Cancer Research Center animal farm as 4-week-old weanlings, all within 3 days of the same age. The animals were housed within the test facility for 2 weeks and then were assigned four rats to a cage and five mice to a cage on a weight basis for a given species and sex. For use in the chronic study, male rats were required to weigh 90 to 105 g, averaging at least 100 g; female rats, 80 to 95 g, averaging at least 90 g; male mice, 18 to 22 g, averaging at least 19.5 g; and female

mice, 17 to 21 g, averaging at least 18.5 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products, Inc., Garfield, N.J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice. The cages were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N.Y.). The feed supplied was presterilized Wayne® Sterilizable Lab Meal containing 4% fat, provided ad libitum in suspended stainless steel hoppers and replenished at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from sipper tubes attached to glass water bottles (Lab Products, Inc.) suspended through the tops of the cages.

The contaminated bedding was disposed of through an enclosed vacuum line that led to a holding tank from which the bedding was fed periodically into an incinerator. The cages were sanitized twice per week and the feed hoppers twice per month at 82 to

88°C in a tunnel-type cagewasher (Industrial Washing Corp., Mataway, N. J.), using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.).

The water bottles were sanitized at 82 to 88°C in a tunnel-type bottle washer (Consolidated Equipment Supply Co., Mercersburg, Pa.) three times per week, using a Calgen Commercial Division detergent (St. Louis, Mo.). The racks for the cages were sanitized at or above 82°C in a rack washer (Consolidated Equipment Supply Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

The air in the animal rooms was regulated automatically at a temperature of 22 to 24°C and a relative humidity of 45 to 55%. Fresh air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake and through a "Z"-type roughing filter of 30% efficiency and a bag system of 90 to 95% efficiency at the exhaust (American Air Filters, Louisville, Ky.; Mine Safety Appliances, Pittsburgh, Pa.) and was not recirculated. The rate of movement allowed 15 changes of room air per hour. The air pressure was maintained negative to a

clean hallway and positive to a return hallway. Fluorescent lighting was provided automatically on a 12-hour-per-day cycle.

Both the control and dosed rats were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 20941-65-5) ethyl tellurac
(CAS 97-77-8) tetraethylthiuram disulfide

Both the control and dosed mice were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 156-62-7) calcium cyanamide
(CAS 999-81-5) (2-chloroethyl) trimethylammonium chloride (CCC)
(CAS 95-80-7) 2,4 diaminotoluene
(CAS 088-96-0) phthalamide
(CAS 120-62-7) piperonyl sulfoxide
(CAS 086-30-6) N-nitrosodiphenylamine
(CAS 137-17-7) 2,4,5-trimethylaniline

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of lead dimethyldithiocarbamate, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats of each sex and five mice of each sex were administered feed containing lead dimethyldithiocarbamate at one of several doses. Groups of five control

animals of each species and sex were administered basal diet only. The period of administration of the test chemical was 7 weeks, followed by 1 week of additional observation.

At the end of the subchronic studies, all animals were killed using CO_2 inhalation and necropsied. The lowest dose at which relevant histopathologic findings were observed in male rats was 62 ppm. The principal changes due to the administration of lead dimethyldithiocarbamate in groups dosed at 500 and 250 ppm were in the kidneys. Moderate (500 ppm) or slight-to-moderate (250 ppm) diffuse hypertrophy of the proximal convoluted tubular epithelium was associated with nuclear swelling. Many enlarged nuclei contained smooth, eosinophilic inclusion bodies of varying sizes. Occasional nuclei contained two to four small round inclusions which were acid-fast when stained by Kinyon's method. Similar inclusions were observed in the group at 125 ppm; however, in the group at 62 ppm, both the number and size of the intranuclear inclusions were greatly diminished and were not seen in groups at lower doses. Rare mitotic figures were observed in the tubular epithelium and mild degenerative changes were sometimes seen. These lesions were considered to be consistent with lead nephropathy.

Less prominent, dose-related changes were present in the blood

and hematopoietic tissues. There was evidence of mild anemia in the groups dosed at 500 and 250 ppm as shown by slight anisocytosis, poikilocytosis, and polychromatophilia in their blood smears. Slight anisocytosis was found in the group dosed at 125 ppm. Very slight to slight increased splenic extramedullary hematopoiesis occurred in one male and two female rats in the group dosed at 500 ppm and in three male and two female rats in the group dosed at 250 ppm. A slight increase in cellularity of femoral bone marrow was detected in the group dosed at 500 ppm and a very slight increase was noted in the group dosed at 250 ppm.

It was concluded that the renal lesions, mild anemia, and lead nephropathy were induced by administration of 250 and 500 ppm lead dimethyldithiocarbamate to rats during the subchronic studies. Similar signs of anemia were slightly detectable in rats given 125 ppm lead dimethyldithiocarbamate; however, lead nephropathy was similar to that observed in the higher dosed groups. Lead nephropathy was minimal at 62 ppm. It was concluded that administration of 62 ppm or more of lead dimethyldithiocarbamate would result in lead nephropathy.

In both male and female mice, the 125 and 250 ppm were the lowest doses at which histopathologic findings were observed. A very

small number of tiny, rounded intranuclear inclusions and rare mitotic figures of the renal tubular epithelium were observed in both males and females. Similar changes were not observed in mice at lower doses. Vacuolar degeneration in the proximal convoluted tubular epithelium of the kidney, which was considered to be lipid accumulation, was found in the male mice. These changes were slight to moderate in the group at 250 ppm, slight in the groups at 62 and 125 ppm, and in only trace amounts in the control group. These changes were considered to be dose related. Very slight to slight hydronephrosis, which was not considered to be dose related was observed in control and dosed male mice. It was concluded that lead nephropathy did not occur in mice given 62 ppm or less lead dimethyldithiocarbamate.

Based on the histopathologic data, the low and high doses for rats and mice were set at 25 and 50 ppm for the chronic studies.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in table 1.

Table 1. Lead Dimethyldithiocarbamate Chronic Feeding Studies in Rats and Mice

Sex and Test Group	Initial No. of Animals (a)	Lead Dimethyldithiocarbamate in Diet (b) (ppm)	Time on Study (weeks)
RATS			
Males			
Matched-Control	20	0	104
Low-Dose	50	25	104
High-Dose	50	50	104
Females			
Matched-Control	20	0	104
Low-Dose	50	25	104
High-Dose	50	50	104
MICE			
Males			
Matched-Control	20	0	105
Low-Dose	50	25	105
High-Dose	50	50	105
Females			
Matched-Control	20	0	105
Low-Dose	50	25	105
High-Dose	50	50	105

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

G. Clinical and Pathologic Examinations

All animals were checked twice daily for deaths. Observations for sick, tumor-bearing, and moribund animals were recorded daily. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and animals that survived to the end of the bioassay were killed using CO_2 and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all observed lesions. The tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum and cerebellum),

and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. 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 appropriate 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 section.

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 dosed animals at each dose level. When results for a number of dosed 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 less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with 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 dosed 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 dosed 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 dosed 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 dosed 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 less than 0.025 one-tailed test when the control incidence is not zero, P less than 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)

Mean body weights of the high-dose male rats were slightly lower than those of the corresponding controls beginning with week 30; the depression in the amount of body weight gained increased in the males during the last 20 weeks of the bioassay and in the females during the last 10 weeks (figure 1). Other clinical signs, such as corneal opacity, tissue masses, and wasting were observed in dosed and control groups of the rats.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered lead dimethyldithiocarbamate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The results of the Tarone tests indicated no significant dose-related trend in mortality in either sex.

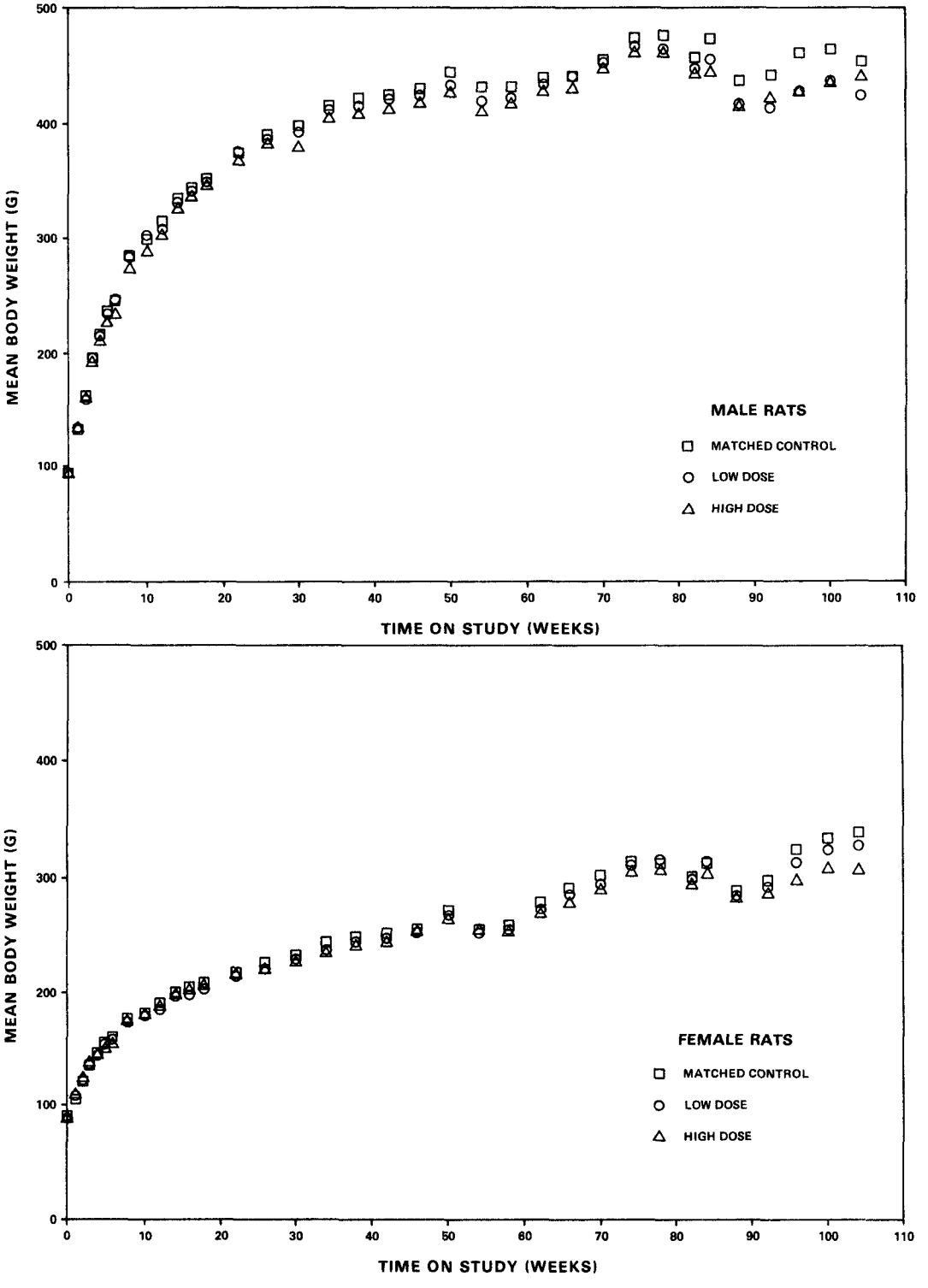


Figure 1. Growth Curves for Rats Administered Lead Dimethyldithiocarbamate in the Diet

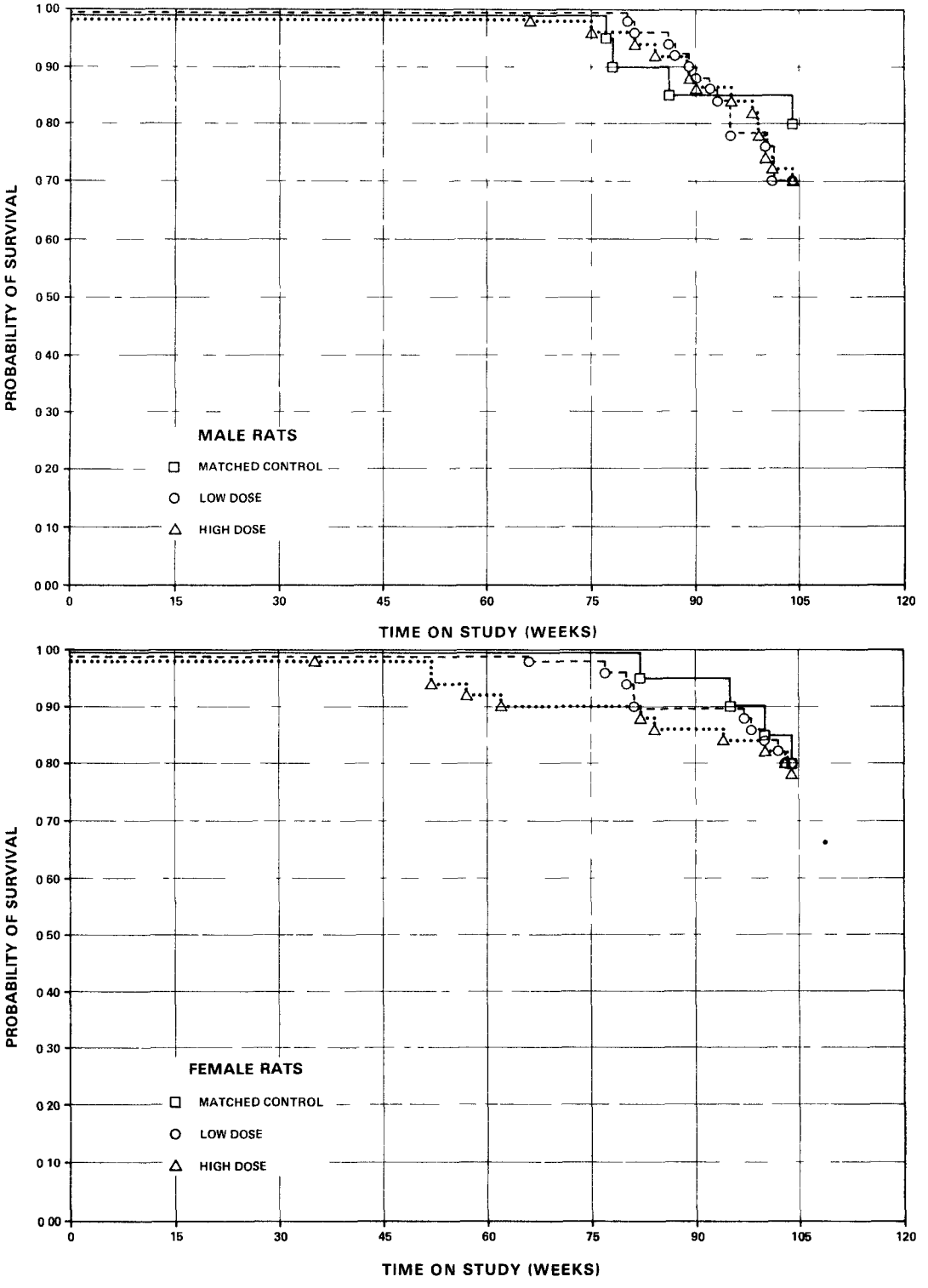


Figure 2. Survival Curves for Rats Administered Lead Dimethyldithiocarbamate in the Diet

In male rats, 35/50 (70%) of the high-dose group, 35/50 (70%) of the low-dose group, and 16/20 (80%) of the control group lived to the end of the bioassay. In females, 39/50 (78%) of the high-dose group, 40/50 (80%) of the low-dose group, and 16/20 (80%) of the control group lived to the end of the bioassay.

Sufficient numbers of rats of each sex were at risk for the 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 commonly seen in aged F344 rats occurred with approximately equal frequency in dosed and control rats. The low incidence, distribution, and nature of these neoplasms are similar, however, to spontaneously occurring neoplasms in aged F344 rats.

Several inflammatory, degenerative, and proliferative lesions commonly seen in aged F344 rats occurred with approximately equal frequency in dosed and control animals. Among the groups receiving lead dimethyldithiocarbamate, only one animal was reported to have renal pelvic epithelial hyperplasia, and no lead inclusions were reported.

Based on the histopathologic examination, administration of lead dimethyldithiocarbamate at the doses used in this bioassay did not induce either neoplastic or nonneoplastic lesions in F344 rats of either sex under conditions of this bioassay.

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 occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for dose-related trend in the incidences of tumors and the results of the Fisher exact test comparing the incidences of tumors in the dosed groups with those in corresponding control groups are not significant in either sex.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive 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 lead dimethyldithiocarbamate, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male mice were essentially the same as those of corresponding controls throughout the bioassay; however, the mean body weights of the dosed females were slightly lower than those of the corresponding controls after week 20 (figure 3). Other clinical signs, such as corneal opacity and tissue masses, were observed in dosed and control groups of the mice.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered lead dimethyldithiocarbomate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. The results of the Tarone tests indicate no significant dose-related trend in mortality in either sex.

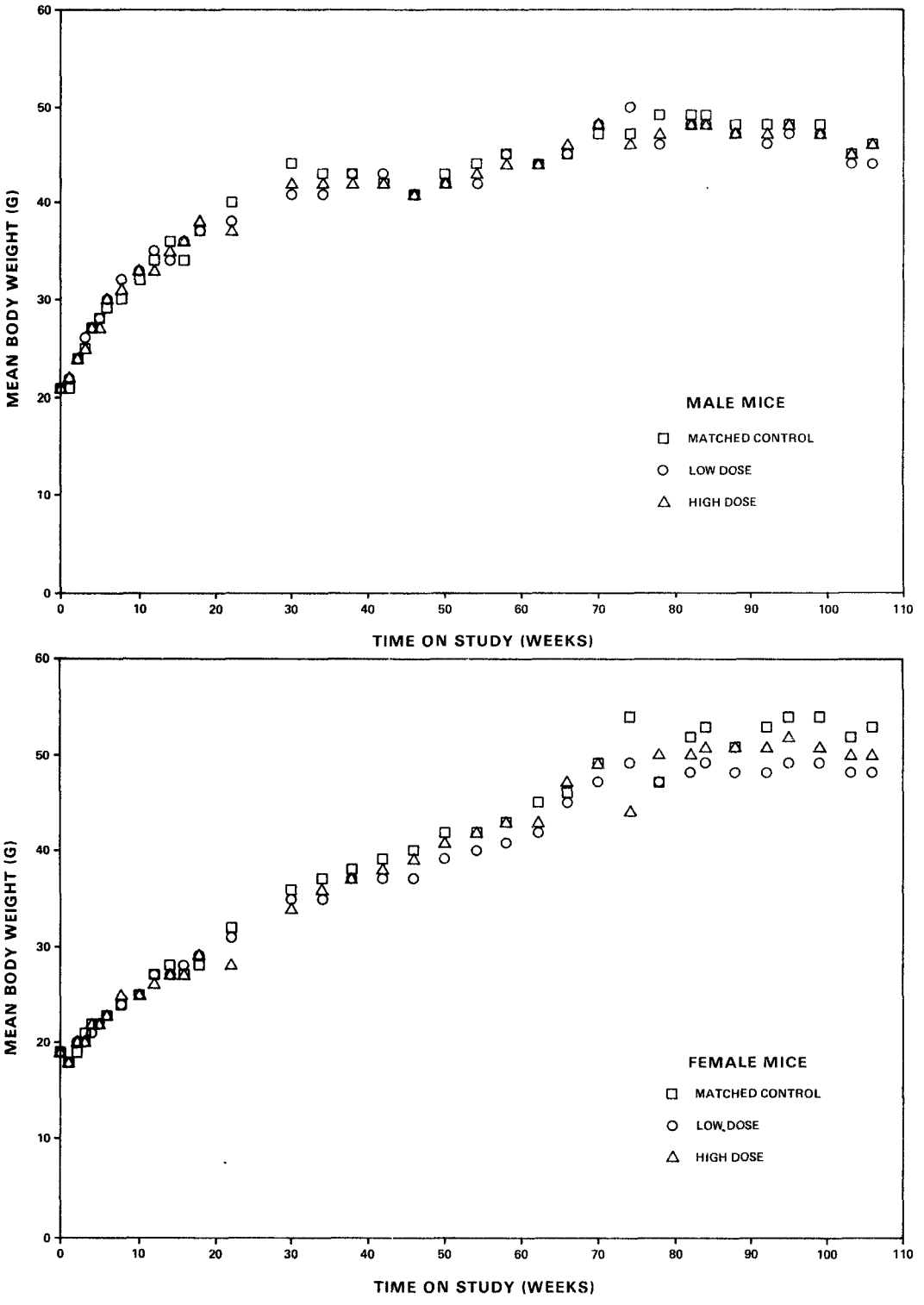


Figure 3. Growth Curves for Mice Administered Lead Dimethyldithiocarbamate in the Diet

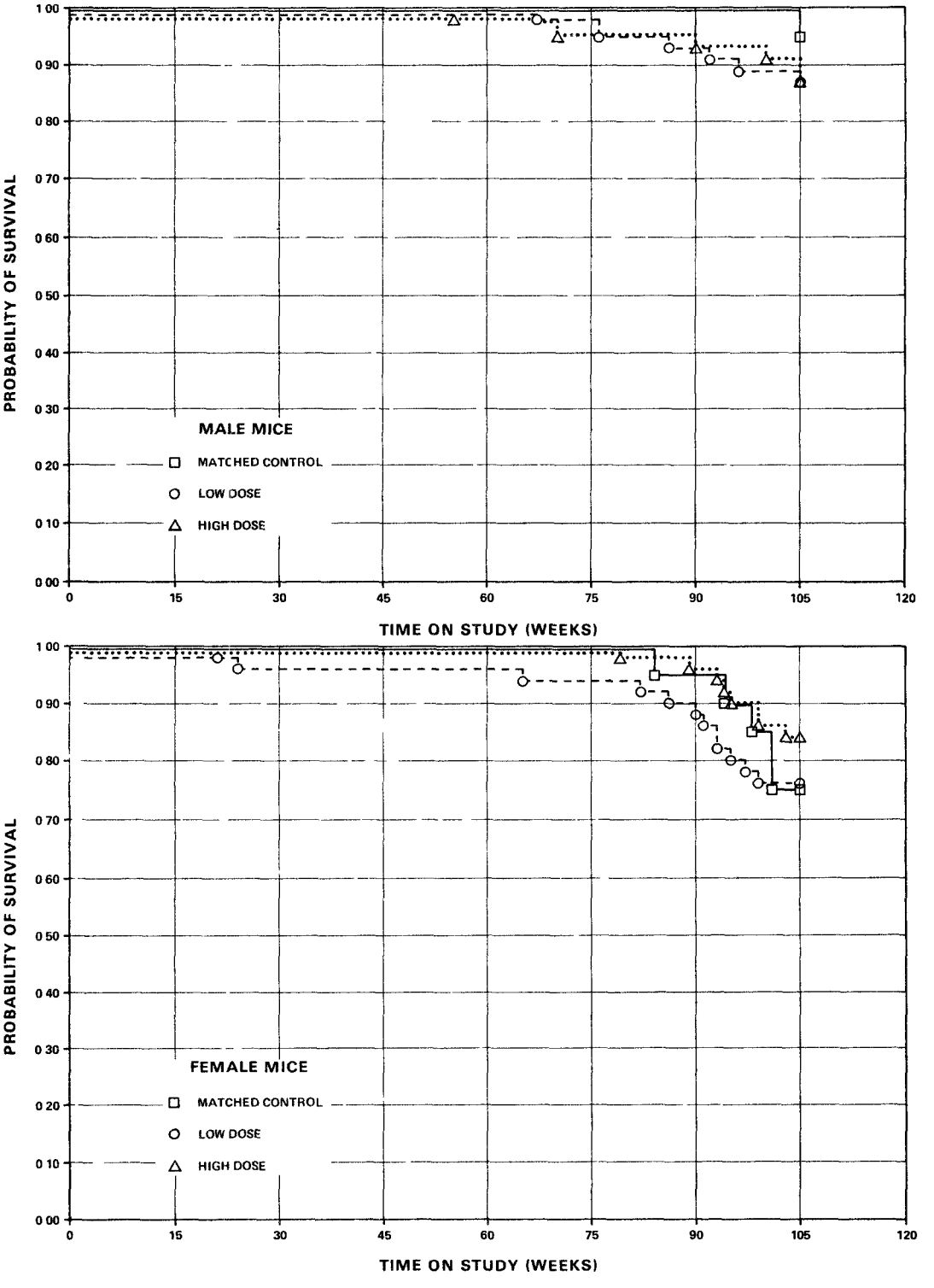


Figure 4. Survival Curves for Mice Administered Lead Dimethyldithiocarbamate in the Diet

In male mice, 43/50 (86%) of the high-dose group, 43/50 (86%) of the low-dose group, and 19/20 (95%) of the control group lived to the end of the bioassay. In females, 42/50 (84%) of the high-dose group, 38/50 (76%) of the low-dose group, and 15/20 (75%) of the control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

A variety of neoplasms commonly seen in aged B6C3F1 mice occurred with approximately equal frequency in dosed and control mice

Other proliferative or neoplastic lesions were of single occurrence or low incidence, with no obvious differences in incidences in dosed and control groups of the mice.

In addition to the proliferative lesions, there were occasional

inflammatory and degenerative lesions commonly seen in aged B6C3F1 mice which occurred with approximately equal frequency in dosed and control animals. Intranuclear inclusion bodies characteristic of lead toxicity were not reported.

Based on the histopathologic examination, there was no evidence that the administration of lead dimethyldithiocarbamate exerted any influence on the incidence of proliferative or other lesions in B6C3F1 mice under the conditions of this bioassay.

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 occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The result of the Cochran-Armitage test for dose-related trend in the incidences of tumors and the results of the Fisher exact test comparing the incidences of tumors in the dosed groups with those in corresponding control groups are not significant in either sex.

In each of the 95% confidence intervals for relative risk, shown

in the tables, the value of one is included; this indicates the absence of significant positive 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 lead dimethyldithiocarbamate, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the high-dose male rats and the dosed female mice were slightly lower than those of the corresponding controls; mean body weights of the dosed female rats and male mice were essentially the same as those of the corresponding controls. Other clinical signs, such as corneal opacity and tissue masses, were observed in both dosed and control groups of rats and mice. Survival rates of both species were unaffected by administration of the test chemical.

The results of the subchronic studies indicated that higher doses could have caused toxicity due to the lead in the test chemical. In the rats, doses of 250 or 500 ppm of the test chemical administered for only 7 weeks caused diffuse hypertrophy of the proximal convoluted tubular epithelium, and the hypertrophy was associated with enlarged nuclei containing eosinophilic inclusion bodies. The occurrence of the nuclear inclusion bodies was observed at doses as low as 62 and 125 ppm. The lesions of the kidney were considered to be consistent with lead nephropathy. In the mice, evidence of lead nephropathy was observed at doses above 62 ppm but not at 62 ppm or below.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups.

In the chronic study the essential absence of toxic signs in the dosed rats and mice at 25 and 50 ppm under the conditions of the bioassay as well as the lack of mortality and weight depression suggests that both species may have been able to tolerate higher doses. Therefore, the studies may not have been conducted using maximum sensitivity for the assessment of the possible carcinogenicity of the test compound. Moreover, in previous tests for tumorigenicity with two different hybrid mice (C57BL/6 x 63H/Anf and C57BL/6 x AKR) (NTIS, 1968; Innes et al., 1969), it was reported that when higher doses of the test chemical were administered, i.e., 46.4 mg/kg body weight by stomach tube for 3 weeks, followed by 130 ppm in the diet for 18 months, an elevated incidence of reticulum-cell sarcoma (P less than 0.01) was observed in the first indicated hybrid mice.

It is concluded that under the conditions of this bioassay, lead dimethyldithiocarbamate was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
UNDIFFERENTIATED CARCINOMA	1 (5%)		
ADENOCARCINOMA, NOS			1 (2%)
SARCOMA, NOS		1 (2%)	
FIBROMA		1 (2%)	2 (4%)
FIBROSARCOMA		1 (2%)	2 (4%)
LIPOMA	1 (5%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	5 (10%)	5 (10%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)	6 (12%)	7 (14%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	6 (30%)	9 (18%)	5 (10%)
MAST-CELL LEUKEMIA			1 (2%)
#SPLEEN	(19)	(50)	(50)
FIBROMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA			1 (2%)
#LARGE INTESTINE	(20)	(33)	(43)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY/PELVIS	(20)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
ADENOMA, NOS	7 (35%)	16 (33%)	9 (18%)
#ADRENAL	(20)	(50)	(50)
CORTICAL ADENOMA		2 (4%)	1 (2%)
PHEOCHROMOCYTOMA	3 (15%)	11 (22%)	8 (16%)
#THYROID	(20)	(49)	(50)
FOLLICULAR-CELL CARCINOMA	1 (5%)		1 (2%)
C-CELL ADENOMA	1 (5%)	3 (6%)	6 (12%)
C-CELL CARCINOMA		2 (4%)	1 (2%)
#PANCREATIC ISLETS	(18)	(50)	(47)
ISLET-CELL ADENOMA	1 (6%)	3 (6%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA		1 (2%)	
#PROSTATE	(16)	(49)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#TESTIS	(20)	(49)	(50)
INTERSTITIAL-CELL TUMOR	16 (80%)	40 (82%)	37 (74%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
MENINGIOMA			1 (2%)
#BRAIN	(20)	(50)	(50)
GLIOMA, NOS		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS	(20)	(50)	(50)
FIBROMA		1 (2%)	
MESOTHELIOMA, NOS	1 (5%)	2 (4%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
SARCOMA, NOS			1 (2%)
MESOTHELIOMA, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	9	13
MORIBUND SACRIFICE	1	6	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	35	35
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	49	47
TOTAL PRIMARY TUMORS	42	108	96
TOTAL ANIMALS WITH BENIGN TUMORS	18	49	44
TOTAL BENIGN TUMORS	31	84	74
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	21	18
TOTAL MALIGNANT TUMORS	10	21	22
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	
TOTAL UNCERTAIN TUMORS	1	3	
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 ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
SARCOMA, NOS			1 (2%)
LIPOMA	1 (5%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	4 (8%)	3 (6%)
PHEOCHROMOCYTOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	5 (10%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		7 (14%)	5 (10%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
NEOPLASTIC NODULE	1 (5%)		1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
URINAPY SYSTEM			
#UPINARY BLADDEP	(20)	(49)	(49)
TRANSITIONAL-CELL CARCINOMA	1 (5%)		
LEIOMYOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITAPY	(19)	(50)	(48)
ADENOMA, NOS	4 (21%)	13 (26%)	17 (35%)
#ADPENAL	(20)	(50)	(50)
COPTICAL ADENOMA	1 (5%)		
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (5%)		
#THYROID	(20)	(50)	(48)
C-CELL ADENOMA		4 (8%)	4 (8%)
C-CELL CAPCINOMA		1 (2%)	1 (2%)
#PANCPEATIC ISLETS	(20)	(50)	(49)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCAPCINOMA, NOS		2 (4%)	
FIBROADENOMA	6 (30%)	8 (16%)	6 (12%)
*CLITORAL GLAND	(20)	(50)	(50)
ADENOMA, NOS			2 (4%)
*VAGINA	(20)	(50)	(50)
ANGIOSARCOMA		1 (2%)	
#UTEPUS	(20)	(50)	(49)
ENDOMETRIAL STROMAL POLYP	4 (20%)	7 (14%)	5 (10%)
#OVARY	(20)	(50)	(50)
GRANULOSA-CELL TUMOR	1 (5%)	1 (2%)	
NERVOUS SYSTEM			
#BPAIN	(20)	(50)	(49)
GLIOMA, NOS			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	6	10
MORIBUND SACRIFICE		4	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	40	39
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	33	36
TOTAL PRIMARY TUMORS	22	55	54
TOTAL ANIMALS WITH BENIGN TUMORS	12	29	26
TOTAL BENIGN TUMORS	17	39	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	14	13
TOTAL MALIGNANT TUMORS	3	15	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	1	1
TOTAL UNCERTAIN TUMORS	2	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADIMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(48)	(49)
CARCINOMA, NOS, METASTATIC		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (20%)	4 (8%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (25%)	10 (21%)	12 (24%)
HEMANGIOSARCOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	2 (4%)
*BLOOD	(20)	(49)	(49)
LEUKEMIA,NOS			1 (2%)
#BONE MARROW	(20)	(48)	(49)
CARCINOMA, NOS, METASTATIC		1 (2%)	
HEMANGIOSARCOMA	1 (5%)		
#SPLEEN	(20)	(47)	(47)
HEMANGIOMA		3 (6%)	1 (2%)
HEMANGIOSARCOMA	1 (5%)	2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(20)	(48)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#LIVER	(20)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#SMALL INTESTINE	(20)	(47)	(48)
MALIGNANT LYMPHOMA, NOS	1 (5%)	3 (6%)	
#THYMUS	(17)	(43)	(43)
HEMANGIOMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(49)
CARCINOMA, NOS, METASTATIC		1 (2%)	
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEPATOCELLULAR ADENOMA	1 (5%)	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	3 (15%)	10 (20%)	6 (12%)
#PANCREAS	(20)	(48)	(45)
CARCINOMA,NOS		2 (4%)	
#SMALL INTESTINE	(20)	(47)	(48)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(20)	(48)	(45)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
GLIOMA, NOS		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(49)	(49)
ADENOMA, NOS	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(49)	(49)
LIPOMA			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(49)
SARCOMA, NOS			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	6	6
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	43	43
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	32	28
TOTAL PRIMARY TUMORS	18	39	35
TOTAL ANIMALS WITH BENIGN TUMORS	6	7	8
TOTAL BENIGN TUMORS	6	8	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	27	23
TOTAL MALIGNANT TUMORS	12	31	27
TOTAL ANIMALS WITH SECONDARY TUMORS#		3	
TOTAL SECONDARY TUMORS		5	
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 FEMALE MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
FIBROSARCOMA	1 (5%)		
HEMANGIOSARCOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
HEMANGIOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
CARCINOMA, NOS, METASTATIC	1 (5%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)	11 (22%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MAST-CELL TUMOR	1 (5%)		
#SPLEEN	(20)	(50)	(50)
HEMANGIOMA			2 (4%)
HEMANGIOSARCOMA			1 (2%)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(20)	(47)	(49)
MALIGNANT LYMPHOMA, NOS			2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SMALL INTESTINE	(19)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(41)	(48)
ADENOMA, NOS	1 (5%)		
#ADRENAL	(20)	(48)	(50)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(20)	(46)	(49)
FOLLICULAR-CELL ADENOMA	1 (5%)		2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
CARCINOMA,NOS	1 (5%)		
ADENOMA, NOS			2 (4%)
CYSTADENOMA, NOS			1 (2%)
#UTERUS	(20)	(49)	(50)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA			1 (2%)
NERVOUS SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
NEUROFIBROSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	11	8
MORIBUND SACRIFICE	2	1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	38	42
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	18	18
TOTAL PRIMARY TUMORS	11	22	24
TOTAL ANIMALS WITH BENIGN TUMORS	4	3	10
TOTAL BENIGN TUMORS	5	3	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	17	10
TOTAL MALIGNANT TUMORS	5	19	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
BRONCHOPNEUMONIA, NOS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(50)	(50)
HYPERPLASTIC NODULE		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS			1 (2%)
#MANDIBULAR L. NODE	(20)	(50)	(50)
LYMPHANGIECTASIS	1 (5%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(20)	(50)	(50)
LYMPHANGIECTASIS	1 (5%)	2 (4%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
FIBROSIS	2 (10%)	12 (24%)	5 (10%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
METAMORPHOSIS FATTY	1 (5%)	1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CYTOPLASMIC VACUOLIZATION			1 (2%)
FOCAL CELLULAR CHANGE		2 (4%)	8 (16%)
HEPATOCYTOMEGALY			2 (4%)
ANGIECTASIS			1 (2%)
#BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	3 (15%)	10 (20%)	13 (26%)
#PANCREATIC ACINUS	(18)	(50)	(47)
ATROPHY, NOS		8 (16%)	4 (9%)
#STOMACH	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)	5 (10%)	1 (2%)
ULCER, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS			1 (2%)
INFLAMMATION, CHRONIC	17 (85%)	42 (84%)	44 (88%)
#KIDNEY/CORTEX	(20)	(50)	(50)
CYST, NOS			1 (2%)
#KIDNEY/PELVIS	(20)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(17)	(49)	(48)
CAST, NOS		3 (6%)	1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(49)
CYST, NOS			3 (6%)
ANGIECTASIS		2 (4%)	1 (2%)
#ADRENAL CORTEX	(20)	(50)	(50)
CYST, NOS	1 (5%)		
LIPOIDOSIS		1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	5 (10%)
#ADRENAL MEDULLA	(20)	(50)	(50)
HYPERPLASIA, NOS		3 (6%)	3 (6%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(20)	(49)	(50)
FOLLICULAR CYST, NOS			2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	3 (15%)	2 (4%)	12 (24%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
REPRODUCTIVE SYSTEM			
#PROSTATE	(16)	(49)	(50)
INFLAMMATION, ACUTE	3 (19%)	8 (16%)	3 (6%)
#TESTIS	(20)	(49)	(50)
ATROPHY, NOS	1 (5%)		1 (2%)
ASPERMATOGENESIS		2 (4%)	
*EPIDIDYMIS	(20)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
HEMORRHAGE	1 (5%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
HEMOSIDEROSIS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ADIPOSE TISSUE			
STEATITIS	1	2	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
PNEUMONIA, ASPIRATION	1 (5%)		
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(50)	(50)
HEMOSIDEROSIS		2 (4%)	3 (6%)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
HEMATOPOIESIS		1 (2%)	1 (2%)
#SPLENIC CAPSULE	(20)	(50)	(50)
GRANULATION, TISSUE		1 (2%)	
#MANDIBULAR L. NODE	(20)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
FIBROSIS		1 (2%)	
PERIARTERITIS	1 (5%)		
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, FOCAL	1 (5%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS		1 (2%)	2 (4%)
#ENDOCARDIUM	(20)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
NECROSIS, NOS		3 (6%)	1 (2%)
NECROSIS, FOCAL	1 (5%)		
METAMORPHOSIS FATTY		1 (2%)	
FOCAL CELLULAR CHANGE	7 (35%)	21 (42%)	4 (8%)
#HEPATIC CAPSULE	(20)	(50)	(50)
FIBROSIS, FOCAL	1 (5%)		
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
DEGENERATION, NOS	1 (5%)	1 (2%)	2 (4%)
#BILE DUCT	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)	1 (2%)	
HYPERPLASIA, NOS		6 (12%)	2 (4%)
#PANCREAS	(20)	(50)	(49)
FIBROSIS, FOCAL		1 (2%)	
#PANCREATIC ACINUS	(20)	(50)	(49)
ATROPHY, NOS		9 (18%)	7 (14%)
#STOMACH	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
#PEYERS PATCH	(20)	(50)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#SMALL INTEST./SEROSA	(20)	(50)	(48)
GRANULATION, TISSUE		1 (2%)	
#LARGE INTESTINE	(12)	(45)	(45)
NEMATODIASIS	1 (8%)	1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
MINERALIZATION		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYDRONEPHROSIS		1 (2%)	
INFLAMMATION, CHRONIC	11 (55%)	24 (48%)	16 (32%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
CALCIFICATION, NOS			2 (4%)
#KIDNEY/PELVIS	(20)	(50)	(50)
NECROSIS, NOS		1 (2%)	
#URINARY BLADDER	(20)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(50)	(48)
CYST, NOS	1 (5%)	5 (10%)	3 (6%)
ANGIECTASIS	4 (21%)	4 (8%)	4 (8%)
#ADRENAL	(20)	(50)	(50)
ANGIECTASIS	1 (5%)		
#ADRENAL CORTEX	(20)	(50)	(50)
LIPOIDOSIS		1 (2%)	1 (2%)
HYPERPLASIA, NOS	3 (15%)	9 (18%)	10 (20%)
#ADRENAL MEDULLA	(20)	(50)	(50)
HYPERPLASIA, NOS		2 (4%)	
#THYROID	(20)	(50)	(48)
FOLLICULAR CYST, NOS			3 (6%)
HYPERPLASIA, C-CELL	10 (50%)	12 (24%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS	4 (20%)	3 (6%)	3 (6%)
#UTERUS	(20)	(50)	(49)
DECIDUA		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(50)	(49)
CYST, NOS	1 (5%)	2 (4%)	1 (2%)
#OVARY	(20)	(50)	(50)
CYST, NOS	1 (5%)	2 (4%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FOLLICULAR CYST, NOS			1 (2%)
CORPUS LUTEUM CYST		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT	1 (5%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	4

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(49)
ABSCESS, NOS		1 (2%)	
*SUBCUT TISSUE	(20)	(49)	(49)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(48)	(49)
HEMORRHAGE		2 (4%)	
ALVEOLAR MACROPHAGES		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(47)	(47)
HEMORRHAGIC CYST	1 (5%)		
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	6 (13%)	1 (2%)
HEMATOPOIESIS	1 (5%)		
#MESENTERIC L. NODE	(20)	(48)	(47)
CYST, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#THYMUS	(17)	(43)	(43)
ATROPHY, NOS	1 (6%)		
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(48)	(49)
PERIARTERITIS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(20)	(48)	(49)
INFLAMMATION, FOCAL	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)		
NECROSIS, FOCAL		1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	2 (10%)		2 (4%)
BASOPHILIC CYTO CHANGE		2 (4%)	
#LIVER/HEPATOCYTES	(20)	(49)	(49)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#STOMACH	(20)	(49)	(49)
INFLAMMATION, FOCAL		1 (2%)	
#SMALL INTESTINE	(20)	(47)	(48)
POLYPOID HYPERPLASIA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(49)
HYDRONEPHROSIS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(45)	(45)
CYST, NOS	1 (5%)		1 (2%)
#THYROID	(19)	(48)	(49)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS	1 (5%)		3 (6%)
#PANCREATIC ISLETS	(20)	(48)	(45)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(49)
HYPERPLASIA, CYSTIC			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(20)	(48)	(49)
ATROPHY, NOS		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
MINERALIZATION	7 (35%)	20 (41%)	17 (35%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*LUMBAR VERTEBRA	(20)	(49)	(49)
SPONDYLOLISTHESIS		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	5	8
ANIMAL MISSING/NO NECROPSY		1	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (15%)	2 (4%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(50)	(50)
LEUKOPENIA, NOS			1 (2%)
#SPLEEN	(20)	(50)	(50)
ECTOPIA		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (10%)	1 (2%)	4 (8%)
HEMATOPOIESIS	7 (35%)	1 (2%)	1 (2%)
#MANDIBULAR L. NODE	(20)	(47)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(20)	(47)	(49)
INFLAMMATION, GRANULOMATOUS	1 (5%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(19)	(44)	(47)
LIPOIDOSIS	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, FOCAL	1 (5%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(18)	(46)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (6%)		
#LIVER	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	3 (6%)
NECROSIS, FOCAL	1 (5%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	
HEPATOCYTOMEGALY			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS	1 (5%)		2 (4%)
#LIVER/HEPATOCYTES	(20)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
#BILE DUCT	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
#PANCREAS	(20)	(45)	(49)
CYST, NOS			1 (2%)
CYSTIC DUCTS	1 (5%)		
INFLAMMATION, GRANULOMATOUS	1 (5%)		
#STOMACH	(20)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (5%)	1 (2%)	1 (2%)
#SMALL INTESTINE	(19)	(50)	(50)
POLYPOID HYPERPLASIA		1 (2%)	
#LARGE INTESTINE	(19)	(49)	(50)
PERIARTERITIS	1 (5%)		
HYPERPLASIA, LYMPHOID			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS			2 (4%)
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)	4 (8%)	6 (12%)
PERIARTERITIS	1 (5%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFARCT, NOS		1 (2%)	
AMYLOIDOSIS		1 (2%)	
#URINARY BLADDER	(17)	(47)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (4%)
PERIARTERITIS	1 (6%)		
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(48)	(50)
CYST, NOS			1 (2%)
#ADRENAL CORTEX	(20)	(48)	(50)
HYPERPLASIA, NOS	1 (5%)		
#THYROID	(20)	(46)	(49)
FOLLICULAR CYST, NOS	1 (5%)	4 (9%)	4 (8%)
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(20)	(49)	(50)
CYST, NOS	11 (55%)	23 (47%)	22 (44%)
#OVARY	(19)	(47)	(49)
CYST, NOS	7 (37%)	9 (19%)	10 (20%)
NERVOUS SYSTEM			
#BRAIN	(20)	(47)	(50)
MINERALIZATION	8 (40%)	18 (38%)	18 (36%)
PERIARTERITIS	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PLEURA	(20)	(50)	(50)
INFLAMMATION, FOCAL	1 (5%)	1 (2%)	
*MESENTERY	(20)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		6	4
AUTO/NECROPSY/HISTO PERF		1	1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma(b)	2/20 (10)	5/50 (10)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	1.000
Lower Limit		0.184	0.184
Upper Limit		10.007	10.007
Weeks to First Observed Tumor	104	104	104
Hematopoietic System: Lymphomas (b)	8/20 (40)	15/50 (30)	12/50 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.750	0.600
Lower Limit		0.373	0.280
Upper Limit		1.765	1.471
Weeks to First Observed Tumor	77	87	89

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas or Leukemias (b)	8/20 (40)	15/50 (30)	13/50 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.750	0.650
Lower Limit		0.373	0.311
Upper Limit		1.765	1.570
Weeks to First Observed Tumor	77	87	89
Pituitary: Adenomas, NOS (b)	7/20 (35)	16/49 (33)	9/49 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.933	0.525
Lower Limit		0.448	0.211
Upper Limit		2.331	1.464
Weeks to First Observed Tumor	104	89	99

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	3/20 (15)	11/50 (22)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.467	1.067
Lower Limit		0.450	0.295
Upper Limit		7.594	5.813
Weeks to First Observed Tumor	104	81	66
Thyroid: C-Cell Adenoma or Carcinoma (b)	1/20 (5)	5/49 (10)	7/50 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.041	2.800
Lower Limit		0.254	0.403
Upper Limit		94.440	123.407
Weeks to First Observed Tumor	104	95	85

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-Cell Adenoma (b)	1/18 (6)	3/50 (6)	2/47 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.080	0.766
Lower Limit		0.096	0.043
Upper Limit		55.565	44.252
Weeks to First Observed Tumor	104	104	104
Testis: Interstitial-Cell Tumor (b)	16/20 (80)	40/49 (82)	37/50 (74)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.020	0.925
Lower Limit		0.813	0.732
Upper Limit		1.419	1.334
Weeks to First Observed Tumor	77	80	89

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

(a) Dosed groups received 25 or 50 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P less than 0.05; otherwise, not significant (N.S.) is indicated.

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	1/20 (5)	4/50 (8)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.600	1.200
Lower Limit		0.175	0.106
Upper Limit		77.169	61.724
Weeks to First Observed Tumor	104	104	104
Pituitary: Adenoma, NOS (b)	4/19 (21)	13/50 (26)	17/48 (35)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.235	1.682
Lower Limit		0.454	0.658
Upper Limit		4.716	6.170
Weeks to First Observed Tumor	104	81	82

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: All Lymphomas (b)	1/20 (5)	8/50 (16)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.200	4.000
Lower Limit		0.482	0.642
Upper Limit		138.771	169.457
Weeks to First Observed Tumor	99	77	35
Thyroid: C-Cell Adenoma or Carcinoma (b)	0/20 (0)	5/50 (10)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.525	0.547
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	94

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	6/20 (30)	8/50 (16)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.533	0.400
Lower Limit		0.194	0.126
Upper Limit		1.669	1.345
Weeks to First Observed Tumor	82	100	104
Uterus: Endometrial Stromal Polyp (b)	4/20 (20)	7/50 (14)	5/49 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.700	0.510
Lower Limit		0.207	0.126
Upper Limit		2.994	2.367
Weeks to First Observed Tumor	82	80	104

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

(a) Dosed groups received 25 or 50 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P less than 0.05; otherwise, not significant (N.S.) is indicated.

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED LEAD DIMETHYLDITHIOCARBAMATE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	5/20 (25)	10/48 (21)	12/49 (24)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.833	0.980
Lower Limit		0.309	0.384
Upper Limit		2.794	3.184
Weeks to First Observed Tumor	105	86	105
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	9/20 (45)	14/48 (29)	15/49 (49)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.648	0.680
Lower Limit		0.331	0.354
Upper Limit		1.451	1.506
Weeks to First Observed Tumor	105	86	105

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas or Leukemias (b)	2/20 (10)	5/49 (10)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.020	0.816
Lower Limit		0.188	0.131
Upper Limit		10.204	8.603
Weeks to First Observed Tumor	105	105	90
All Sites: Hemangioma (b)	0/20 (0)	3/49 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.255	0.125
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma or Hemangiosarcoma (b)	1/20 (5)	5/49 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.041	1.224
Lower Limit		0.254	0.108
Upper Limit		94.440	62.958
Weeks to First Observed Tumor	105	76	100
Liver: Hepatocellular Carcinoma (b)	3/20 (15)	10/49 (20)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.361	0.816
Lower Limit		0.406	0.199
Upper Limit		7.138	4.706
Weeks to First Observed Tumor	105	67	55

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	4/20 (20)	11/49 (22)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.122	0.714
Lower Limit		0.392	0.211
Upper Limit		4.404	3.052
Weeks to First Observed Tumor	105	67	55

(a) Dosed groups received 25 or 50 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P less than 0.05; otherwise, not significant (N.S.) is indicated.

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/20 (5)	3/50 (6)	3/50 (6)
P Values (c,d)	N. S.	N.S.	N.S.
Relative Risk (f)		1.200	1.200
Lower Limit		0.106	0.106
Upper Limit		61.724	61.724
Weeks to First Observed Tumor	105	99	105
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	3/20 (15)	4/50 (8)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.533	0.667
Lower Limit		0.102	0.147
Upper Limit		3.410	4.014
Weeks to First Observed Tumor	105	99	95

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphomas (b)	2/20 (10)	13/50 (26)	7/50 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.600	1.400
Lower Limit		0.677	0.303
Upper Limit		22.444	13.138
Weeks to First Observed Tumor	94	24	99
All Sites: Hemangioma (b)	1/20 (5)	0/50 (0)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	1.200
Lower Limit		0.000	0.106
Upper Limit		7.475	61.724
Weeks to First Observed Tumor	105	--	78

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Lead Dimethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma or Hemangiosarcoma (b)	1/20 (5)	1/50 (2)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.400	1.600
Lower Limit		0.005	0.175
Upper Limit		30.802	77.169
Weeks to First Observed Tumor	105	105	78

(a) Dosed groups received 25 or 50 ppm.

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

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P less than 0.05; otherwise, not significant (N.S.) is indicated.

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

(e) The probability level for departure from linear trend is given when P less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

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

December 13, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute on the 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, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Lead Dimethyldithiocarbamate.

The reviewer for the report on the bioassay of Lead Dimethyldithiocarbamate agreed with the conclusion in the report that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that there were no highlights worth noting. He opined that maximum tolerated doses (MTD) may not have been tested, since there were no chronic signs of toxicity. Also an earlier study had reported using much higher dose levels. Based on the results of the study, he said that there was no evidence that Lead Dimethyldithiocarbamate posed a carcinogenic hazard to man.

One Subgroup member wondered if the compound dissociated such that the lead component itself would be available to induce tumors. A discussion ensued as to whether the treated animals exhibited any of the biological effects usually associated with lead.

There was no objection to the reviewer's motion that 1) the report on the bioassay of Lead Dimethyldithiocarbamate be accepted as written and 2) the compound be considered for retest since the MTD may not have been attained in the chronic study.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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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 the review may no longer be appropriate.

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