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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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Mar 22, 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Malathion Reregistration; Reregistration Case No. 0248; Review of Carcinogenicity Study in Mice, Guideline 83-2(b). **6(a)(2) Issue.**

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Case 818961
Submission S475557

Tox. Chem. No. 535
PC Code No. 057701
MRID No. 434072-01

FROM: Edwin R. Budd, Toxicologist
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THRU: Karen Hamernik, Ph.D., Section Head
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K. Hamernik 2/10/95

THRU: Karl Baetcke, Ph.D., Chief
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Karl Baetcke 2/27/95

Please find attached the Data Evaluation Report (DER) for a carcinogenicity study in mice using malathion as the test material (MRID No. 434072-01). The study was sponsored by Cheminova Agro A/S (Lemvig, Denmark) and performed by International Research and Development Corporation (IRDC; Mattawan, Michigan). The study was submitted to EPA on October 13, 1994 by Jellinek, Schwartz & Connolly, Inc. (Arlington, Virginia), the authorized representative of Cheminova Agro A/S.

Treatment-related increased incidences of hepatocellular tumors were observed in the male and female mice in this study.

It is anticipated that it will be necessary to present the findings in this study to the HED Carcinogenicity Peer Review Committee for discussion and classification of the carcinogenic potential of malathion. The results of this evaluation process will be forwarded to you in a separate memorandum when they are available. Statistical analyses of the liver tumor data in this study will also be provided to you by the Science Analysis Branch, HED in a separate report. It cannot be determined at this time whether the RfD for malathion will be affected.

The HED Carcinogenicity Peer Review Committee will also be asked to specifically address the issue of how to interpret the increased numbers of hepatocellular tumors observed in the male mice in this study at 100 ppm as compared to the lower numbers of hepatocellular tumors observed at 800 ppm. See below for more information.

EXECUTIVE SUMMARY:

In an 18-month carcinogenicity study, technical grade malathion (96.4% pure) was administered in the diet to groups of 65 male and 65 female B6C3F1 BR strain mice at dose levels of 0 (control), 100 ppm, 800 ppm, 8000 ppm or 16000 ppm (equivalent to 0, 17.4, 143, 1476 or 2978 mg/kg/day in males and to 0, 20.8, 167, 1707 or 3448 mg/kg/day in females). Ten mice/sex/group were sacrificed at 12 months and the remaining survivors were sacrificed at 18 months. Mortality, clinical signs of toxicity, body weights and food consumption were monitored at appropriate times during the study. Hematological examinations and determinations of plasma, erythrocyte and brain cholinesterase activity levels were made on 8-10 mice/sex/group at 9 (erythrocyte cholinesterase only), 12 and 18 months. Necropsy examinations were performed on all animals and organ weight determinations were made on all animals at the 12-month interim and 18-month terminal sacrifices. Histopathological examinations were made on a complete set of organs/tissues from all animals that died or were sacrificed in extremis during the study and on all control and 16000 ppm animals at the 12 month and 18 month scheduled sacrifices. Histopathological examinations were also performed on a more limited set of organs/tissues from the other dose level groups at the scheduled sacrifices.

At 16000 ppm and 8000 ppm in both males and females, treatment related effects included decreased absolute body weights throughout the entire duration of the study (14.3-20.0% decrease in males and 9.7-16.1% decrease in females at 18 months), decreased food consumption (2.0-5.9% in males and 5.4-12.5% in females), decreased plasma cholinesterase activity levels at 12 and 18 months ($\geq$ 86%), decreased erythrocyte cholinesterase activity levels at 9, 12 and 18 months ($\geq$ 61%) and decreased brain cholinesteraase activity levels at 18 months (37-43%) at 16000 ppm only. Mortality rates, clinical signs of

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toxicity and hematological parameters were not affected by treatment with malathion at any dose.

A treatment-related increased incidence of hepatocellular tumors was observed in both male and female mice in this study at 8000 ppm and 16000 ppm. For male mice which died during the final 6 months of the study or were killed at the terminal sacrifice at 18 months, the percent incidences of hepatocellular adenomas were 1.9%, 7.3%, 3.6%, 21.8% and 94.1%; of hepatocellular carcinomas were 0.0%, 10.9%, 5.5%, 10.9% and 2.0%; and of combined hepatocellular adenomas/carcinomas were 1.9%, 18.2%, 9.1%, 32.7% and 96.1% for the 0 (control), 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For female mice which died during the final 6 months of the study or were killed at the terminal sacrifice at 18 months, the percent incidences of hepatocellular adenomas were 0.0%, 1.8%, 0.0%, 17.0% and 80.8%; of hepatocellular carcinomas were 1.8%, 0.0%, 3.7%, 1.9% and 3.8%; and of combined hepatocellular adenomas/carcinomas were 1.8%, 1.8%, 3.7%, 18.9% and 84.6% for the 0 (control), 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

The dose-related increases in hepatocellular adenomas and in combined adenomas/carcinomas at 8000 ppm and 16000 ppm in both males and females were attributed to treatment with malathion. Although some hepatocellular carcinomas were also observed in nearly all of the malathion treated groups, the incidences were not dose-related and overall the relationship of these carcinomas to treatment with malathion was equivocal. The increased numbers of hepatocellular tumors observed in this study in both males and females were due primarily to increased numbers of adenomas.

Regarding the male mice in this study, more hepatocellular tumors (adenomas, carcinomas and combined adenomas/carcinomas) were observed at 100 ppm than at 800 ppm. Thus, a dose-related response was not observed at the lower dose levels of 100 ppm and 800 ppm, whereas a dose-related response was observed at the higher dose levels of 8000 ppm and 16000 ppm. How to interpret the increased numbers of hepatocellular tumors at 100 ppm, but not at 800 ppm, for the male mice in this study is not clear at this time.

The increased tumor incidences in the livers of both males and females at 16000 ppm and 8000 ppm were accompanied by concurrent observations of masses, nodules and foci in the livers of these animals at the terminal sacrifice and also by increased liver weights and highly increased incidences of hepatocellular hypertrophy in the livers at 12 and 18 months. The data for hepatocyte hypertrophy was quite remarkable in that an extremely steep dose-response curve was observed for both males and females in this study. Thus, in the control, 100 ppm and 800 ppm groups, no case of hepatocellular hypertrophy was observed in any animal at any time during the entire duration of this study whereas at

8000 ppm and 16000 ppm, a ≥ 50% incidence was observed at 12 months and a 100% incidence at 18 months.

Other findings were observed in this study that appeared to be related to treatment, but their biological significance was uncertain. These findings included the following: decreased vacuolation in the convoluted tubules of the kidneys in males; increased mineralization of the kidneys in females; decreased fibrous osteodystrophy of the femur and sternum in females; and early disappearance of the "x zone" in the the adrenal cortex of females.

The NOEL for cholinesterase inhibition for both sexes was estimated to be 100 ppm for plasma and erythrocyte cholinesterase and 8000 ppm for brain cholinesterase. Although there was some decrease in cholinesterase activity at these doses, the decreases were not statisticaly significant and the data were considered to be too variable to conclude that the inhibition seen was really related to treatment. Cholinesterase activities were assayed using a Boehringer Mannheim Diagnostics kit and a Technicon AutoAnalyzer I. The NOEL for systemic effects was 800 ppm. The LEL was 8000 ppm, based on decreased body weights and food consumption in males and females, increased liver weight in males and females and increased hepatocellular hypertrophy in males and females. The biological significance of the decreased vacuolization of convoluted tubules in the kidney in males, increased mineralization of the kidney in females, decreased fibrous osteodystrophy in females and early disappearance of the "x zone" of the adrenal cortex in females at this and other doses is uncertain.

This study is classified as Core Guideline and satisfies the guideline requirement for a carcinogenicity study in mice, Guideline 83-2(b).

NOTE--The 2 highest dose levels used in this study, 16000 ppm (equivalent to 2978 mg/kg/day in males and 3448 mg/kg/day in females) and 8000 ppm (equivalent to 1476 mg/kg/day in males and 1707 mg/kg/day in females), both exceeded the limit dose of 1000 mg/kg/day which is oftentimes used by EPA to establish an upper dose level for carcinogenicity studies in mice and rats. In this instance, however, EPA required that the highest dose levels in this particular study be 16000 ppm and 8000 ppm in order to duplicate the dose levels used in a previously conducted 1978 National Cancer Institute (NCI) carcinogenicity study in B6C3F1 mice in which the results were equivocal.

Reviewed by: Edwin R. Budd, M.A.
Review Section III, Toxicology Branch I (7509C)
Secondary Reviewer: Karen Hamernik, Ph.D., Section Head
Review Section III, Toxicology Branch I (7509C)

Budd 2/10/95
K. Hamernik 2/10/95

DATA EVALUATION REPORT

Study Type: Carcinogenicity Study, Mice
EPA Subdivision F Guideline 83-2(b)

Test Material: Malathion (CAS No. 121-75-5)

Tox. Chem. No.: 535

PC Code No.: 057701

MRID No.: 434072-01 (Original Report, 5 volumes, 1454 pages)

Study Title: 18-Month Oral (Dietary) Oncogenicity Study in Mice

Testing Laboratory: International Research and Development Corporation (IRDC)
Mattawan, Michigan

Lab. Project ID.: 668-001

Author: Richard W. Slauter, Ph.D.

Study Completion Date: October 12, 1994

Sponsor: Cheminova Agro A/S
Lemvig, Denmark

I. EXECUTIVE SUMMARY:

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18 months. Mortality, clinical signs of toxicity, body weights and food consumption were monitored at appropriate times during the study. Hematological examinations and determinations of plasma, erythrocyte and brain cholinesterase activity levels were made on 8-10 mice/sex/group at 9 (erythrocyte cholinesterase only), 12 and 18 months. Necropsy examinations were performed on all animals and organ weight determinations were made on all animals at the 12-month interim and 18-month terminal sacrifices. Histopathological examinations were made on a complete set of organs/tissues from all animals that died or were sacrificed in extremis during the study and on all control and 16000 ppm animals at the 12 month and 18 month scheduled sacrifices. Histopathological examinations were also performed on a more limited set of organs/tissues from the other dose level groups at the scheduled sacrifices.

At 16000 ppm and 8000 ppm in both males and females, treatment related effects included decreased absolute body weights throughout the entire duration of the study (14.3-20.0% decrease in males and 9.7-16.1% decrease in females at 18 months), decreased food consumption (2.0-5.9% in males and 5.4-12.5% in females), decreased plasma cholinesterase activity levels at 12 and 18 months ($\geq$ 86%), decreased erythrocyte cholinesterase activity levels at 9, 12 and 18 months ($\geq$ 61%) and decreased brain cholinesteraase activity levels at 18 months (37-43%) at 16000 ppm only. Mortality rates, clinical signs of toxicity and hematological parameters were not affected by treatment with malathion at any dose.

A treatment-related increased incidence of hepatocellular tumors was observed in both male and female mice in this study at 8000 ppm and 16000 ppm. For male mice which died during the final 6 months of the study or were killed at the terminal sacrifice at 18 months, the percent incidences of hepatocellular adenomas were 1.9%, 7.3%, 3.6%, 21.8% and 94.1%; of hepatocellular carcinomas were 0.0%, 10.9%, 5.5%, 10.9% and 2.0%; and of combined hepatocellular adenomas/carcinomas were 1.9%, 18.2%, 9.1%, 32.7% and 96.1% for the 0 (control), 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For female mice which died during the final 6 months of the study or were killed at the terminal sacrifice at 18 months, the percent incidences of hepatocellular adenomas were 0.0%, 1.8%, 0.0%, 17.0% and 80.8%; of hepatocellular carcinomas were 1.8%, 0.0%, 3.7%, 1.9% and 3.8%; and of combined hepatocellular adenomas/carcinomas were 1.8%, 1.8%, 3.7%, 18.9% and 84.6% for the 0 (control), 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

The dose-related increases in hepatocellular adenomas and in combined adenomas/carcinomas at 8000 ppm and 16000 ppm in both males and females were attributed to treatment with malathion. Although some hepatocellular carcinomas were also observed in nearly all of the malathion treated groups, the incidences were not dose-related and overall the relationship of these carcinomas to treatment with malathion was equivocal. The increased numbers of hepatocellular tumors observed in this study in both males and females were due primarily to increased numbers of adenomas.

Regarding the male mice in this study, more hepatocellular tumors (adenomas, carcinomas and combined adenomas/ carcinomas) were observed at 100 ppm than at 800 ppm. Thus, a dose-related response was not observed at the lower dose levels of 100 ppm and 800 ppm, whereas a dose-related response was observed at the higher dose levels of 8000 ppm and 16000 ppm. How to interpret the increased numbers of hepatocellular tumors at 100 ppm, but not at 800 ppm, for the male mice in this study is not clear at this time.

The increased tumor incidences in the livers of both males and females at 16000 ppm and 8000 ppm were accompanied by concurrent observations of masses, nodules and foci in the livers of these animals at the terminal sacrifice and also by increased liver weights and highly increased incidences of hepatocellular hypertrophy in the livers at 12 and 18 months. The data for hepatocyte hypertrophy was quite remarkable in that an extremely steep dose-response curve was observed for both males and females in this study. Thus, in the control, 100 ppm and 800 ppm groups, no case of hepatocellular hypertrophy was observed in any animal at any time during the entire duration of this study whereas at 8000 ppm and 16000 ppm, a $\geq$ 50% incidence was observed at 12 months and a 100% incidence at 18 months.

Other findings were observed in this study that appeared to be related to treatment, but their biological significance was uncertain. These findings included the following: decreased vacuolation in the convoluted tubules of the kidneys in males; increased mineralization of the kidneys in females; decreased fibrous osteodystrophy of the femur and sternum in females; and early disappearance of the "x zone" in the the adrenal cortex of females.

The NOEL for cholinesterase inhibition for both sexes was estimated to be 100 ppm for plasma and erythrocyte cholinesterase and 8000 ppm for brain cholinesterase. Although there was some decrease in cholinesterase activity at these doses, the decreases were not statisticaly significant and the data were considered to be too variable to conclude that the inhibition seen was really related to

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treatment. Cholinesterase activities were assayed using a Boehringer Mannheim Diagnostics kit and a Technicon AutoAnalyzer I. The NOEL for systemic effects was 800 ppm. The LEL was 8000 ppm, based on decreased body weights and food consumption in males and females, increased liver weight in males and females and increased hepatocellular hypertrophy in males and females. The biological significance of the decreased vacuolization of convoluted tubules in the kidney in males, increased mineralization of the kidney in females, decreased fibrous osteodystrophy in females and early disappearance of the "x zone" of the adrenal cortex in females at this and other doses is uncertain.

This study is classified as Core Guideline and satisfies the guideline requirement for a carcinogenicity study in mice, Guideline 83-2(b).

NOTE--The 2 highest dose levels used in this study, 16000 ppm (equivalent to 2978 mg/kg/day in males and 3448 mg/kg/day in females) and 8000 ppm (equivalent to 1476 mg/kg/day in males and 1707 mg/kg/day in females), both exceeded the limit dose of 1000 mg/kg/day which is oftentimes used by EPA to establish an upper dose level for carcinogenicity studies in mice and rats. In this instance, however, EPA required that the highest dose levels in this particular study be 16000 ppm and 8000 ppm in order to duplicate the dose levels used in a previously conducted 1978 National Cancer Institute (NCI) carcinogenicity study in B6C3F1 mice in which the results were equivocal.

II. DETAILED REVIEW OF STUDY

A. Test Material: Malathion, technical grade (CAS # 121-75-5). Description: Clear amber liquid; Product no. 30 0791; Batch no. 11029-01; 96.4% ± 0.3% purity; obtained from Cheminova Agro A/S (Lemvig, Denmark); storage conditions: not given.

Samples of the test material were collected at 28, 56 and 76 weeks and assayed for storage stability of the bulk chemical. Means ± S.D. of analyses, expressed as percent of target concentration, were 99.8 ± 4.09%, 98.4 ± 3.29% and 92.9 ± 1.09% for weeks 28, 56 and 76 respectively. These results indicate that the bulk chemical was stable under the conditions of storage over the duration of the study.

B. Test Animals: Mice, B6C3F1 BR strain, males and females. Description: obtained from Charles River Laboratories (Portage, Michigan); 4 weeks old when received (2/3/92); acclimated 4 weeks prior to commencement of treatment (3/2/92); all animals were given detailed physical examinations prior to treatment; a pretest viral screen was conducted on 5 animals/sex (results were negative); the mean weight of males was about 23 gm and of females was about 20 gm in each of the various groups at the commencement of treatment.

Environment: All mice were individually housed (since receipt) in wire-mesh cages in an environmentally controlled room under standard environmental conditions; temperature and humidity were monitored and recorded continuously; 12 hour light/dark cycle; diet and water (IRDC well water supply, analyzed quarterly for contaminants) were available ad libitum during the acclimation period and entire treatment period; water was provided via an automatic watering system.

C. Study Design: Animals were randomized and assigned to treatment groups as shown below "utilizing a block randomization procedure in which animals were stratified by body weight." Main study animals (55/sex/group) were given control or treated diet mixtures for 18 months; interim kill animals (10/sex/group) were sacrificed at 12 months.

Dose Level Malathion (ppm)	Main Study		Interim Kill	
	Males	Females	Males	Females
0	55	55	10	10
100	55	55	10	10
800	55	55	10	10
8000	55	55	10	10
16000	55	55	10	10

Treatment was commenced on 3/2/92. The interim kill was on 3/1/93 to 3/5/93. The last days of treatment and terminal sacrifices were on the same days viz. 8/30/93 to 8/31/93, 9/1/93 to 9/3/93 and 9/7/93 to 9/9/93.

Based on food consumption and body weight data, the mean consumption of test material for each of the treatment groups was later calculated in units of mg/kg/day for the entire duration of the study. For males, the mean consumption of test material was 0.0, 17.4, 143, 1476 and 2978 mg/kg/day for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For females, the mean consumption of test material was 0.0, 20.8, 167, 1707 and 3448 mg/kg/day for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

Note--During week 6, control animals were inadvertently given the low dose (100 ppm) diet mixture for 2 days and low dose (100 ppm) animals were given control diet for the same 2 days. This mistake in dosing would not be expected to affect the study results.

D. Rationale for Selection of Dose Levels: In a Data-Call-In notice dated 6/15/92, EPA required that the 2 highest dose levels in this study be 8000 ppm and 16000 ppm. These 2 dose levels duplicated dose levels used in a 1978 National Cancer Institute (NCI) 80-week carcinogenicity study in B6C3F1 mice (NCI-CG-TR-24). In this NCI study, possibly increased incidences of hepatocellular carcinomas and of combined neoplastic nodules and hepatocellular carcinomas were observed in male mice at 16000 ppm. There was also a dose-related trend in male mice for combined neoplastic nodules and hepatocellular carcinomas when compared to pooled controls. The results in this study, however, were equivocal and a clear association between liver neoplasms and malathion could not be established. In addition, study design flaws, uncertainties about the conduct of the study, and lack of sufficient detail to allow independent statistical analyses of the data further compromised the usefulness of this study. Hence, EPA required a new study to be performed under similar conditions in order to resolve the question of possible carcinogenicity of malathion in B6C3F1 mice.

E. Diet Preparation and Analyses of Diet Mixtures: The test material was diluted in acetone and then incorporated into ground Certified Rodent Chow #5002 (Purina Mills, Inc.; St. Louis, Missouri). Control diets were prepared with acetone only. Fresh diet mixtures and control diets were prepared weekly and stored in closed, polyethylene containers under refrigeration (see results of stability analyses below).

Homogeneity and Stability: Prior to commencement of treatment, the low (100 ppm) and high (16000 ppm) diet mixtures were sampled as follows.

1. Triplicate sets of samples from each side of the containers at the top, middle and bottom were taken (3 x 6 = 18 total samples).

2. One set of samples (6 samples) was assayed immediately for malathion content (homogeneity analysis).

3. The remaining 2 sets of samples (6 samples each) were both stored in standard containers at room temperature in the laboratory and then assayed at 7 days or at 14 days (stability analysis). Additional refrigerated samples were also assayed at 7 days or at 14 days.

Results for Homogeneity: The mean concentration of malathion in the low diet mixture for the 6 samples was 101 ppm (range: 95.5 - 107 ppm). The mean percent of target concentration and percent coefficient of variation were 100% ± 4.5%. The mean concentration of malathion in the high diet mixture for the 6 samples was 16000 ppm (range: 14900 - 17100 ppm). The mean percent of target concentration and percent coefficient of variation were 98% ± 4.4%. These data indicate satisfactory homogeneity of the low and high diet mixtures.

Results for Stability: Assays for malathion content in the low (100 ppm) diet mixture subjected to room temperature in the laboratory for 7 or 14 days indicated mean concentrations of 87% and 83%, respectively, of the day 0 concentration. Assays of similar samples kept under refrigeration for 7 or 14 days indicated means of 88% and 95% respectively. Both of these analyses were repeated about 2 months later. At this time, assays for malathion content in the low (100 ppm) diet mixture subjected to room temperature in the laboratory for 7 or 14 days indicated mean concentrations of 89% and 92%, respectively, of the day 0 concentration. Assays of similar samples kept under refrigeration in a sealed, stainless steel container for 7 or 14 days indicated means of 96% and 100% respectively.

Assays for malathion content in the high (16000 ppm) diet mixture subjected to room temperature in the laboratory for 7 or 14 days indicated mean concentrations of 100% and 98%, respectively, of the day 0 concentration. Assays of similar samples kept under refrigeration for 7 or 14 days indicated means of 102% and 103% respectively.

Results for the low diet mixture indicated moderate loss of test material over a 7 day interval (up to 13%) and over a

14 day interval (up to 17%). Since shorter storage durations and refrigeration were observed to decrease losses, actual diet mixtures in the study were prepared weekly and stored under refrigeration.

Concentration Analyses: All diet mixtures, including the control diet, were assayed for malathion content weekly for the first 8 weeks and monthly thereafter. The control diet and low (100 ppm) diet mixture were also assayed for weeks 9, 10, 11, 13, 14 and 15.

Results: For the entire duration of the study (analyses for weeks 1 to 76), the mean concentrations ± S.D. of malathion in the diet mixtures were 0, 98.4 ± 4.88, 763 ±36.0, 8030 ± 303 and 15900 ± 908 ppm. In terms of percent of target concentrations, these mean concentrations corresponded to 0%, 98%, 95%, 100% and 99% respectively. The vast majority of individual analyses were between 90% and 110%. The extreme range of values for individual samples was 84% to 117%. These data indicate that satisfactory concentrations of test material in the diet mixtures were achieved at all dosage levels throughout the entire duration of the study.

F. Quality Assurance, GLP Compliance and EPA Flagging Statements: Quality assurance inspections were conducted throughout the study from 2/6/92 to 10/11/94. The Quality Assurance statement was signed on 10/12/94. The GLP Compliance statement was signed, but not dated. The EPA Flagging Statement was signed, but not dated, and stated that "this study meets or exceeds the criteria numbered 1,2" [1.: an incidence of neoplasms in male or female animals which increases with dose; 2.: a statistically significant ($p \leq 0.05$) incidence of any type of neoplasm in any test group (male or female animals at any dose level) compared to concurrent control animals of the same sex].

G. Statistical Evaluation: Quoted from p. 19 of the report.

"Body weight, food consumption and clinical pathology laboratory values and organ weights (absolute and relative) were analyzed using analysis of variance (one-way classification) and Bartlett's test for homogeneity of variance. Treatment groups were compared to the control group, by sex, using the appropriate t-statistic (for equal or unequal variance) as described by Steel and Torrie[1]. Dunnett's[2] multiple comparison tables or pairwise comparisons with a Bonferroni correction[3] were used to determine the significance of differences. Nonparametric analyses were conducted as appropriate by transforming the data into ranks prior to analysis, as described by Conover and Iman[4]. All statistical analyses were performed with $p \leq 0.05$ and $p \leq 0.01$ as levels of significance."

"Analysis of tumor incidence data was performed as described by Huff[5] . These procedures include life table tests, the Hoel-Walburg 'incidental tumor' tests, Fisher's exact tests and Cochran-Armitage trend tests."

See References [1] - [5] on p. 33 of the report.

H. Observations and Results:

1. Mortality: All animals were observed twice each day for mortality and morbidity.

   Results: The fates of all animals in the study are presented in Table 1. For males, in the first 39 weeks of the study, 4 unscheduled deaths occurred in the 16000 ppm group whereas during the same period, no unscheduled deaths occurred in the control or any other treatment group. After 39 weeks, however, there were considerably fewer mortalities in the 8000 ppm and 16000 ppm groups than in the control, 100 ppm or 800 ppm groups. At the terminal sacrifice, 48 - 54 males per group were subjected to postmortem procedures. The pattern of deaths in the male groups did not indicate a relationship between mortality and the test material. For females, few unscheduled deaths occurred during the study in any group and no relationship to treatment with the test material was evident. At the terminal sacrifice, 51 - 55 females per group were subjected to postmortem procedures.

   Conclusion: Treatment with malathion had no apparent effect on the rate of mortality for either males or females in this study.

2. Clinical Signs: All animals were observed twice each day for clinical signs of toxicity. The onset and duration of signs were recorded. In addition, all animals were given a detailed clinical examination, including palpation for masses, once each week.

   Results: Clinical signs and palpable masses were summarized and listed for individual animals in the study report. There were no clinical signs in either males or females that could be attributed to treatment with malathion. The recorded signs were few and were typical for mice of this strain and age. Decreased incidences of hair loss in males at 8000 ppm and 16000 ppm and in females at 16000 ppm were not considered to be biologically meaningful. It should be particularly noted that clinical signs of toxicity ordinarily associated with cholinesterase poisoning (e.g. tremors, hyperactivity, salivation, malaise, etc.) were not

observed at any time in either the male or female mice in this study. Externally palpable masses were also few in number and could not be related to treatment with the test material.

Conclusion: The observed clinical signs and palpable masses in males and females in this study could not be directly related to treatment with malathion. Clinical signs of toxicity ordinarily associated with cholinesterase poisoning were not observed in this study in either males or females at any time.

3. Body Weights: Body weights for all mice were recorded prior to treatment, weekly for the first 14 weeks of the study, biweekly for weeks 14 - 26, and monthly thereafter.

Results: Mean absolute body weights for males and females at selected weeks during the study are presented in Table 2. Also, graphical representations of mean absolute body weights for males and females are presented in Figure 1 (copied from p. 34 and p. 35 of the study report). See pp. 35-36 in this DER. Changes in body weight gains were not presented in the study report (and are not considered by TB-I to be necessary for this particular study). For males, starting at week 1 and continuing for the entire duration of the study, absolute body weights were significantly decreased ($p \leq 0.01$) in a dose-related manner for both the 8000 ppm and 16000 ppm groups when compared to the control group. Mean body weights were not significantly decreased for male mice at 100 ppm or 800 ppm. At 78 weeks, the percentage decreases in mean absolute body weights for male mice, compared to the control group, were 14.3% and 20.0% for the 8000 ppm and 16000 ppm groups respectively. For females, starting at week 0 and continuing for the entire duration of the study, absolute body weights were also significantly decreased ($p \leq 0.01$) in a dose-related manner for both the 8000 ppm and 16000 ppm groups when compared to the control group. Mean body weights were not significantly decreased for female mice at 100 ppm or 800 ppm. At 78 weeks, the percentage decreases in mean absolute body weights for female mice, compared to the control group, were 9.7% and 16.1% for the 8000 ppm and 16000 ppm groups respectively.

Conclusion: Statistically significant ($p \leq 0.01$) dose-related decreases in mean absolute body weights for both males and females throughout the entire duration of the study at 8000 ppm and at 16000 ppm were clearly related to treatment with malathion.

4. Food Consumption: Food consumption for all mice was recorded weekly for the first 14 weeks of the study, biweekly for weeks 14 - 26, and monthly thereafter.

Results: Mean food consumption values for males and females at selected weeks during the study are presented in Table 3. Also, graphical representations of mean food consumption data for males and females are presented in Figure 2 (copied from p. 36 and p. 37 of the study report). See pp. 37-38 in this DER. For males, for the first 3 weeks of the study, mean food consumption for the 16000 ppm group was reduced considerably, possibly due to poor palatability of the diet mixture or to lack of appetite resulting from lower plasma and erythrocyte cholinesterase activity levels presumably present in these animals at that time (see 10. below). Food consumption for the 16000 ppm males then approached that of the control group for weeks 4-26. After 26 weeks and for the remainder of the study, however, food consumption was significantly decreased ($p \leq 0.01$) in a dose-related manner for both the 8000 ppm and 16000 ppm groups when compared to the control group. Mean food consumption was not affected for the male 100 ppm and 800 ppm groups. For the entire duration of the study, the percent differences from the control group for male mice were 0.0%, +2.0%, -2.0% and -5.9% for the 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For females, the pattern of food consumption was quite similar to that observed for the males, except that the period of initial reduction for the 16000 ppm females lasted about 13 weeks. As for males, after 26 weeks and for the remainder of the study, food consumption was significantly decreased ($p \leq 0.01$) in a dose-related manner for both the 8000 ppm and 16000 ppm groups when compared to the control group. Mean food consumption was not affected for the female 100 ppm and 800 ppm groups. For the entire duration of the study, the percent differences from the control group for female mice were 0.0%, 0.0%, -5.4% and -12.5% for the 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

Conclusion: Statistically significant ($p \leq 0.01$) decreases in food consumption were observed for 16000 ppm males and females during the first 3 weeks and 13 weeks of the study respectively. These decreases were possibly due to poor palatability of the diet mixture or to lack of appetite resulting from lower plasma and erythrocyte cholinesterase activity levels presumably present in these animals at that time. After 26 weeks and for the remainder of the study, however, statistically significant ($p \leq 0.01$) dose-related

decreases in food consumption for both males and females were observed at 8000 ppm and at 16000 ppm. These latter decreases were attributed to treatment with malathion.

5. Consumption of Test Material: Based on food consumption and body weight data, the mean consumption of test material for each of the treatment groups was calculated in units of mg/kg/day for the entire duration of the study. For males, the mean consumption of test material was 0.0, 17.4, 143, 1476 and 2978 mg/kg/day for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For females, the mean consumption of test material was 0.0, 20.8, 167, 1707 and 3448 mg/kg/day for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

6. Water Consumption: Not performed.

7. Ophthalmoscopy: Not performed.

8. Hematology: Samples of whole blood were collected from the orbital sinus of 8-10 randomly selected mice/sex/group at 12 and at 18 months. Animals were not fasted prior to blood collection. The following parameters were determined:

Total RBC	Total WBC
Hemoglobin	Differential white count
Hematocrit	Platelets
Mean Cell Volume (MCV)	
Mean Cell Hemoglobin (MCH)	
Mean Cell Hemoglobin Conc (MCHC)	

Results: For male mice, there were no statistically significant differences between treated groups and the control group for any of the hematology parameters examined at either 12 or 18 months, except for an increased MCHC in 16000 ppm males ($p \leq 0.01$) at 12 months. This increase was not considered to be biologically meaningful because no other differences in erythrocyte parameters were observed in these same animals. Similarly, for female mice, there were no statistically significant differences between treated groups and the control group for any of the hematology parameters examined at either 12 or 18 months, except for a decreased MCV in 16000 ppm females ($p \leq 0.01$) at 12 and 18 months. Again, these decreases were not considered to be biologically meaningful because no other differences in erythrocyte parameters were observed in these same animals.

Conclusion: There was no apparent effect on any of the hematology parameters examined in either male or female mice as a result of treatment with malathion.

9. Clinical Chemistries: Other than cholinesterase activity determinations (see below), no clinical chemistry assays were performed on the animals in this study.

10. Cholinesterase Activity Determinations: Samples of whole blood were collected by cardiac puncture from the 8-10 mice/sex/group that were sacrificed at the 12 month interim sacrifice. At 18 months, whole blood was collected from the orbital sinus of 10 mice/sex/group. As much as possible, blood was collected from the same randomly selected animals that were used for the hematology examinations. The animals were not fasted prior to blood collection. Cholinesterase activity determinations were performed for plasma, erythrocyrte and brain at these times (i.e. at 12 and 18 months). In addition, at 9 months, blood was collected from 10 randomly selected mice/sex/group and assayed for erythrocyte cholinesterase activity only. For all cholinesterase activity determinations, a Technicon AutoAnalyzer I was used in accordance with the analytical methodology decribed in the following reference:

Cholinesterase Reagent Set package insert (1981).
CAT # 124117.
Boehringer Mannheim Diagnostics, Houston, TX.

No further description of the analytical methodology utilized for the cholinesterase activity determination was provided in the study report.

Results: Residual cholinesterase activities for plasma, erythrocyte and brain for males and females at 12 and 24 months and for erythrocyte activity (only) for males and females at 9 months are presented in Table 4. Residual cholinesterase activity, as used here, is defined as "percent of cholinesterase activity remaining as compared to the mean of the control group for the same sex". Results for males and females were very similar. Plasma cholinesterase activity was decreased in a dose-related manner for both males and females at 12 and 18 months. The decreases at 8000 ppm and 16000 ppm were considerable ($\geq$ 86%; $p \leq 0.01$) and were clearly related to treatment with malathion. The decreases at 800 ppm (18-36%) were not statistically significant in males but were statistically significant ($p \leq 0.05$) in females. It is likely, however, that the

decreases in males, although not statistically significant, were nevertheless related to the test material. At 100 ppm, plasma cholinesterase inhibition was considered to be equivocal.

Erythrocyte cholinesterase activity was also decreased in a dose-related manner for both males and females at 9, 12 and 18 months. The decreases at 8000 ppm and 16000 ppm were considerable ($\geq$ 61%; $p \leq 0.05$) and were clearly related to treatment with malathion. Some of the decreases at 800 ppm (35-58%) were also statistically significant in males and females. Effects at 800 ppm, therefore, were also related to treatment with the test material. At 100 ppm, although not statistically significant in either males or females, erythrocyte values at 18 months were decreased 15% in males and 31% in females. It is possible that these decreases at 100 ppm at 18 months were also related to treatment with malathion but the data is equivocal.

Brain cholinesterase activity was decreased for both males and females at 12 and 18 months at 16000 ppm. The decreases (20-43%) were not statistically significant in males or females at 12 months but were statistically significant ($p \leq 0.05$) in both sexes at 18 months. It is likely, however, that the decreases at 12 months, although not statistically significant, were nevertheless related to treatment with the test material. At 8000 ppm, nonsignificant decreases in brain cholinesterase activity were observed in both males and females at 18 months (20-23%). These decreases may also be related to the test material, but again the data is equivocal.

Conclusion: Plasma cholinesterase activity was decreased in both males and females in a dose-related manner at 800 ppm, 8000 ppm and 16000 ppm. The decreases at 8000 ppm and 16000 were particularly substantial ($\geq$ 86%) and were significant ($p \leq 0.01$). Erythrocyte cholinesterase activity was also decreased in both males and females in a dose-related manner at 800 ppm, 8000 ppm and 16000 ppm. The decreases at 8000 ppm and 16000 were particularly substantial ($\geq$ 61%) and most were significant ($p \leq 0.01$). It was difficult to tell whether or not there was any true reduction in plasma or erythrocyte cholinesterase activity in either sex at 100 ppm or in brain cholinesterase in either sex at 8000 ppm (even though decreases were part of a dose-related trend) because the decreases were not statistically significant and there was a large degree of variability associated with them (coefficients of

variation generally ranged from 20 to 46%). Although the data are equivocal, 100 ppm could be considered as an approximate NOEL for plasma and erythrocyte cholinesterase inhibition (both sexes) and 8000 ppm could be considered as an approximate NOEL for brain cholinesterase inhibition (both sexes) in this study.

11. Urinalyses: Not performed.

12. Necropsy: All animals in this study, regardless of time of death, were given a complete postmortem examination under the direct supervision of a pathologist, in accordance with standard gross dissection and necropsy procedures. Animals sacrificed at the scheduled sacrifice times of 12 and 18 months and animals sacrificed in extremis were euthanized by carbon dioxide inhalation overdose.

Results:

0 - 12 Months: Negative. No gross effects were observed in animals that died or were sacrificied during the first 12 months of the study that could be attributed to treatment with malathion.

12-Month interim Sacrifice: Negative. No gross effects were observed in animals that were sacrificed at 12 months (8-10 mice/sex/group) that could be atributed to treatment with the test material.

12 - 18 Months: Negative. No gross effects were observed in animals that died or were sacrificed during the last 6 months of the study that could be attributed to treatment with malathion. It might be recalled, however, that for the 8000 ppm and 16000 ppm groups, only 2 males and 1 female died during this period of the study.

Terminal Sacrifice: Selected macroscopic observations for male and female mice sacrificed at 18 months are presented in Table 5. For both males and females, gross effects attributed to treatment with malathion were observed in the liver. No macroscopic changes related to the test material were noted in any other organ/tissue.

For males, increased numbers of masses were observed in the livers of all malathion treatment groups when compared to the number in the control group. The incidences were 0, 8, 4, 5 and 18 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm

groups respectively. Increased numbers of liver nodules were also observed in the 8000 ppm and 16000 ppm male groups when compared to the control group. The incidences were 5, 2, 3, 10 and 19 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. An increased incidence of focus/foci (tan/yellow) was also observed in the livers of the 16000 ppm male group. The incidences were 0, 0, 1, 2 and 18 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. A very small increase in enlarged hepatic lymph nodes was also noted in malathion treated groups at 800 ppm, 8000 ppm and 16000 ppm. The relationship of this finding to treatment with malathion is uncertain. Finally, a decreased incidence of alopecia was observed in 8000 ppm and 16000 ppm males (data not shown). There is probably no biological significance related to this observation.

For females, an increased number of masses was observed in the livers of the 16000 ppm group when compared to the control group. The incidences were 1, 0, 3, 2 and 10 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Increased numbers of liver nodules were also observed in the 8000 ppm and 16000 ppm female groups when compared to the control group. The incidences were 1, 2, 0, 9 and 29 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. An increased incidence of focus/foci (tan/yellow) was also observed in the livers of the 16000 ppm female group. The incidences were 0, 0, 0, 2 and 9 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. The significance of the small increase at 8000 ppm is uncertain. Decreased numbers of female mice with alopecia, clear cysts in the ovary and dilated uterus were also noted at 16000 ppm. There is probably no biological significance related to these latter observations.

Conclusion: Increased numbers of liver masses, compared to control groups, were observed in the 100 ppm, 800 ppm, 8000 ppm and 16000 ppm male groups and the 16000 ppm female group at the terminal sacrifice. Also at the terminal sacrifice, increased numbers of liver nodules were observed in the 8000 ppm and 16000 ppm male and female groups. Finally, an increased incidence of liver focus/foci (tan/yellow) was observed in the 16000 ppm male and female groups at the terminal sacrifice. No other macroscopic changes were noted in

any organ/tissue that were attributed to the test material.

13. Organ Weights, Organ/Body Weight Ratios and Organ/Brain Weight Ratios: For all animals sacrificed at the scheduled sacrifice times of 12 and 18 months, the following organs were weighed and organ/body weight and organ/brain weight ratios calculated.

adrenal (2)	kidney (2)
brain	liver
ovary (2)	lung
testes (2)	spleen
heart	

Results: See Tables 6 and 7. For male mice, dose-related statistically significant ($p \leq 0.01$) increases in absolute liver weights, liver/body weight ratios and liver/brain weight ratios were observed at 12 and 18 months for the 8000 ppm and 16000 ppm groups. The percent increases in absolute liver weights at 18 months were 19% and 40% for the 8000 ppm and 16000 ppm groups respectively. These increased liver weights were attributed to treatment with the test material. Decreases in absolute brain weight at 12 and 18 months and in kidney and heart weights at 18 months for the 16000 ppm group were also noted. Increased lung/body weight ratios and testes/body weight ratios at 18 months for 8000 ppm and 16000 ppm males were considered to be the result of the significantly decreased body weights ($p \leq 0.01$) and not related to treatment with malathion. Other differences, such as increased kidney weights at 12 months for the 100 ppm group, were not considered to be biologically significant.

For female mice, statistically significant ($p \leq 0.01$) increases in absolute liver weights, liver/body weight ratios and liver/brain weight ratios were observed at 12 months in the 16000 ppm group. At 18 months, absolute liver weights, liver/body weight ratios and liver/brain ratios were also increased, but only the increase for liver/body weight ratio was statistically significant ($p \leq 0.01$). The percent increase in absolute liver weight at 18 months was 13% for the 16000 group. It is likely, however, that the increased liver weights at 16000 ppm at both 12 and 18 months are related to treatment with malathion. Decreases in absolute brain and spleen weights for the 8000 ppm and 16000 ppm groups and in heart and lung weights for the 16000 ppm group were also noted at 18 months. Although statistically significant increases in kidney weight values were frequently observed in all malathion treated female groups at 12 and/or 18 months, these

differences were either not dose-related or were probably due to the significantly decreased ($p \leq 0.01$) body weights at 8000 ppm and 16000 ppm. Therefore, the increased kidney weights in female mice were not attributed to treatment with the test material.

Conclusion: Treatment-related increases in liver weights were observed in male mice at 8000 ppm and 16000 ppm and in female mice at 16000 ppm at 12 and 18 months. None of the other changes in absolute or relative organ/body weight ratios were considered to be related to treatment with the test material.

14. Fixing and Processing of Tissues/Organs: The following tissues/organs were collected from all animals at the time of necropsy and were fixed in phosphate-buffered neutral formalin.

Adrenal (2)
Aorta
Bone (femur)
Bone marrow (femur)
Bone marrow smear (2)
Brain (fore, mid and hind)
Eye including optic N. with contiguous Harderian gl (2)
Gallbladder
Gastrointestinal tract:
 esophagus
 stomach (glan & nonglan)
 duodenum
 jejunum
 ileum
 cecum
 colon
 rectum
Gonads:
 ovary (2)
 testis with epididymis (2)
Gross lesions
Heart
Kidney (2)
Lacrimal gl (exorbital)(2)
Larynx
Liver (2 lobes examined; 3 sections collected)
Lung with bronchi (2)
Lymph Nodes: mandibular, mediastinal, mesenteric and regional when applicable
Mammary gland (females only)
 Oviduct (2)
 Pancreas
 Pituitary
Prostate & Seminal Vesic (2)
Salivary gl, mandib/subling
Sciatic nerve
Skeletal muscle (thigh)
Skin
Spinal cord (cer,thor & lum)
Spleen
Sternum
Thymus
Thyroid/parathyroid (2)
Tissue masses
Tongue
 Trachea
Urinary bladder
Uterus (both horns)
Uterus, cervix
 Vagina

Following fixation, representative samples of or the whole of the tissues/organs listed above were trimmed, sectioned, blocked in paraffin, and stained (H & E) according to standard histologic techniques.

15. Microscopic Examination: All the tissues/organs listed above were microscopically examined from all mice in the control and high dose (16000 ppm) groups at the interim and terminal sacrifices and from all mice which died or were sacrificed in extremis during the study. In addition, at the interim and terminal sacrifices, the following tissues/organs were examined from all mice in the 100 ppm, 800 ppm and 8000 ppm groups: liver, kidney (2), lung and adrenal (2). At the terminal sacrifice (only), samples of bone (femur and sternum) were also examined for all female mice in the 100 ppm, 800 ppm and 8000 ppm groups. All tissue masses and all gross lesions from all animals in the study were also examined. Gradable lesions were graded by a 4 step grading system of trace, mild, moderate and severe.

NONNEOPLASTIC FINDINGS

Results:

0 - 12 Months, Including 12-Month Interim Sacrifice: Selected nonneoplastic microscopic findings for male and female mice which died or were sacrificed in extremis during the first 12 months of the study or were sacrificed at the 12-month interim sacrifice are presented in Table 8. For males, effects attributed to treatment with malathion were observed in the liver and kidney. For females, treatment related effects were observed in the liver and adrenal cortex. No microscopic changes related to the test material were noted in any other organ/tissue during the first 12 months of the study.

For males, hepatocyte hypertrophy was observed in the livers of numerous animals at 8000 ppm and 16000 ppm whereas none was observed at lower doses or in the control group. The incidences were 0/11, 0/10, 0/10, 7/10 and 12/14 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Also, the average severity score was increased at 16000 ppm (2.3) as compared to the score at 8000 ppm (1.0). In the kidney, the incidence of vacuolation in the convoluted tubules, a normal finding in male mice at 12 months and older, was clearly decreased at 8000 ppm and 16000 ppm. The incidences were 11/11, 10/10, 10/10, 1/10 and 0/14 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Also in the kidney, an increased incidence of mineralization in the 16000 ppm group

(6/14) as compared to the control group (3/11) was observed. Chronic interstitial nephritis, a common finding in older male mice, was also noted in several mice in all groups, but was not considered to be related to treatment with malathion. Microscopic findings in the adrenal cortex of male mice were negative.

Hepatocyte hypertrophy was also observed in the livers of numerous female mice at 8000 ppm and 16000 ppm. The incidences and average severity scores were very similar to those observed for male mice. The incidences were 0/10, 0/10, 0/11, 6/12 (average score = 1.0) and 13/13 (average score = 2.2) for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Microscopic findings in the kidney were negative. In the adrenal cortex, however, a region described as the "x zone", which is present only in females and normally disappears in older mice, was observed to have disappeared sooner than expected in the 8000 ppm and 16000 ppm mice. This "x zone" was present in 10/10, 8/10, 9/11, 1/12 and 0/13 female mice for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. The early disappearance of the "x zone" in the adrenal cortex of female mice is considered to be related to treatment with malathion. Also in the adrenal cortex, A cell hyperplasia, a normal finding in female mice of 12 months and older, was observed in nearly all control and malathion treated mice. In addition, cysts were frequently observed in the uterus of control and malathion treated mice, but were not considered to be treatment related.

For both males and females, the following additional lesions were frequently reported in the control and 16000 ppm treatment groups, but were not attributed to treatment with the test material (data not shown in Table 8): brain/ mineralization, Harderian gland/chronic inflammation, urinary bladder/mononuclear cell infiltration.

<u>12 - 18 Months, Including 18-Month Terminal Sacrifice</u>: Selected nonneoplastic microscopic findings for male and female mice which died or were sacrificed <u>in extremis</u> after 12 months or were sacrificed at the 18-month terminal sacrifice are presented in Table 9. For males, effects attributed to treatment with the test material were observed in the liver and kidney. For

females, treatment related lesions were noted in the liver, kidney and bone (femur and sternum).

For males, hepatocyte hypertrophy was observed in all malathion treated mice at 8000 ppm and 16000 ppm whereas none was observed at 100 ppm or 800 ppm or in the control group. The incidences were 0/54, 0/55, 0/55, 55/55 (average score = 2.1) and 51/51 (average score = 3.1) for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. These lesions were clearly induced by treatment with malathion. Slightly increased incidences of mononuclear cell infiltration in the portal areas and of necrosis were also reported in the 8000 ppm and 16000 ppm groups. Mononuclear cell foci in the parenchyma was reported with about equal frequency in the control and treatment groups. In the kidney, a decreased incidence of vacuolation in the convuloted tubules was again observed in the 8000 ppm and 16000 ppm groups (as during the first 12 months of the study). Incidences were 54/54, 55/55, 55/55, 33/55 and 0/51 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Mineralization of the kidney and chronic interstitial nephritis were also observed in most male kidneys in the control and all treatment groups and were considered to be normal findings in male mice of this age. In the adrenal cortex, an increase in brown degeneration was noted in the 8000 ppm and 16000 ppm groups. The incidence of this lesion, however, was not dose related and when considered together with the frequent observation of this same finding in females, where there was no relationahip to treatment with malathion, the increase in males was considered to be most likely also not related to treatment with malathion. A cell hyperplasia was also frequently observed in the adrenal cortex, but was not attributed to treatment with the test material.

Also for males, increased incidences of mineralization in the lungs (a normal finding) and of brown pigment in the mandibular lymph node (not observed in other lymph nodes) were observed in the 16000 ppm group. The possible relationship of either of these findings to treatment with malathion, although somewhat suggestive based solely on numerical incidences, is equivocal. Incidences of other lesions in other organs listed in Table 9 were included in the table only for purposes of comparison with similar lesions in the

female groups. None of these lesions in male mice were considered to be related to treatment with malathion.

For females, as with males, hepatocyte hypertrophy was observed in all 8000 ppm and 16000 ppm animals, but in none of the animals at 100 ppm or 800 ppm or in the control group. Incidences were 0/55, 0/55, 0/54, 53/53 (average score = 1.7) and 52/52 (average score = 3.1) for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. These lesions were induced by the test material. Mononuclear cell infiltration in the portal areas, mononuclear cell foci in the parenchyma and necrosis occurred at similar incidences in the control and all treatment groups. In the kidney, a dose-related increased incidence of mineralization was observed in the 8000 ppm and 16000 ppm mice. This increase in kidney mineralization was considered to be treatment related. Chronic interstitial nephritis, observed in numerous control and treated mice, was not related to treatment. In the adrenal cortex, the "x zone" had disappeared in nearly all mice, as is normal. A cell hyperplasia and brown degeneration were also frequently reported, but were not attributed to treatment with malathion.

A dose-related decreased incidence of fibrous osteodystrophy of the bone (femur) was observed in all malathion treated female groups. Incidences were 23/55, 14/55, 7/54, 3/53 and 2/52 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. A decreased incidence was also observed in the bone (sternum) for the 16000 ppm group. Incidences were 51/55, 48/55, 50/54, 50/53 and 10/52 for the 0, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. These decreased incidences of fibrous osteodystrophy in the femur and sternum were considered to be related to treatment with the test material. The biological significance of this observation is uncertain.

Additional lesions in female mice that were increased in the 16000 ppm group were the following: increased acinar atrophy in the lacrimal gland, increased mineralization and peribronchial lymphoid infiltration in the lung (also increased at 8000 ppm), increased hemorrhage and brown pigment in the mandibular lymph node,

and increased dilatation in the uterus (also increased at 8000 ppm). Although increased incidences of these lesions in the 8000 ppm and/or 16000 ppm groups suggest a possible treatment related effect, the relationship to treatment is nevertheless considered to be equivocal because many of these lesions occur normally in older mice. Many mice in the control and treatment groups had cysts in the uterus and/or uterine cervix. These cysts were not related to treatment.

The following additional lesions were frequently reported for both males and females in the control and 16000 ppm groups, but were not attributed to treatment with malathion (data not shown in Table 9): brain/mineralization, Harderian gland/chronic inflammation, urinary bladder/mononuclear cell infiltration, mandibular salivary gland/ mononuclear cell infiltration, skin/acanthosis.

Conclusion: The following nonneoplastic microscopic findings in the liver were attributed to treatment with malathion. The biological significance of the findings in the kidney, adrenal cortex and bone are uncertain.

Liver
--hepatocyte hypertrophy in nearly all treated male and female mice at 8000 ppm and 16000 ppm, regardless of time of death or sacrifice

Kidney
--decreased incidence of vacuolation in the convoluted tubules in male mice at 8000 ppm and 16000 ppm, regardless of time of death or sacrifice

--increased incidence of mineralization in female mice at 8000 ppm and 16000 ppm at the 18-month terminal sacrifice

Adrenal Cortex
--early disappearance of the "x zone" in female mice at 8000 ppm and 16000 ppm at the 12-month interim sacrifice

Bone (femur and sternum)
--dose-related decreased incidence of fibrous osteodystrophy in the femur in female mice at 100 ppm, 800 ppm, 8000 ppm and 16000 ppm at the 18-month terminal sacrifice

--decreased incidence of fibrous osteodystrophy in the sternum in female mice at 16000 ppm at the 18-month terminal sacrifice.

NEOPLASTIC FINDINGS

Results:

0 - 12 Months, Including 12-Month Interim Sacrifice: Only a few tumors were observed in either male or female mice during the first 12 months of this study. Other than 1 hepatocellular adenoma observed in 1 male mouse in the 16000 ppm group at the 12-month interim sacrifice, none of these tumors were attributed to treatment with malathion.

12 - 18 Months, Including 18-Month Interim Sacrifice: Treatment-related liver tumors were observed in both male and female mice in this study. No other types of tumors were observed in either male or female mice that were related to treatment with the test material. A slightly increased incidence of cystadenomas in the ovary of 16000 ppm females during the last 6 months of the study (0/54, 0/10, 0/14, 0/11 and 3/51 for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively), in the absence of any other pathological findings in the ovary, was not considered to be related to treatment with malathion. All other tumors that were noted in both male and female mice in this study were few in number and not dose-related.

Incidences of hepatocellular adenomas, hepatocellular carcinomas and combined hepatocellular adenomas and carcinomas for the male and female mice in this study are presented in Table 10 and Table 11 respectively (p. 53 and p. 54 respectively). Some incidences presented in these tables may appear different than those presented in summary tables in the study report because animals with both an adenoma and a carcinoma were counted twice in the study report (i.e. as one adenoma and one carcinoma) whereas in Tables 10 and 11 in this DER these animals were counted only once (as one carcinoma). Also, although the data for liver tumors were statistically analyzed in the study report, the analysis was based on incidences which "double counted" animals with both an adenoma and a carcinoma (as explained above). For the purpose

of statistical analyses, it has been standard practice in HED to count these animals only once. Hence, statistical analyses of the liver tumor data in the study will be provided by HED in a separate report.

Historical control data for liver tumors in B6C3F1 mice for studies conducted at International Research and Development Corporation are presented in Table 12 (p. 55). It should be noted that the percent incidences presented in Table 12 are based on incidences per number of animals examined microscopically only at the terminal sacrifice, and therefore are most comparable to the percent incidences in Tables 10 and 11 for the period 12 months - termination. Even here, however, the data are not strictly comparable because the data in Tables 10 and 11 also include the few animals that died or were sacrificed in extremis during the last 6 months of the study.

For males, a hepatocellular adenoma was noted in one 16000 ppm animal at the 12-month interim sacrifice and a hepatocellular carcinoma in one 800 ppm animal found dead at 15 months. All other liver tumors were observed at the 18-month terminal sacrifice. For the last 6 months of the study (including the terminal sacrifice), a dose-related increased incidence of hepatocellular adenomas was observed at 8000 ppm and 16000 ppm. In percentage units, incidences of 1.9%, 7.3%, 3.6%, 21.8% and 94.1% were observed for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. The study report also indicated that 35 male mice at 16000 ppm had multiple adenomas present whereas multiple adenomas were not present in any other group of male mice. It should be noted that the percent incidences in the control (1.9%), 100 ppm (7.3%) and 800 ppm (3.6%) groups were far below the percent incidence range reported for the male historical control animals for 18 month studies (14.3-21.7%). For hepatocellular carcinomas during the same period, percent incidences were 0.0%, 10.9%, 5.5%, 10.9% and 2.0% for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. Although increased at all doses compared to the concurrent control group, the response was not dose-related. The percent incidence at 100 ppm (10.9%) and at 8000 ppm (10.9%), however, did exceed the upper historical control percent incidence for 18-month studies

(0.0-6.4%). For combined adenomas and carcinomas during the last 6 months of the study, the percent incidences were 1.9%, 18.2%, 9.1%, 32.7% and 96.1% for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. For the male mice in this study, more hepatocellular tumors (adenomas, carcinomas and combined adenomas/ carcinomas) were observed at 100 ppm than at 800 ppm. Thus, a dose-related response was not observed at the lower dose levels of 100 ppm and 800 ppm, whereas a dose-related response was clearly observed at the higher dose levels of 8000 ppm and 16000 ppm. How to interpret the increased numbers of hepatocellular tumors at 100 ppm, but not at 800 ppm, for the male mice in this study is not clear at this time.

For females, no liver tumors were found in any animals until a hepatocellular adenoma was observed in one animal that died following blood collection just prior to the terminal sacrifice at 18 months. All other liver tumors were observed at the 18-month terminal sacrifice. For the last 6 months of the study (including the terminal sacrifice), a dose-related increased incidence of hepatocellular adenomas was observed at 8000 ppm and 16000 ppm. The percent incidences were 0.0%, 1.8%, 0.0%, 17.0% and 80.8% for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. One mouse at 8000 ppm and 23 mice at 16000 ppm had multiple adenomas present. The incidences at 8000 ppm (17.0%) and 16000 ppm (80.8%) exceeded the upper historical control percent incidence for 18 month studies (0.0-10.6%). For hepatocellular carcinomas during the same period, relatively few were observed (not more than 2 in any dose group) and they were not dose-related. Percent incidences were 1.8%, 0.0%, 3.7%, 1.9% and 3.8% for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively. The percent incidence at 800 ppm (3.7%) and at 16000 ppm (3.8%) exceeded the upper historical control percent incidence for 18 month studies (0.0-2.3%). For combined adenomas and carcinomas during the last 6 months of the study (including the terminal sacrifice), the percent incidences were 1.8%, 1.8%, 3.7%, 18.9% and 84.6% for the control, 100 ppm, 800 ppm, 8000 ppm and 16000 ppm groups respectively.

Conclusion: For both male and female mice in this study, the dose-related increased incidences of hepatocellular adenomas and of combined adenomas/carcinomas at 8000 ppm and 16000 ppm were attributed to treatment with malathion. For male mice, however, it is noted that the percent incidences of hepatocellular adenomas in the control, 100 ppm and 800 ppm groups were far below the percent incidence range reported for the male historical control animals for 18 month studies. Regarding hepatocellular carcinomas, the data are equivocal. Incidences at 100 ppm and 8000 ppm in males and at 800 ppm and 16000 ppm in females were above concurrent control incidences and also above the upper historical control percent incidences for 18 month studies. However, for both males and females, the numbers of hepatocellular carcinomas were rather low in all groups and the incidences were not dose-related. The increased numbers of hepatocellular tumors observed in this study in both males and females were due primarily to increased numbers of adenomas.

For the male mice in this study, more hepatocellular tumors (adenomas, carcinomas and combined adenomas/carcinomas) were observed at 100 ppm than at 800 ppm. Thus, a dose-related response was not observed at the lower dose levels of 100 ppm and 800 ppm. How to interpret the increased numbers of hepatocellular tumors at 100 ppm, but not at 800 ppm, for the male mice in this study is not clear at this time.

Since all the hepatocellular tumors observed in this study in both male and female mice, except for 2 tumors in male mice and 1 tumor in a female mouse, were observed at the terminal sacrifice, there was no apparent decreased time to tumor for the malathion-treated mice in this study.

III. SUMMARY OF STUDY RESULTS AND DISCUSSION

A. Summary

1. Malathion was administered in the diet to male and female B6C3F1 mice at dose levels of 0 (control), 100 ppm, 800 ppm, 8000 ppm and 16000 ppm for 18 months.

2. At 16000 ppm (equivalent to 2978 mg/kg/day in males and 3448 mg/kg/day in females), the following treatment-related effects were observe

   a. decreased absolute body weights in males and females

--statistically significant dose-related decreases throughout entire duration of study
--decreased 20.0% in males and 16.1% in females at 18 months

b. decreased food consumption in males and females
--statistically significant dose-related decreases after 26 weeks
--equivocal decreases prior to 26 weeks
--decreased 5.9% in males and 12.5% in females for entire duration of study

c. decreased plasma cholinesterase activity in males and females
--statistically significant dose-related decrease at 12 and 18 months
--$\geq$ 93 %

d. decreased erythrocyte cholinesterase activity in males and females
--statistically significant dose-related decrease at 9, 12 and 18 months
--$\geq$ 67%

e. decreased brain cholinesterase activity in males and females
--statistically significant decrease at 18 months
--37-43%

f. increased liver weights in males and females
--statistically significant dose-related increase at 12 and 18 months in males
--increase at 12 and 18 months in females was not consistently statistically significant
--absolute liver weight increased 40% in males and 13% in females at 18 months

g. increased hepatocellular hypertrophy in liver of males and females
--in nearly all animals at 12 months and in all animals at 18 months

h. decreased vacuolation in convoluted tubules in kidney of males
--in all animals at 12 and 18 months

i. increased mineralization in kidney of females
--at 18 months

j. decreased fibrous osteodystrophy in femur and sternum of females
--at 18 months

k. early disappearance of "x zone" in adrenal cortex of females
--at 12-month interim sacrifice

l. increased hepatocellular adenomas in livers of males and females

--dose-related increase during last 6 months of study
--94.1% incidence in males and 80.8% incidence in females

m. equivocal increase in hepatocellular carcinomas in females
--3.8% incidence during last 6 months of study

n. increased combined hepatocellular adenomas/carcinomas in males and females
--dose-related increase during last 6 months of study
--96.1% incidence in males and 84.6% incidence in females

3. At 8000 ppm (equivalent to 1476 mg/kg/day in males and 1707 mg/kg/day in females), the following treatment-related effects were observed.

a. decreased absolute body weights in males and females
--statistically significant dose-related decreases throughout entire duration of study
--decreased 14.3% in males and 9.7% in females at 18 months

b. decreased food consumption in males and females
--statistically significant dose-related decreases after 26 weeks
--decreased 2.0% in males and 5.4% in females for entire duration of study

c. decreased plasma cholinesterase activity in males and females
--statistically significant dose-related decrease at 12 and 18 months
--$\geq$ 86%

d. decreased erythrocyte cholinesterase activity in males and females
--statistically significant dose-related decrease at 9, 12 and 18 months
--$\geq$ 61%

e. increased liver weights in males
--statistically significant dose-related increase at 12 and 18 months
--absolute liver weight increased 19% at 18 months

f. increased hepatocellular hypertrophy in liver of males and females
--in nearly all animals at 12 months and in all animals at 18 months

g. decreased vacuolation in convoluted tubules in kidney of males
h. increased mineralization in kidney of females
--at 18 months
i. decreased fibrous osteodystrophy in femur of females
--at 18 months
j. early disappearance of "x zone" in adrenal cortex of females
--at 12-month interim sacrifice
k. increased hepatocellular adenomas in livers of males and females
--dose-related increase during last 6 months of study
--21.8% incidence in males and 17.0% incidence in females
l. equivocal increase in hepatocellular carcinomas in males
--10.9% incidence during last 6 months of study
m. increased combined hepatocellular adenomas/carcinomas in males and females
--dose-related increase during last 6 months of study
--32.7% incidence in males and 18.9% incidence in females

3. At 800 ppm (equivalent to 143 mg/kg/day in males and 167 mg/kg/day in females), the following treatment-related effects were observed.

a. decreased plasma cholinesterase activity in males and females
--non-significant dose-related decrease at 12 and 18 months in males (23-24%)
--statistically significant dose-related decrease at 12 and 18 months in females (18-36%)
b. decreased erythrocyte cholinesterase activity in males and females
--dose-related decrease at 9, 12 and 18 months in males (37-44%, statistically significant only at 12 months)
--dose-related decrease at 9, 12 and 18 months in females (35-58%, statistically significant at 9 and 18 months)
c. decreased fibrous osteodystrophy in femur of females
--at 18 months
d. equivocal increase in hepatocellular carcinomas in females

--3.7% incidence during last 6 months of study

e. equivocal increase in combined hepatocellular adenomas/carcinomas in males and females
--increased during last 6 months of study
--9.1% incidence in males and 3.7% incidence in females

4. At 100 ppm (equivalent to 17.4 mg/kg/day in males and 20.8 mg/kg/day in females), the following treatment-related effects were observed.

a. decreased fibrous osteodystrophy in femur of females (biological significance is uncertain)
--at 18 months

b. equivocal increase in hepatocellular carcinomas in males
--10.9% incidence at 18 months

c. equivocal increase in combined hepatocellular adenomas/carcinomas in males
--increased during last 6 months of study
--18.2% incidence in males

B. Discussion

The design, conduct and reporting of this study were satisfactory and in accordance with the Subdivision F Guidelines 83-2(b) for carcinogenicity studies in mice and in compliance with the FIFRA Good Laboratory Practice (GLP) standards. The study is classified as Core Guideline.

The 2 highest dose levels used in this study, 16000 ppm (equivalent to 2978 mg/kg/day in males and 3448 mg/kg/day in females) and 8000 ppm (equivalent to 1476 mg/kg/day in males and 1707 mg/kg/day in females), both exceeded the limit dose of 1000 mg/kg/day which is oftentimes used by EPA to establish an upper dose level for carcinogenicity studies in mice and rats. In this instance, however, it should be recalled that EPA required that the highest dose levels in this particular study be 16000 ppm and 8000 ppm in order to duplicate the dose levels used in a previously conducted 1978 NCI carcinogenicity in B6C3F1 mice in which the results were equivocal.

At the highest dose levels used in this study (16000 ppm and 8000 ppm), life-threatening effects were not observed in either males or females as evidenced by the

very few deaths which occurred during the 18 month in-life phase of the study and the lack of any differences in survival rates between control and malathion-treated groups. This finding is noteworthy because these same animals did have substantially decreased mean plasma and erythrocyte cholinesterase activity levels at 12 and 18 months and also highly increased incidences of hepatocellular adenomas and combined hepatocellular adenomas/carcinomas at 18 months. Clearly, neither of these conditions had any effect on survival in this study.

Levels of plasma cholinesterase activity at 12 and 18 months were $\leq$ 7% of the control level for 16000 ppm animals and $\leq$ 14% of the control level for 8000 ppm animals. Levels of erythrocyte cholinesterase activity at these times were $\leq$ 33% of the control level for 16000 ppm animals and $\leq$ 39% of the control level for 8000 ppm animals. In addition, at 18 months, brain cholinesterase activity for 16000 ppm animals was 57-63% of the control level and for 8000 ppm animals was 77-80% of the control level. It is also noteworthy that in spite of these low plasma, erythrocyte and brain cholinesterase activity levels that no clinical signs of toxicity ordinarily associated with poisoning by cholinesterase inhibitor compounds (such as tremors, hyperactivity, salivation, malaise etc.) were observed in these animals at any time during the study.

At 16000 ppm and 8000 ppm, absolute body weights were significantly decreased in a dose-related manner in both males and females throughout the study. At 16000 ppm, body weights for males and females were decreased 20.0% and 16.1% respectively at 18 months and at 8000 ppm, body weights were decreased 14.3% and 9.7% for males and females respectively at 18 months. Food consumption was also reduced in 16000 ppm animals during the first several weeks of the study, but returned to control levels by 13 weeks. It is thought that this initial reduction in food intake may have been due to poor palatability of the diet mixture or possibly to lack of appetite resulting from the low plasma and cholinesterase activity levels presumably present in these animals at that time. After 26 weeks, however, food consumption in both 16000 ppm and 8000 ppm males and females was observed to decrease in a dose-related manner and was apparently treatment-related. The decreases in food consumption were probably not sufficient in magnitude to account fully for the decreased body weights observed in these same animals.

Of most concern in this study was the treatment-related and dose-related increased incidence of hepatocellular tumors observed in both male and female mice at 16000 ppm and 8000 ppm. For mice which died during the last 6 months of the study or were killed at the terminal sacrifice at 18 months, the percent incidences of combined adenomas/carcinomas at 16000 ppm were 96.1% and 84.6% in males and females respectively and at 8000 ppm were 32.7% and 18.9% in males and females respectively. The large majority of these tumors in both males and females were hepatocellular adenomas, which were clearly related to treatment with malathion. Although hepatocellular carcinomas were also observed in these groups and in other treated groups, the incidences were not dose-related and overall the relationship of these carcinomas to treatment with malathion was equivocal. It might be noted that the authors of the study report did not consider the hepatocellular carcinomas observed in the mice in this study to be test substance-related.

Regarding the male mice in this study, more hepatocellular tumors (adenomas, carcinomas and combined adenomas/ carcinomas) were observed at 100 ppm than at 800 ppm. Thus, a dose-related response was not observed at the lower dose levels of 100 ppm and 800 ppm, whereas a dose-related response was clearly observed at the higher dose levels of 8000 ppm and 16000 ppm. How to interpret the increased numbers of hepatocellular tumors at 100 ppm, but not at 800 ppm, for the male mice in this study is not clear at this time.

As would be expected, the increased tumor incidences in the livers of both males and females at 16000 ppm and 8000 ppm were accompanied by concurrent observations of masses, nodules and foci in the livers of these animals at the terminal sacrifice and also by increased liver weights and highly increased hepatocellular hypertrophy in the livers at 12 and 18 months. The data for hepatocyte hypertrophy was quite remarkable in that an extremely steep dose-response curve was observed for both males and females in this study. Thus, in the control, 100 ppm and 800 ppm groups, <u>no</u> case of hepatocellular hypertrophy was observed in any animal at any time during the entire duration of this study. At 16000 ppm and 8000 ppm, however, the incidence of hepatocellular hypertrophy during the first year of the study (including the 12-month interim sacrifice) was $\geq$ 70% in males and $\geq$ 50% in females and during the last 6 months of the study (including the 18-month terminal sacrifice) was <u>100%</u> in both males and females.

Other findings were observed in this study that appeared to be related to treatment, but their biological significance was uncertain. These findings included the following: decreased vacuolation in the convoluted tubules of the kidneys in males; increased mineralization of the kidneys in females; decreased fibrous osteodystrophy of the femur and sternum in females; and early disappearance of the "x zone" in the the adrenal cortex of females.

The NOEL for cholinesterase inhibition for both sexes was estimated to be 100 ppm for plasma and erythrocyte cholinesterase and 8000 ppm for brain cholinesterase. The NOEL for systemic effects was 800 ppm, based on decreased body weights and food consumption in males and females, increased liver weight in males and females and increased hepatocellular hypertrophy in males and females. The biological significance of the decreased vacuolization of convoluted tubules in the kidney in males, increased mineralization of the kidney in females, decreased fibrous osteodystrophy in females and early disappearance of the "x zone" of the adrenal cortex in females at this and other doses is uncertain.

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Table 1. Fates of Animals on Study -- Male and Female Mice Given Malathion in the Diet for 78 Weeks [1]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Unscheduled [2]					
Deaths (Weeks)					
0 - 13	0	0	0	0	1
14 - 26	0	0	0	0	1
27 - 39	0	0	0	0	2
40 - 52	3	0	0	0	0
53 - 65	2	1	4	0	1
66 - 78	2	3	3	1 [3]	0
Interim Sacrifice					
52 weeks	8	10	10	10	10
Terminal Sacrifice					
78 weeks	50	51	48	54	50 [4]
Total	65	65	65	65	65

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Unscheduled [2]					
Deaths (Weeks)					
0 - 13	0	0	0	1	1
14 - 26	0	0	0	1 [5]	1
27 - 39	0	0	1	0	1 [5]
40 - 52	0	0	0	0	0
53 - 65	0	0	1	0	0
66 - 78	0	3	1	0	1 [3]
Interim Sacrifice					
52 weeks	10	10	10	10	10
Terminal Sacrifice					
78 weeks	55	52	52	53 [4]	51
Total	65	65	65	65	65

(1) Data extracted from Table 1 (p. 38) and Appendix C (pp. 253-273) of study report.
(2) Includes animals found dead, sacrificed *in extremis* and died prior to sacrifice *in extremis* except as noted in footnotes below.
(3) Died following blood collection (at 77+ weeks).
(4) One died following blood collection at terminal sacrifice.
(5) Accidental death.

Table 2. Mean Absolute Body Weights (gm) for Male and Female Mice Given Malathion in the Diet for 78 Weeks [1]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Week of Study					
0	23	23	23	23	22
1	23	24	23	22 **	21 **
3	25	25	25	24 **	22 **
5	26	26 *	26	25	24 **
7	26	27	27	26 **	24 **
9	27	27	27	26 **	25 **
11	28	28	28	27 **	25 **
13	28	28	28	27 **	25 **
26	31	31	30	28 **	27 **
39	32	32	31	29 **	28 **
51	34	35	33	30 **	28 **
64	34	35	34	30 **	29 **
78	35	34	34	30 **	28 **

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Week of Study					
0	20	20	20	20 *	20 **
1	21	21	21	20 **	18 **
3	23	23	22	21 **	19 **
5	24	24	24	22 **	20 **
7	24	25	25	23 **	21 **
9	25	26 **	25	24 **	22 **
11	26	26	26	24 **	22 **
13	26	26	26	24 **	22 **
26	28	28	28	26 **	24 **
39	29	29	29	26 **	24 **
51	31	31	32	27 **	25 **
64	31	31	31	28 **	25 **
78	31	31	31	28 **	26 **

[1] Data extracted from Table 3 (pp. 56-63) of study report.

* Significantly different from the control group ($p \leq 0.05$).
** Significantly different from the control group ($p \leq 0.01$).

Table 3. Mean Food Consumption (gm/animal/day) for Male and Female Mice Given Malathion in the Diet for 78 Weeks [1]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Week of Study					
1	4.9	5.0 **	5.2 **	5.0	3.9 **
3	5.1	5.2 *	5.2	5.2	4.7 **
5	5.0	5.0	5.1	5.3 **	4.8 **
7	5.2	5.2	5.4	5.4	5.2
9	5.2	5.3	5.4 *	5.6 **	5.0 **
11	5.0	5.1	5.3 **	5.3 *	5.1
13	5.4	5.3	5.5	5.6	5.4
26	5.0	5.9	5.0	5.1	4.8
39	5.1	5.0	5.1	4.9 **	4.6 **
51	5.1	5.2	5.1	4.7 **	4.7 **
64	5.3	5.2	5.1	4.7 **	4.6 **
78	5.1	5.2	5.1	4.7 **	4.6 **

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Week of Study					
1	5.2	5.4 **	5.3	5.2	3.9 **
3	5.5	5.6	5.6	5.5	4.5 **
5	5.4	5.6	5.7	5.5	4.6 **
7	5.8	5.8	5.7	5.7	5.1 **
9	5.8	5.8	5.8	5.6	5.2 **
11	5.6	5.7	5.7	5.5	5.2 **
13	6.0	5.9	6.0	5.7 *	5.7 *
26	5.5	5.5	5.5	5.0 **	4.9 **
39	5.5	5.5	5.5	5.0 **	4.7 **
51	5.7	5.5	5.6	5.2 **	5.0 **
64	5.8	5.4	5.6	4.8 **	4.7 **
78	5.6	5.4	5.4	4.8 **	4.4 **

[1] Data extracted from Table 4 (pp. 64-71) of study report.

* Significantly different from the control group ($p \leq 0.05$).
** Significantly different from the control group ($p \leq 0.01$).

Table 4. Residual Cholinesterase Activity [1] for Plasma, Erythrocyte and Brain for Male and Female Mice Given Malathion in the Diet for 18 Months [2]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Plasma					
12 mo.	100%	94%	77%	14% **	7% **
18 mo	100	110	76	10 **	5 **
Erythrocyte					
9 mo.	100	108	63	29 *	29 *
12 mo.	100	92	63 *	35 **	31 **
18 mo.	100	85	56	10 **	8 **
Brain					
12 mo.	100	110	112	96	76
18 mo.	100	101	93	77	63 **

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
Plasma					
12 mo.	100%	100%	82% *	11% **	6% **
18 mo	100	88	64 *	8 **	4 **
Erythrocyte					
9 mo.	100	100	61 **	39 **	33 **
12 mo.	100	102	65	35 **	31 **
18 mo.	100	69	42 *	8 **	8 **
Brain					
12 mo.	100	104	98	109	80
18 mo.	100	90	97	80	57 **

[1] Percent of cholinesterase activity remaining as compared to mean of control group for the same sex.

[2] Data extracted from Table 7 (pp. 88-91) of study report.

* Significantly different from the control group ($p \leq 0.05$).
** Significantly different from the control group ($p \leq 0.01$).

Table 5. Selected Macroscopic Observations at Terminal Sacrifice for Male and Female Mice Given Malathion in the Diet for 18 Months [1]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
No. Exam.	50	51	48	54	50
Liver					
Mass	0	8	4 [2]	5	18
Nodule	5	2	3	10	19
Focus/foci (tan/yellow)					
--trace	0	0	0	1	4
--mild	0	0	1	1	13
--moderate	0	0	0	0	1
Lymph Node, Hepatic					
Enlarged	0	0	2 [3]	1	1

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
No. Exam.	55	52	52	53	51
Liver					
Mass	1	0	3	2	10
Nodule	1	2	0	9	29
Focus/foci (tan/yellow)					
--trace	0	0	0	1	6 [4]
--mild	0	0	0	1	3
--moderate	0	0	0	0	0
Lymph Node, Hepatic					
Enlarged	0	0	0	0	1

(1) Data extracted from Table 8 (pp. 92-104) of study report.

(2) One additional mass was found in a mouse which died at 12 - 18 months.

(3) One additional enlarged hepatic lymph node was found in a mouse which died at 12 - 18 months.

(4) One additional focus/foci (tan/yellow; trace) was found in a mouse which died at 12 - 18 months.

Table 6. Mean Organ Weights, Organ/Body Weight Ratios and Organ/Brain Weight Ratios for Male Mice Given Malathion in the Diet for 12 Months and for 18 Months [1]

Males	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
12 Months					
Body Weight	31	32	33	28 **	29 **
Brain					
Absolute	0.47	0.47	0.48	0.45	0.45 *
Brain/BW	14.9	14.6	14.6	16.0	15.6
Kidney					
Absolute	0.69	0.78 *	0.77	0.63	0.64
Kidney/BW	2.21	2.38 *	2.35	2.21	2.23
Kidney/Brain	1.5	1.7 *	1.6	1.4	1.4
Liver					
Absolute	1.62	1.71	1.78	1.98 **	2.38 **
Liver/BW	5.15	5.19	5.42	6.95 **	8.30 **
Liver/Brain	3.45	3.69	3.73	4.37 **	5.32 **
18 Months					
Body Weight	34	34	34	30 **	28 **
Brain					
Absolute	0.47	0.47	0.47	0.46	0.46 **
Brain/BW	13.9	13.9	13.9	15.5 **	16.1 **
Kidney					
Absolute	0.84	0.86	0.88	0.79	0.68 **
Kidney/BW	2.46	2.51	2.62	2.66	2.38
Kidney/Brain	1.8	1.8	1.9	1.7	1.5 **
Liver					
Absolute	1.90	2.09	1.96	2.26 **	2.66 **
Liver/BW	5.59	6.15	5.82	7.51 **	9.38 **
Liver/Brain	4.05	4.46	4.21	4.87 **	5.85 **
Heart					
Absolute	0.22	0.23	0.22	0.21	0.18 **
Heart/BW	6.58	6.77	6.62	6.95	6.40
Heart/Brain	4.76	4.90	4.76	4.48	3.99 **
Lung					
Absolute	0.27	0.28	0.27	0.28	0.28
Lung/BW	8.01	8.32	8.00	9.46 **	9.71 **
Lung/Brain	5.81	6.00	5.79	6.09	6.06
Testes					
Absolute	0.21	0.21	0.22	0.22	0.21
Testes/BW	6.30	6.30	6.46	7.29 **	7.56 **
Testes/Brain	4.55	4.54	4.64	4.70	4.72

[1] Data extracted from Table 9 (pp. 105-128) of study report.

* Significantly different from the control group ($p \leq 0.05$).
** Significantly different from the control group ($p \leq 0.01$).

Table 7. Mean Organ Weights, Organ/Body Weight Ratios and Organ/Brain Weight Ratios for Female Mice Given Malathion in the Diet for 12 Months and for 18 Months [1]

Females	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
12 Months					
Body Weight	30	31	30	27 **	26 **
Brain					
Absolute	0.48	0.49	0.48	0.47	0.46
Brain/BW	16.3	15.7	16.1	17.5	18.2 **
Kidney					
Absolute	0.50	0.54 *	0.55 *	0.50	0.51
Kidney/BW	1.66	1.75	1.82 *	1.88 **	1.99 **
Kidney/Brain	1.0	1.1	1.2	1.1	1.1
Liver					
Absolute	1.55	1.68	1.56	1.66	1.92 **
Liver/BW	5.22	5.39	5.22	6.21 **	7.56 **
Liver/Brain	3.23	3.45	3.24	3.55	4.16 **
18 Months					
Body Weight	31	31	31	28 **	26 **
Brain					
Absolute	0.50	0.49	0.50	0.48 **	0.46 **
Brain/BW	16.2	16.0	15.9	17.3 *	17.8 **
Kidney					
Absolute	0.58	0.59	0.63 **	0.59	0.55
Kidney/BW	1.88	1.94	2.03 **	2.15 **	2.16 **
Kidney/Brain	1.2	1.2	1.3 **	1.2 **	1.2
Liver					
Absolute	1.93	1.77	1.96	1.92	2.18
Liver/BW	6.19	5.76	6.26	6.90	8.51 **
Liver/Brain	3.95	3.64	3.97	4.04	4.79
Heart					
Absolute	0.19	0.19	0.19	0.18	0.15 **
Heart/BW	6.16	6.26	6.07	6.50	5.84
Heart/Brain	3.84	3.95	3.84	3.78	3.29 **
Lung					
Absolute	0.29	0.31	0.27	0.27	0.24 **
Lung/BW	9.54	10.45	8.76	9.92	9.39
Lung/Brain	5.95	6.46	5.52	5.79	5.29
Spleen					
Absolute	0.14	0.17	0.14	0.11 *	0.08 **
Spleen/BW	4.68	5.29	4.64	3.84	3.24
Spleen/Brain	2.92	3.48	2.93	2.24	1.82

[1] Data extracted from Table 9 (pp. 105-128) of study report.

* Significantly different from the control group ($p \leq 0.05$).
** Significantly different from the control group ($p \leq 0.01$).

Table 8. Selected Nonneoplastic Microscopic Findings for Male and Female Mice Given Malathion in the Diet for 18 Months [1]

0 - 12 MONTHS

MALES	0 ppm		100 ppm		800 ppm		8000 ppm		16000 ppm	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
0 - 12 Mo [2]	3	8	0	10	0	10	0	10	4	10
Liver										
No. Exam.	3	8	0	10	0	10	0	10	4	10
Hepatocyte hypertrophy	0/11		0/10		0/10		7/10 (1.0) [3]		12/14 (2.3)	
Kidney										
No. Exam.	3	8	0	10	0	10	0	10	4	10
Mineralization	3/11 (1.0)		0/10		0/10		0/10		6/14 (1.0)	
Nephritis, interstitial	3/11 (1.0)		6/10 (1.2)		7/10 (1.0)		4/10 (1.0)		7/14 (1.0)	
Vacuolation, conv tubules	11/11 (2.5)		10/10 (1.8)		10/10 (2.4)		1/10 (1.0)		0/14	
Adrenal Cortex										
No. Exam.	3	8	0	10	0	10	0	10	4	10
A cell hyperplasia	3/11 (1.0)		6/10 (1.0)		1/10 (1.0)		5/10 (1.0)		1/14 (1.0)	
x zone present [4]	0/11		0/10		0/10		0/10		0/14	

FEMALES	0 ppm		100 ppm		800 ppm		8000 ppm		16000 ppm	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
0 - 12 Mo [2]	0	10	0	10	1	10	2	10	3	10
Liver										
No. Exam.	0	10	0	10	1	10	2	10	3	10
Hepatocyte hypertrophy	0/10		0/10		0/11		6/12 (1.0)		13/13 (2.2)	

Table 8. Cont.

0 - 12 MONTHS

FEMALES (Cont.)

Kidney					
No. Exam.	0 10	0 10	1 10	2 10	3 10
Mineralization	0/10	0/10	0/11	0/12	1/13 (1.0)
Nephritis, interstitial	3/10 (1.0)	1/10 (1.0)	3/11 (1.0)	3/12 (1.0)	3/13 (2.0)
Vacuolation, conv tubules	0/10	0/10	0/11	0/12	0/13
Adrenal Cortex					
No. Exam.	0 10	0 10	1 10	2 10	3 10
A cell hyperplasia	10/10 (2.0)	10/10 (1.9)	11/11 (1.4)	12/12 (1.1)	11/13 (1.7)
x zone present	10/10	8/10	9/11	1/12	0/13
Uterus					
No. Exam.	0 10	0 8	1 7	2 3	3 10
Cyst	9/10 (2.0)	8/8 (2.3)	7/8 (3.0)	3/5 (2.7)	8/13 (1.6)

(1) Data extracted from Table 10 (pp. 129-178) of study report.

(2) Includes mice that died or were sacrificed in extremis during 0 - 12 months (DOS) and mice sacrificed at 12 month interim sacrifice (SAC).

(3) Numbers in parentheses indicate average severity score as follows: trace = 1, mild = 2, moderate = 3, severe = 4.

(4) Males do not have a "x zone" in the adrenal cortex.

Table 9. Selected Nonneoplastic Microscopic Findings for Male and Female Mice Given Malathion in the Diet for 18 Months [1]

12 MONTHS - TERMINATION

MALES	0 ppm		100 ppm		800 ppm		8000 ppm		16000 ppm	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
12 Mo-Term [2]	4	50	4	51	7	48	1	54	1	50
Liver										
No. Exam.	4	50	4	51	7	48	1	54	1	50
Hepatocyte hypertrophy	0/54		0/55		0/55		55/55 (2.1)		51/51 (3.1)	
Mononuclear cell infilt, portal	0/54		2/55 (1.0)		0/55		4/55 (1.0)		4/51 (1.5)	
Mononuclear cell foci parenchyma	5/54 (1.0)		4/55 (1.0)		7/55 (1.0)		9/55 (1.2)		4/51 (1.3)	
Necrosis	2/54 (1.5)		2/55 (2.0)		1/55 (2.0)		3/55 (2.0)		5/51 (2.0)	
Kidney										
No. Exam.	4	50	4	51	7	48	1	54	1	50
Mineralization	45/54 (1.0)		50/55 (1.0)		50/55 (1.0)		55/55 (1.0)		50/51 (1.0)	
Nephritis, interstitial	49/54 (1/0)		51/55 (1.0)		47/55 (1.0)		52/55 (1.0)		43/51 (1.0)	
Vacuolation, conv tubules	54/54 (2.2)		55/55 (1.9)		55/55 (2.1)		33/55 (1.0)		0/51	
Adrenal Cortex										
No. Exam.	4	50	4	51	7	48	1	54	1	50
A cell hyperplasia	31/54 (1.2)		38/55 (1.0)		38/55 (1.0)		38/55 (1.0)		39/51 (1.2)	
x zone present [4]	0/54		0/55		0/55		0/55		0/51	
Degeneration, brown	1/54		6/55		1/55		17/55		7/51	

Table 9. Cont.

12 MONTHS - TERMINATION

MALES (Cont.)

Bone, Femur					
No. Exam.	4 50	4 0	7 0	1 0	1 50
Fibrous osteo-dystrophy	0/54	0/4	0/7	0/1	0/51
Bone, Sternum					
No. Exam.	4 50	4 0	7 0	1 0	1 49
Fibrous osteo-dystrophy	0/54	0/4	0/7	0/1	0/50
Lacrimal Gland					
No. Exam.	4 50	4 0	7 0	1 0	1 50
Acinar atrophy	0/54	0/4	0/7	0/1	0/51
Mononuclear cell infilt	18/54 (1.0)	0/4	1/7 (1.0)	0/1	18/51 (1.1)
Lung					
No. Exam.	4 50	4 51	7 48	1 54	1 50
Mineralization	10/54 (1.0)	10/55 (1.0)	12/55 (1.0)	15/55 (1.0)	28/51 (1.0)
Peribronchial lymph infilt	0/54	0/55	0/55	0/55	0/51
Perivascular mononuc infil	1/54 (1.0)	3/55 (1.0)	2/55 (1.0)	2/55 (1.0)	5/51 (1.2)
Lymph Node, Mandibular					
No. Exam.	4 50	3 0	7 0	1 0	1 49
Hemorrhage	15/54 (1.0)	0/3	1/7 (2.0)	1/1 (1.0)	9/50 (1.4)
Pigment, brown	5/54 (1.2)	1/3 (1.0)	1/7 (1.0)	0/1	12/50 (1.1)

Table 9. Cont.

12 MONTHS - TERMINATION

FEMALES	0 ppm		100 ppm		800 ppm		8000 ppm		16000 ppm	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
12 Mo-Term [2]	0	55	3	52	2	52	0	53	1	51
Liver										
No. Exam.	0	55	3	52	2	52	0	53	1	51
Hepatocyte hypertrophy	0/55		0/55		0/54		53/53 (1.7)		52/52 (3.1)	
Mononuclear cell infilt, portal	8/55 (1.0)		7/55 (1.3)		4/54 (1/0)		5/53 (1.0)		7/52 (1.0)	
Mononuclear cell foci parenchyma	19/55 (1.0)		21/55 (1.0)		12/54 (1.1)		18/53 (1.1)		24/52 (1.0)	
Necrosis	1/55 (1.0)		0/55		0/54		0/53		0/52	
Kidney										
No. Exam.	0	55	3	52	2	52	0	53	1	51
Mineralization	1/55 (1.0)		6/55 (1.0)		8/54 (1.0)		32/53 (1.0)		36/52 (1.0)	
Nephritis, interstitial	27/55 (1.0)		18/55 (1.0)		27/54 (1.0)		33/53 (1.0)		29/52 (1.0)	
Vacuolation, conv tubules	0/55		0/55		0/54		0/53		0/52	
Adrenal Cortex										
No. Exam.	0	55	3	52	2	52	0	53	1	51
A cell hyperplasia	55/55 (2.2)		53/55 (1.9)		54/54 (1.9)		53/53 (1.8)		52/52 (2.2)	
x zone present	2/55		1/55		1/54		0/53		0/52	
Degeneration, brown	23/55 (1.0)		48/55 (1.0)		42/54 (1.0)		25/53 (1.0)		16/52 (1.0)	

Table 9. Cont.

12 MONTHS - TERMINATION

FEMALES (Cont.)

Bone, Femur					
No. Exam.	0 55	3 52	2 52	0 53	1 51
Fibrous osteo-dystrophy	23/55 (1.2)	14/55 (1.2)	7/54 (1.3)	3/53 (1.0)	2/52 (1.0)
Bone, Sternum					
No. Exam.	0 55	3 52	2 52	0 53	1 51
Fibrous osteo-dystrophy	51/55 (1.7)	48/55 (1.6)	50/54 (1.8)	50/53 (1.5)	10/52 (1.0)
Lacrimal Gland					
No. Exam.	0 55	3 0	2 0	0 0	1 51
Acinar atrophy	3/55 (2.0)	0/3	0/2	0/0	10/52 (1.7)
Mononuclear cell infilt	52/55 (1.5)	0/3	1/2 (1.0)	0/0	47/52 (1.6)
Lung					
No. Exam.	0 55	3 52	2 52	0 53	1 51
Mineralization	8/55 (1.0)	6/55 (1.0)	4/54 (1,0)	18/53 (1.0)	26/52 (1.0)
Peribronchial lymph infilt	1/55 (1.0)	0/55	0/54	7/53 (1.6)	6/52 (1.5)
Perivascular mononuc infil	12/55 (1.1)	8/55 (1.5)	17/54 (1.1)	10/53 (1.4)	9/52 (1.2)
Lymph Node, Mandibular					
No. Exam.	0 55	3 1	2 0	0 1	1 51
Hemorrhage	5/55 (1.0)	0/4	1/2 (2.0)	0/1	12/52 (1.1)
Pigment, brown	5/55 (1.0)	0/4	0/2	0/1	12/52 (1.0)

Table 9. Cont.

12 MONTHS - TERMINATION

FEMALES (Cont.)

Uterus					
No. Exam.	0 55	3 42	2 38	0 39	1 51
Cyst	55/55 (2.7)	43/45 (2.9)	36/40 (2.8)	30/39 (2.9)	33/52 (2.1)
Dilatation	1/55 (3.0)	4/45 (4.0)	6/40 (3.3)	12/39 (3.7)	17/52 (3.0)
Uterus, Cervix					
No. Exam.	0 55	3 0	2 0	0 1	1 51
Cyst	53/55 (2.5)	2/3 (1.5)	1/2 (2.0)	0/1	46/52 (2.2)

(1) Data extracted from Table 10 (pp. 129-178) of study report.

(2) Includes mice that died or were sacrificed in extremis during 13 - 18 months (DOS) and mice sacrificed at 18 month terminal sacrifice (SAC).

(3) Numbers in parentheses indicate average severity score as follows: trace = 1, mild = 2, moderate = 3, severe = 4.

(4) Males do not have a "x zone" in the adrenal cortex.

Table 10. Liver Tumors in Male Mice Given Malathion in the Diet for 18 Months [1] [2]

MALES	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
0 - 12 Months [3]					
Hepatocellular adenoma	0/11 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	1/14 (7.1%)
12 Months - Termination [4]					
Hepatocellular adenoma	1/54 (1.9%)	4/55 (7.3%)	2/55 (3.6%)	12/55 (21.8%)	48/51[6] (94.1%)
Hepatocellular carcinoma	0/54 (0.0%)	6/55 (10.9%)	3/55 (5.5%)	6/55 (10.9%)	1/51 (2.0%)
Combined	1/54 (1.9%)	10/55 (18.2%)	5/55 (9.1%)	18/55 (32.7%)	49/51[6] (96.1%)
0 - Termination [5]					
Hepatocellular adenoma	1/65 (1.5%)	4/65 (6.2%)	2/65 (3.1%)	12/65 (18.5%)	49/65[6] (75.4%)
Hepatocellular carcinoma	0/65 (0.0%)	6/65 (9.2%)	3/65 (4.6%)	6/65 (9.2%)	1/65 (1.5%)
Combined	1/65 (1.5%)	10/65 (15.4%)	5/65 (7.7%)	18/65 (27.7%)	50/65[6] (76.9%)

(1) Data extracted from Table 11 (pp. 179-234) of study report.

(2) Mice with both an adenoma and a carcinoma were listed only one time in this table (under carcinoma).

(3) Includes mice that died or were sacrificed in extremis during 0 - 12 months (DOS) and mice sacrificed at 12 month interim sacrifice (SAC).

(4) Includes mice that died or were sacrificed in extremis during 13 - 18 months (DOS) and mice sacrificed at 18 month terminal sacrifice (SAC).

(5) Includes all mice in study.

(6) 35 of these mice had multiple adenomas present.

Table 11. Liver Tumors in Female Mice Given Malathion in the Diet for 18 Months [1] [2]

FEMALES	0 ppm	100 ppm	800 ppm	8000 ppm	16000 ppm
0 - 12 Months [3]					
Hepatocellular adenoma	0/10 (0.0%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/13 (0.0%)
12 Months - Termination [4]					
Hepatocellular adenoma	0/55 (0.0%)	1/55 (1.8%)	0/54 (0.0%)	9/53[6] (17.0%)	42/52[7] (80.8%)
Hepatocellular carcinoma	1/55 (1.8%)	0/55 (0.0%)	2/54 (3.7%)	1/53 (1.9%)	2/52 (3.8%)
Combined	1/55 (1.8%)	1/55 (1.8%)	2/54 (3.7%)	10/53[6] (18.9%)	44/52[7] (84.6%)
0 - Termination [5]					
Hepatocellular adenoma	0/65 (0.0%)	1/65 (1.5%)	0/65 (0.0%)	9/65[6] (13.8%)	42/65[7] (64.6%)
Hepatocellular carcinoma	1/65 (1.5%)	0/65 (0.0%)	2/65 (3.1%)	1/65 (1.5%)	2/65 (3.1%)
Combined	1/65 (1.5%)	1/65 (1.5%)	2/65 (3.1%)	10/65[6] (15.4%)	44/65[7] (67.7%)

(1) Data extracted from Table 11 (pp. 179-234) of study report.

(2) Mice with <u>both</u> an adenoma and a carcinoma were listed only <u>one</u> time in this table (under carcinoma).

(3) Includes mice that died or were sacrificed <u>in extremis</u> during 0 - 12 months (DOS) and mice sacrificed at 12 month interim sacrifice (SAC).

(4) Includes mice that died or were sacrificed <u>in extremis</u> during 13 - 18 months (DOS) and mice sacrificed at 18 month terminal sacrifice (SAC).

(5) Includes all mice in study.

(6) 1 of these mice had multiple adenomas present.

(7) 23 of these mice had multiple adenomas present.

Table 12. Historical Control Data for Liver Tumors in B6C3F1 Mice for Studies Conducted at International Research and Development Corporation from 1983 Through 1992 [1]

MALES	Percent Incidence (Range) [2]
18-Month Studies [3]	
Hepatocellular adenoma	14.3 - 21.7%
Hepatocellular carcinoma	0.0 - 6.4%
24-Month Studies [4]	
Hepatocellular adenoma	9.5 - 29.6%
Hepatocellular carcinoma	6.4 - 11.6%
FEMALES	
18-Month Studies [3]	
Hepatocellular adenoma	0.0 - 10.6%
Hepatocellular carcinoma	0.0 - 2.3%
24-Month Studies [4]	
Hepatocellular adenoma	0.0 - 11.6%
Hepatocellular carcinoma	0.0 - 11.1%

(1) Data extracted from Appendix O (pp. 1398-1451) of study report.

(2) Percent incidence based on incidence/number of animals examined microscopically from terminal necropsy.

(3) Control group data from 5 studies (2 dietary, 1 gavage, 1 drinking water, 1 IP injection); 50-60 mice/sex initiated on study.

(4) Control group data from 7 studies (all dietary); 50-80 mice/sex initiated on study.

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