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

OCT 09 1992

009790

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Methyl Parathion - Mouse Carcinogenicity Study

TO: Larry Schnaubelt PM 72
Special Review and Reregistration Division (H7508W)

FROM: K. Clark Swentzel K. Clark Swentzel 10/8/92
Toxicology Branch II
HED (H7509C)

THROUGH: Marcia van Gemert, Ph.D. Marcia van Gemert 10/8/92
Branch Chief, Toxicology Branch II
HED (H7509C)

BARCODE: D178857
SUBMISSION: S418776
CASE: 818931
PC#: 053501
MRID#: 422154-01
CASWELL#: 372
REGISTRANT: Cheminova Agro A/S

Requested Action

Review mouse oncogenicity study with methyl parathion.

Conclusions

Methyl parathion was fed to male and female $B_6C_3F_1$ mice for 2 years at dietary levels of 0, 1, 7 or 50 ppm, corresponding to average compound intakes of 0, 0.2, 1.6 and 9.2 mg/kg/day in males and 0, 0.3, 2.1 and 13.7 mg/kg/day in females. Survival at 104 weeks was 92-98% and 86-92% in treated males and females, respectively. There was no significant evidence of a carcinogenic effect in either sex. The dosages were considered adequate based on adverse effects observed at a dietary level of 75 ppm in two 9-week studies. Sporadic cholinergic effects were observed in high-dose animals. The NOEL and LOEL for cholinesterase inhibition were 1 and 7 ppm, respectively.

Core classification: Core-guideline. This study satisfies the requirements set forth under Subdivision F Guidelines for a carcinogenicity study in mice (83-2a).

Doc 93022

FINAL

DATA EVALUATION REPORT 009790

Methylparathion

Combined Chronic Toxicity/Oncogenicity Study in Mice

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
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October 5, 1992

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Contract Number: 68D10075
Work Assignment Number: 1-099
Clement Number: 93-133
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Guideline Series 83-2: Oncogenicity Study in Mice

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Signature: K. Clark Swentzel
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EPA Section Head: Clark Swentzel
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Signature: K. Clark Swentzel
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DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/carcinogenicity study in mice

TEST MATERIAL: Methylparathion

SYNONYMS: E 120 technical; O,O-dimethyl-O-(4-nitrophenyl)-phosphorothioate

Tox Chem. Number:

MRID Number: 422164-01

STUDY NUMBER: T 4027023

SPONSOR: CHEMINOVA AGRO A/S, Lemvig, Denmark

TESTING FACILITY: BAYER AG, Fachbereich Toxicologie, Wuppertal, Germany

TITLE OF REPORT: Study for Chronic Toxicity and Carcinogenicity in B6C3F1 Mice

AUTHOR: Eiben, R.

REPORT ISSUED: May 17, 1991

CONCLUSIONS: Methylparathion was fed to B6C3F1 mice for 2 years at dietary levels of 0, [illegible], 7, or 50 ppm, corresponding to average compound intakes of 0, 0.2, 1.6, and [illegible].2 mg/kg/day in males and 0, 0.3, 2.1, and 13.7 mg/kg/day in females. Survival at 104 weeks was 92%-98% in dosed males and 86%-92% in dosed females. No carcinogenic effect was observed in either sex. The dosing was considered adequate based on results of two 9-week studies where a dietary level of 75 ppm caused an increase in tremors and poor general condition. In the present study, tremors were observed in one 50-ppm animal and cholinergic effects were infrequent. However, at 12 and 24 months erythrocyte cholinesterase activity was depressed 40%-57% in both sexes at 7 ppm and 76%-89% at 50 ppm. Brain cholinesterase activity was depressed 63% and 67% in high-dose males and 46% and 62% in high-dose females at 12 and 24 months, respectively, compared to controls. Plasma cholinesterase was significantly ($p<0.05$) depressed in high-dose groups. Body weights were slightly increased in high-dose males and females but food consumption tended to be slightly decreased in the high-dose females. There were no effects of clear toxicological importance on clinical laboratory parameters or organ weights. The gross and histologic findings were normal for animals of this strain and age.

A NOEL for systemic toxicity was not established. The LOEL for cholinesterase depression was 7 ppm (1.6 and 2.1 mg/kg/day in males and females, respectively), and the NOEL for both sexes combined was 0.25 mg/kg/day.

CORE CLASSIFICATION: Core Guideline. The study satisfies the guideline requirements (83-2) for an oral carcinogenicity study in mice. It is Core Supplementary for Guideline Series 83-5 (combined carcinogenicity/chronic toxicity study), since all required parameters were not investigated and a NOEL for systemic toxicity was not achieved.

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A. MATERIALS AND METHODS

1. Test Article Description

Name: Methylparathion

Lot number: 233690479

Purity: 95.5%

Physical property: Clear, yellow-brown liquid

Stability: Stable when stored at 4°C in the absence of light

2. Diet Preparation

Methylparathion was mixed weekly with the animals' food (Altromin® 1321 flour, Altromin GmbH & Co. KG) using a Loedige pelletizing mixer. Included in the mixture was peanut oil (1%) to minimize dust formation. Mixes were analyzed prior to intitiation of the study to insure homogeneity of the test compound.

Results: The test compound was stable in diets at storage periods of 0, 4, 7, 10, and 14 days of storage. Homogeneity was acceptable; samples from the left-front, right-front, and right-rear of the mixer were tested at nominal levels of 1 and 60 ppm, yielding concentrations that were 98±2.1% and 97±0.0% of nominal levels, respectively. Analytical data for 10-13 samples at each dietary level gave mean values (±SD) of 0.931±0.117 ppm, 7.000±0.283 ppm, and 48.20±4.29 ppm at nominal levels of 1, 7, and 50 ppm. These values were calculated by the reviewers and exclude samples not accepted for study and samples to check stability (study report, p. 102).

3. Animals

Species: Mouse

Strain: B6C3F1/CrlBR

Age: Mice were approximately 4-6 weeks old at initiation.

Weight at initiation: Weights ranged from 17 to 24 g for males (mean 21 g) and from 15 to 25 g for females (mean 19 g).

Source: Versuchstierzucht Charles River Wiga GmbH in Sulzfeld

4

Animals were acclimated to laboratory conditions, and healthy, symptom-free animals were assigned to the following groups. 009790

Test Group	Dose in Diet (ppm)	Main Study (24 months)		Satellite Study (12 months)	
		Males	Females	Males	Females
1 Control	0	50	50	15	15
2 Low-dose (LDT)	1	50	50	15	15
3 Mid-dose (MDT)	7	50	50	15	15
4 High-dose (HDT)	50	50	50	15	15

The animals were housed in an environmentally controlled room maintained at 22°±2°C and 50% relative humidity. There were 10 air changes per hour and a 12-hour light/dark cycle.

Rationale for dose selection: Doses were selected on the basis of results from two 9-week feeding studies using B6C3F1 mice at doses of 0, 2, 8, 32, 120, and 400 ppm in one study and 0, 50, and 75 ppm in the other. Doses of 8 ppm in males and 32 ppm in females were tolerated without adverse effects. Cholinesterase activity inhibition was observed in all animals at 50 ppm; and doses of 75 ppm or greater led to reduced weights, increased mortality, tremors, and a depression of general condition.

4. Statistics

Means and standard deviations were calculated from individual animal results, and 95% and 99% confidence levels were indicated. The Whitney-Mann U test was used to conduct a two-tailed comparison with control data. Survival curves were analyzed with the BMDP Routine 1L, and the survival was compared with control values with the Breslow test (generalized Wilcoxon test). Cholinesterase activity data were tested for homogeneity of variance with a one-way analysis of variance followed by Dunnett's test. Heterogeneous data were transformed to obtain homogeneous variances. For analysis of organ weight data, outlier values were censored if the values were five times greater than the mean because of a tumor. Implausible data points were also eliminated.

5. Quality Assurance

A signed and dated (May 14, 1991) quality assurance statement was provided.

B. METHODS AND RESULTS

1. General Observations

Animals were inspected twice daily for mortality and moribundity, and clinical symptoms and anomalies were recorded. Detailed individual examinations, inspecting body surfaces, body openings, posture, general behavior, respiration, and excretory products, were conducted weekly. Animals found sick or exhibiting neoplasms that could lead to death were set aside and observed more frequently. Moribund animals were sacrificed prematurely.

Results: A poor general condition was observed primarily in animals that died or became moribund during the latter part of the study. The incidences were 1, 2, 9, and 8 in males receiving 0, 1, 7, and 50 ppm, respectively, and 5, 3, 5, and 1 in females of the same groups. Hair loss was observed in 6-9 males and 10-16 females in the various groups; there was no dose-related change in incidence. Cholinergic signs were infrequent; one female receiving 7 ppm displayed paralysis, and one male at 50 ppm was observed with tremors; piloerection was observed in 2 males each in the control and 7-ppm groups and in one female in the 1-ppm group. No increases in the incidence of masses were observed in the dosed groups. Other observations were sporadic and infrequent.

Table 1 summarizes data on mortality incidences and percent survival at representative intervals. Percent survival was greater than 95% in all groups at week 52. After the interim sacrifice (days 370-372), the number of animals in all groups was adjusted to 50 and percent survival was based on 50 as the denominator. At 104 weeks, survival ranged from 80% to 92% in male groups and from 86% to 92% in female groups. No dose-related effect on survival was seen.

2. Body Weights/Food and Water Consumption/Test Material Intake

Body weights were recorded for individual animals weekly throughout the study. Food consumption was determined individually for the 20 animals in each group with the highest numbers. Consumption values for these animals (10-20) were totaled, divided by the number of days and animals, and values were expressed as g/animal/day or g/kg body weight/day (based on body weight at the first day of the week when food was offered). Weekly and cumulative food consumption data (for the entire study) were tabulated. Water consumption was measured every fourth week and tabulated by group as g/animal/day or g/kg/day; cumulative values were also calculated.

Body Weights

Table 2 summarizes mean body weight data at selected study intervals. The body weights of the 1- and 7-ppm groups were comparable to those of the control groups in both sexes. In the high-dose group, both sexes were significantly heavier than control animals during the latter two-thirds of the study, reaching levels up to 21% higher for males and 20% higher for females at week 68.

Food and Water Consumption

Although statistically significant increases and decreases in food consumption values were observed in the mid- and high-dose groups of both sexes, values were generally within 10% of the control values in all dosed groups. The overall food consumption was decreased in the high-dose groups although these groups tended to have increased mean body weights. The average food consumption values were 6.4, 6.5, 6.8, and 6.0 g/animal/day in males receiving 0, 1, 7, and 50 ppm, respectively, and 8.6, 8.5, 8.0, and 7.9 g/animal/day in females at the same doses. On a body weight basis, 50-ppm females consumed 15% less food than controls. Food efficiency was enhanced, but data on efficiency were not provided. Water intake was variable from week to week, but no important differences between control and dosed groups were observed.

Test Material Intake

The mean compound intake was 0.2, 1.6, and 9.2 mg/kg/day for 1-, 7-, and 50-ppm males and 0.3, 2.1, and 13.7 mg/kg/day for females of the same dose groups.

3. Ophthalmoscopic Examination

Ophthalmoscopic examinations were not performed.

4. Clinical Pathology

Blood samples for hematology and clinical chemistry parameters were obtained from the retro-orbital venous plexus of 20 animals/sex/group at 12 and 24 months. For glucose determinations, samples from nonfasted animals were drawn from the caudal vein. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
Reticulocyte count (RETIC)
X Red cell morphology
X Leukocyte differential count**
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)

**Differential blood counts were also performed on smears from 10/sex/group at 18 months.

*Recommended by Subdivision F (November 1984) Guidelines

Results: No effects on hematology values that were of any biologic importance were observed. Slight shifts in the percentages of monocytes and lymphocytes were observed at 18 months at the 7- and 50-ppm dose levels, but these changes were not large enough to indicate an effect of dosing.

(b) Blood (Clinical) Chemistry

Electrolytes

Calcium*
Chloride*
Magnesium*
Phosphorus*
Potassium*
Sodium*

Enzymes

X Alkaline phosphatase (ALP)*
X Cholinesterase
Creatinine phosphokinase
Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
Gamma glutamyltransferase (GGT)

Other

Albumin*
Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol (total)*
Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results: Table 3 summarizes mean data for cholesterol, urea, glucose, and insulin levels. There was an apparent trend for increased serum cholesterol levels in males and females at 7 and 50 ppm. The increases were significant ($p<0.01$) in 50-ppm males at 12 months and in females receiving 7 and 50 ppm at 24 months. The biological importance of the increases are not clear since the increases were slight and not consistent for all intervals.

Blood urea levels were significantly decreased ($p<0.01$) at 54 weeks in males receiving 50 ppm; no marked decrease was seen in 50-ppm males at 104 weeks and no effects were observed in females. The insulin level was significantly increased ($p<0.01$) in males at 50 ppm; this change was caused by relatively high levels in 2/10 mice; a corresponding change was not observed in females. Decreases in aspartic aminotransferase activity were observed in 50-ppm males at 12 and 24 months and in 50-ppm females at 24 months; increases in the activity of this enzyme, not decreases, are an indication of a toxic effect on liver. Other changes in clinical chemistry parameters were sporadic and not considered related to dosing with methylparathion.

(c) Urinalysis

Urinary parameters were not examined.

(d) Cholinesterase Activity

Plasma and erythrocyte cholinesterase activities were measured for 10 animals/sex/group (using blood samples drawn for clinical laboratory studies) at months 12 and 24 (termination). Brain cholinesterase was determined for 5 randomly selected

animals/sex/group at both the interim and terminal sacrifices. The modified Ellman method was used.

Results: Table 4 summarizes data for cholinesterase activity. Plasma cholinesterase activity was significantly decreased in both males and females receiving 50 ppm at 12 and 24 months. Red cell cholinesterase activities were significantly depressed at 12 and 24 months in both sexes receiving 7 or 50 ppm. The decreases ranged from 40 to 90% compared to controls. Brain cholinesterase activity was significantly depressed at both intervals in males receiving 7 and 50 ppm and in females receiving 50 ppm.

5. Sacrifice and Pathology

Animals that died spontaneously and those that were sacrificed moribund or sacrificed by design at the interim or terminal sacrifice were necropsied and received a detailed gross pathology assessment. The organs marked below with an X were fixed and stained for microscopic examination. In addition, the tissues marked with XX were weighed at terminal sacrifice; only brain, liver, kidneys, adrenals, and testes were weighed at the interim sacrifice.

Digestive System

X Tongue
X Salivary glands*
X Esophagus*
X Stomach*
X Duodenum*
X Jejunum*
X Ileum*
X Cecum*
X Colon*
X Rectum
XX Liver*
X Gallbladder*
X Pancreas*

Respiratory

X Trachea*
XX Lungs*

Cardiovascular/Hematologic

X Aorta*
X Heart*
X Bone marrow*
X Lymph nodes (mesenteric and mandibular)*
XX Spleen

Urogenital

XX Kidneys*
X Urinary bladder*
XX Testes*
X Epididymes*
X Prostate
X Seminal vesicle
XX Ovaries
X Uterus*
X Vagina

Neurologic

XX Brain (3 levels)
X Peripheral nerve (sciatic nerve)*
X Spinal cord (three levels)*
X Pituitary*
X Eyes (optic nerve)*

Glandular

XX Adrenals*
X Lacrimal gland
X Mammary gland
X Thyroids*
Parathyroids*
X Harderian glands

Others

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin
X All gross lesions and masses
X Zymbal gland

*Recommended by Subdivision F (November 1984) Guidelines

(a) Organ Weights

Table 5 summarizes mean data for absolute organ weights and organ-to-body weight ratios for liver and kidney. Slight increases in absolute liver and kidney weights were seen at both the 12- and 24-month sacrifice for 50-ppm males and females. Organ-to-body weights tended to be decreased when compared to controls. The changes are not considered of toxicologic importance since they were slight. They are probably the result of the increase in weight gain in the high-dose males and females compared to that in controls. No important changes were observed in other organs.

(b) Macroscopic Pathology

No toxicologically important gross pathologic findings were observed in the first 372 days of the study (interim sacrifice). Adipose mice were more frequent in the high-dose groups, 4/15 males and 6/11 females compared to controls (1/15 males and 1/14 females). Changes in color and size were observed in several organs in the second year of the study. Table 6 summarizes representative data for gross findings in the main groups. Greater amounts of adipose tissue were found in high-dose males and females; the incidence at terminal sacrifice was 14/42 for males and 4/46 for females receiving 50 ppm compared to no similar findings in 33 control males and 44 control females.

(c) Microscopic Pathology

Nonneoplastic: Table 7 summarizes nonneoplastic findings. Round cell infiltration was a frequent finding in several organs; there was no dose-related pattern although the incidence was significantly increased ($p<0.05$) in a few tissues for high-dose animals. The sites at which round cell infiltration was most frequent were kidneys (78%-90% in male groups and 70%-80% in female groups), peribronchial (64%-72% in groups of both sexes), salivary glands (60%-92% in male groups and 42%-58% in female groups), bladder (24%-36% in male groups and 52%-70% in female groups), and liver (14%-24% in male groups and 44%-56% in female groups). In general, there were no dose-trends. Hyperemia was frequent in several tissues. These and other nonneoplastic findings observed are related to aging and probably of no toxicologic consequence.

Neoplastic: Table 8 summarizes neoplastic findings in the main groups. No oncogenic response was observed, and the frequency of neoplasms was within the normal range for B6C3F1 mice. At the interim sacrifice (15 animals/sex/group), an ovarian carcinoma was observed in one 7-ppm female and adenomas of the Harderian gland were found in one male and one female in the 1-ppm groups.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study was adequately conducted and reporting was a satisfactory; summary tabulation of the data the reviewers validated was supported by the individual animal data. The study author indicated that the increased body weight gains in high-dose males and females compared to controls were due to a test substance-related change in anabolic

metabolism. This was based on an increase in the insulin level in high-dose males. The reviewers assess that the data do not support this conclusion since the increase in insulin level seen in high-dose males was caused by high values in 2 of 10 mice; a similar effect was not observed in females, there was no apparent trend in blood glucose levels, and changes in cholesterol levels were slight with no abnormally high individual values. The increases in absolute weights of liver and kidneys in high-dose mice of both sexes was not considered of toxicologic importance. The changes were due to an increased body weight and the organ-to-body weight ratios were close to controls and in all cases slightly lower.

The reveiwers agree with the study author's conclusions that there was no evidence of carcinogenicity and that nonneoplastic lesions were related to aging and not a consequence of dosing. A NOEL for systemic toxicity was not established. The LOEL and NOEL for cholinesterase activity depression are 7 ppm and 1 ppm, respectively.

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Table 1. Cumulative Mortality and Percent Survival of Mice Fed Methylparathion for 2 Years

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Dose (ppm)		Week 26	52	78[a]	104[a]
		Males			
0	Mortality	0	0	1	8
	Percent survival	100	100	98	84
1	Mortality	0	0	0	1
	Percent survival	100	100	100	98
7	Mortality	1	1	1	10
	Percent survival	98.4	98.4	98	80
50	Mortality	4	4	1	4
	Percent survival	93.9	93.9	98	92
		Females			
0	Mortality	0	1	1	6
	Percent survival	100	95.4	98	88
1	Mortality	2	2	0	6
	Percent survival	96.9	96.9	100	88
7	Mortality	0	1	1	7
	Percent survival	100	95.4	98	86
50	Mortality	2	3	0	4
	Percent survival	96.9	95.4	100	92

Source: Study no. T4027023, part 1, Table 2, p. 35

[a]Since the satellite groups were sacrificed at 54 weeks, subsequent survival data are based on 50 animals at risk.

Table 2. Mean Body Weights (g±SD) at Selected Intervals for Mice Fed Methylparathion for 2 Years

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Dose (ppm)	Week 0	13	26	52	104
			Males		
0	21±1.5	27±1.3	30±2.1	33±3.5	32±3.2
1	21±1.6	29±1.6**	29±1.9*	32±2.8	32±3.1
7	21±1.3	29±1.4**	30±2.5	33±3.1	31±2.5
50	21±1.8	29±1.3**	34±2.5**	38±3.9**	38±5.1**
			Females		
0	18±1.1	24±0.9	26±1.7	30±3.5	30±2.8
1	19±1.1**	26±1.5**	26±2.5	29±3.2	30±3.2
7	17±1.3**	25±1.7	26±2.4	30±4.4	30±3.3
50	20±2.2**	26±1.9**	29±3.4**	34±4.7**	32±5.1*

Source: Study no. T4027023, part 2, pp. 143-158

*Significantly different from control values ($p<0.05$)
**Significantly different from control values ($p<0.01$)

Table 3. Mean Cholesterol, Urea, Glucose, and Insulin Levels of Mice Fed Methylparathion for 2 Years

Parameter/ Dose (ppm)	Week			
	Males		Females	
	54	104	54	104
Cholesterol (mmol/L)				
0	3.44±0.283	3.70±1.145	2.68±0.281	2.29±0.210
1	3.41±0.548	3.35±0.406	2.84±0.124	2.56±0.247*
7	3.61±0.548	4.70±2.760[b]	2.81±0.362	2.66±0.263**
50	4.06±0.436**	4.12±0.332	3.00±0.501	3.10±0.437**
Urea (mmol/L)				
0	10.09±1.055	10.03±1.313	7.97±1.507	10.26±1.102
1	9.38±0.872	9.91±0.918	7.97±0.838	9.58±1.268
7	8.82±1.359	10.19±1.785	7.77±1.170	10.07±0.751
50	7.34±0.685**	9.69±1.266	8.17±1.377	9.56±1.345
Glucose (mmol/L)				
0	5.80±0.775	5.74±0.537	5.52±0.244	5.03±0.919
1	6.32±0.639	5.88±0.643	5.98±0.753*	5.21±0.595
7	5.80±1.083	6.01±0.695	5.59±0.527	5.48±0.654
50	6.12±0.738	5.95±0.678	5.54±0.647	5.54±0.505
Insulin (ng/mL)[a]				
0		0.51±0.28		0.52±0.27
1		0.47±0.25		0.57±0.51
7		0.40±0.15		0.42±0.27
50		1.87±2.21**		0.58±0.28

Source: Study no. T4027023, part 1, Tables 6 and 7, pp. 46-47; part 2, pp. 169-176; part 2, pp. 346-355

[a]Insulin levels were not measured at week 54.
[b]If the outlier value 11.76 mmol/L (animal #294) is omitted, the mean recalculated by the reviewers is 3.91±1.28 mmol/L.
*Significantly different from control values ($p<0.05$)
**Significantly different from control values ($p<0.01$)

Table 4. Mean Cholinesterase Levels and Percent Inhibition of Cholinesterase Activity in Mice Fed Methylparathion for 2 Years

Tissue/ Cholinesterase Level/ % Inhibition	Dietary Level (ppm)							
	Males				Females			
	0	1	7	50	0	1	7	50
Week 52								
Plasma (kU/L)								
ChE	4.85±1.03	5.17±1.04	4.55±1.05	1.43±1.24*	6.51±1.06	6.49±1.10	6.12±1.06	2.27±1.14*
% Inhibition		-6.6	6.3	70.8		0.3	6.0	65.2
Erythrocytes (kU/L)								
ChE/E	0.48±1.08	0.44±1.09	0.21±1.20*	0.07±1.25*	0.32±1.17	0.33±1.14	0.16±1.10*	0.08±1.16*
% Inhibition		8.7	56.9	88.9		-2.8	49.4	75.9
Brain (U/g)								
ChE/B	5.04±1.13	4.40±1.12	3.19±1.04*	0.78±1.19*	2.14±1.14	2.14±1.11	2.13±1.14	1.16±1.2*
% Inhibition		12.7	36.6	84.6		-0.2	0.6	45.7
Week 104								
Plasma (kU/L)								
ChE	5.86±1.19	5.06±1.06	6.09±1.40	1.47±1.13*	5.67±1.17	6.18±1.24	5.87±1.27	2.18±1.26*
% Inhibition		13.7	-3.9	75.0		-9.1	-3.6	61.5
Erythrocytes (kU/L)								
ChE/E	0.70±1.24	0.65±1.23	0.34±1.44*	0.08±1.27*	0.55±1.17	0.50±1.14	0.32±1.40*	0.11±1.28*
% Inhibition		7.0	52.1	88.9		9.8	41.0	80.5
Brain (U/g)								
ChE/B	3.17±1.06	1.76±1.15	1.66±1.15*	0.71±1.25*	2.73±1.21	2.67±1.17	2.52±1.11	1.05±1.36*
% Inhibition		19.8	23.4	67.2		2.6	7.7	61.7

Source: Study no. T4027023, part 1, Table 8, p. 46; part 2, pp. 179-182

*Significantly different from control values ($p<0.05$)

Table 5. Mean Absolute and Relative Liver and Kidney Weights in Mice Fed Methylparathion for 2 Years

Organ/ Abs. Weight/ Rel. Weight	Dietary Level (ppm)							
	Males				Females			
	0	1	7	50	0	1	7	50
Week 52								
Liver								
mg	1552	1564	1528	1787**	1440	1441	1388	1549**
mg/100g	4748	4604	4730	4483**	4811	5132	4932	4489**
Kidney								
mg	597	613	611	719**	431	414	412	437
mg/100g	1824	1811	1890	1808	1444	1477	1477	1266*
Week 104								
Liver								
mg	1720	1653	1715*	1982*	1533	1530	1417	1605**
mg/100g	5288	5170	5543	5623	5148	5227	4832	5138
Kidney								
mg	637	640	613	692**	460	446	450	483*
mg/100g	1923	1993	1990	1880	1559	1532	1548	1552

Source: Study no. T4027023, part 1, Table 9, p. 51

*Significantly different from control values ($p<0.05$)
**Significantly different form control values ($p<0.01$)

Table 6. Gross Findings in Mice (Main Groups) Fed Methylparathion for 2 Years[a]

009790

Organ/Finding	Dietary Level (ppm)							
	Males				Females			
	0	1	7	50	0	1	7	50
Eyes								
Unilateral cataracts	0	3	1	1	2	2	0	0
Lungs								
Nodules	2	8*	4	5	1	0	2	3
Red	3	2	1	1	1	1	1	2
Liver								
Nodules	11	8	12	12	7	4	4	7
Foci	1	0	1	0	0	0	2	0
Pale	1	4	6	1	3	1	1	1
Kidneys								
Cyst	0	1	1	0	0	1	1	3
Pale	1	1	1	2	2	1	1	1
Spleen								
Enlarged	1	1	3	1	7	5	7	4
Nodules	0	1	1	2	2	1	4	3
Ovaries								
Cysts					6	4	4	2

Source: Study no. T4027023, part 3, pp. 549-623

[a]Fifty animals/sex/group were examined; findings that occurred at an incidence of 2% were not necessarily tabulated.

*Significantly different from control incidence ($p<0.05$)

Table 7. Representative Nonneoplastic Histologic Findings in Mice Fed Methylparathion for 2 Years (Main Groups)

Organ/Lesion	Dietary Level (ppm)							
	Males				Females			
	0	1	7	50	0	1	7	50
Brain	(45)[a]	(45)	(45)	(45)	(45)	(45)	(45)	(44)
Calcification in cerebrum	32	28	37	27	34	36	32	36
Lungs	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Hyperemia	31	34	30	32	22	30	23	28
Salivary glands	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)
Round cell infiltration	30	38	31	46**	30	28	21	29
Lymph nodes, mandibular	(39)	(49)	(43)	(42)	(45)	(42)	(49)	(47)
Hemosiderin pigment	0	4	4	6*	3	2	4	3
Deposit of foreign material	2	5	8	15**	8	12	19**	17
Stomach, glandular	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Round cell infiltration	6	2	11	16*	6	13	13	16*
Liver	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Hepatocellular hyperplasia	1	6	2	2	0	0	1	0
Hyperemia	38	36	40	43	39	38	47*	49*
Fat deposition	0	0	1	4	0	0	2	3
Necrosis	2	3	5	2	2	4	8*	4
Kidneys	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Proteinaceous tubular casts	23	34*	34*	38**	34	33	30	29
Positive oil red O reaction	8	12	12	26**	12	11	12	13
Ovaries					(49)	(46)	(50)	(47)
Cysts					15	16	13	5*

Source: Study no. T4027023, part 3, pp. 717-786

[a]The numbers in parentheses are the number of animals with a specific tissue examined microscopically.

*Significantly different from control incidence ($p<0.05$)
**Significantly different from control incidence ($p<0.01$)

Table 8. Neoplastic Lesions in Mice Fed Methylparathion for 2 Years[a]

Organ/Lesion	Dietary Levels (ppm)							
	Males				Females			
	0	1	7	50	0	1	7	50
Pituitary	(49)[b]	(50)	(50)	(49)	(46)	(47)	(45)	(43)
Adenoma	0	0	2	2	4	2	2	4
Harderian gland	(49)	(50)	(50)	(50)	(50)	(49)	(50)	(50)
Adenoma	2	0	5	4	4	2	1	1
Adenocarcinoma	1	1	1	1	1	2	2	0
Lungs	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Adenoma alveolar/bronchiolar	1	6	4	4	2	1	1	2
Adenocarcinoma alveolar/bronchiolar	2	3	3	1	0	0	0	1
Liver	(50)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Hepatocellular adenoma	1	3	0	1	4	1	0	1
Hepatocellular carcinoma	10	8	11	11	4	4	3	6
Uterus					(50)	(50)	(50)	(50)
Carcinoma/sarcoma					1	5	1	0
Lymphoreticular system					10	9	8	10
Malignant lymphoma	2	1	1	0	0	0	3	0
Histiocytic sarcoma	0	0	0	0				
Spleen	(48)	(50)	(50)	(48)	(50)	(50)	(50)	(50)
Hemangiosarcoma	0	1	2	0	0	0	0	0
Lymph nodes, mesenteric	(44)	(50)	(45)	(44)	(48)	(50)	(46)	(50)
Hemangioma	0	2	1	0	1	0	2	1

Source: Study no. T4027023, part 1, Table 11, pp. 55-56; part 3, pp. 649-665

[a]Includes all animals in the main groups; findings for days 373-750

[b]The numbers in parentheses are the numbers of tissues examined microscopically.