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

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OCT 10 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **METHYL PARATHION** - Review of Subchronic Neurotoxicity Screening Batteries in Rats [OPPTS 870.6200, §82-7]

EPA ID NOs.: DP Barcode:: D223087
Submission No.: S500531
PC Code: 053501
MRID Nos.: 434905-01

FROM: Robert F. Fricke, Ph.D. Robt F. Fricke 30oct96
Toxicology Branch II, Section II
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TO: William J. Hazel
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THRU: K. Clark Swentzel K. Clark Swentzel 10/7/96
Toxicology Branch II, Head Section II
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and

Yiannakis M. Ioannou, Ph.D. Y.M. Ioannou 10/8/96
Acting Branch Chief, Toxicology Branch II
Health Effects Division (7509C)

REGISTRANT: Cheminova Agro A/S, Lemvig, Denmark

CHEMICAL: Methyl Parathion

ACTION REQUESTED: Review subchronic neurotoxicity study in rat to support reregistration.

EXECUTIVE SUMMARY: Minima, D.J., (1994); Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats, Hazelton Washington, Inc., Lab Project

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Identification: HWA 2688-103, 19 Dec 1994, MRID No.: 43490501; unpublished.

Methyl parathion was administered to groups of Crl:CD BR (Sprague-Dawley) male and female rats for 13 weeks at dietary concentrations of 0 (basal diet), 0.5, 5 or 50 ppm (equivalent to 0, 0.029, 0.295 or 3.02 mg/kg/day, males; 0, 0.37, 0.365, or 3.96 mg/kg/day, females). Neurobehavioral evaluations (10 animals/sex/dose) were carried out at pre-study and weeks 4, 8 and 13; plasma, RBC and regional brain (week 14 only) ChE activities were evaluated on 5 animals/sex/dose at pre-study and weeks 4, 8 and 14. Additional control and high-dose animals (5 animals/sex) in the main study and ChE substudy were carried over into a treatment-free (basal diet) recovery phase of the study. At the end of the 4-week recovery phase, neurobehavioral and ChE evaluations were carried out.

No treatment-related differences were noted in motor activity or the incidence of gross and neuropathological lesions at any dose level. No treatment-related effects were observed at 0.5 ppm.

A 5 ppm, inhibition in RBC ChE activities in males (-19 to -33%) at weeks 4, 8 and 14 and in females (-23 to -24%) were observed at weeks 8 and 14.

At 50 ppm, females showed significant decreases in mean body weights (-6.6 to - 11.4%) during weeks 2 to 6 and a significant decrease (-13.5%) in mean body weight gain for weeks 1 to 13. FOB findings consisted of tremors in females at weeks 4 and 8, partial (absent) pupillary response in males and females during the week 4 evaluation, slow pupillary constriction in males and females during weeks 8 and 13, and significant decreases in hindlimb grip strength in females at weeks 4 and 13. Plasma (-61 to -66%, males; -80 to -85%, females), RBC (-52 to -66%, males; -55 to -64%, females) and regional brain (-38 to -75%, males; -66 to -93% females) ChE activities were all inhibited. During the treatment-free recovery period, plasma ChE showed complete recovery in males and females. RBC ChE and regional brain (excluding cerebral cortex and cerebellum in males, which showed nearly complete recovery) ChE activities in males and females showed partial recovery but were still significantly lower than the concurrent control values.

Based on the results of this study (inhibition of RBC ChE), the LOEL was established at 5 ppm (0.295 mg/kg/day, males; 0.365 mg/kg/day, females); the NOEL was established at 0.5 ppm (0.029 mg/kg/day, males; 0.037 mg/kg/day, females).

This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§82-7) for a subchronic neurotoxicity screening battery in the rat.

CC: Jude Andreasen, SRRD
Dennis Edwards, RD

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Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 5 Sept 1996 012073
Section II, Tox. Branch II (7509C)

Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 9/10/96
Section II, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Neurotoxicity Screening Battery - Rat
(OPP §82-7, OPPTS 870.6200)

EPA ID NOs: MRID NO.: 434905-01
Pesticide Chemical Code: 053501
Toxicology Chemical Code: 372
DP Barcode: D223087
Submission No.: S500531
CAS Reg No.: 298-00-0

TEST MATERIAL: Methyl Parathion, Technical

CITATION: Minima, D.J., (1994); Subchronic Neurotoxicity Study of Dietary Methyl Parathion in Rats, Hazelton Washington, Inc., Lab Project Identification: HWA 2688-103, 19 Dec 1994, MRID No.: 43490501; unpublished

SPONSOR: Cheminova Agro A/S, Lemvig, Denmark

EXECUTIVE SUMMARY: Methyl parathion was administered to groups of Crl:CD BR (Sprague-Dawley) male and female rats for 13 weeks at dietary concentrations of 0 (basal diet), 0.5, 5 or 50 ppm (equivalent to 0, 0.029, 0.295 or 3.02 mg/kg/day, males; 0, 0.37, 0.365, or 3.96 mg/kg/day, females). Neurobehavioral evaluations (10 animals/sex/dose) were carried out at pre-study and weeks 4, 8 and 13; plasma, RBC and regional brain (week 14 only) ChE activities were evaluated on 5 animals/sex/dose at pre-study and weeks 4, 8 and 14. Additional control and high-dose animals (5 animals/sex) in the main study and ChE substudy were carried over into a treatment-free (basal diet) recovery phase of the study. At the end of the 4-week recovery phase, neurobehavioral and ChE evaluations were carried out.

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This study is classified as **ACCEPTABLE** and satisfies guideline requirements (§82-7) for a subchronic neurotoxicity screening battery in the rat.

COMPLIANCES: Quality assurance was documented by signed and dated GLP and quality assurance statements. A statement of "no confidentiality claims" was provided.

I. MATERIALS

A. Test Compound: Methyl Parathion, technical; Description: Not given; Batch No: 95-IA-84; Purity: 93.1%; Contaminants: Not given

B. Test Animals:

Species: Rat
Strain: Sprague-Dawley, Crl:CD® BR
Age: 6 weeks
Acclimation: 2 weeks
Weight at initiation (g): 239 to 311 (males), 150 to 188 (females);
Source: Charles River Breeding Laboratories, Inc., Raleigh, NC;
Housing: Individually in stainless-steel wire-mesh-bottom cages;
Feed: Agway Prolab Certified Rodent Diet (R-M-H 3200 Meal), *ad libitum*
Water: Tap water, *ad libitum*
Environmental: Temperature: 65.6 to 78.6°F; Humidity: 27.2 to 69.0%; Light/dark cycle (reversed): 12 hr/12 hr; Air changes: ≥ 10/hr.

II. METHODS

A. Study Design: Animals, randomly assigned to main study and cholinesterase (ChE) substudy, were fed methyl parathion at the indicated dietary concentrations for at least 13 weeks (Table 1). Main study animals (10/sex/dose) underwent neurobehavioral and neuropathological evaluation during the study. In the ChE substudy (5 animals/sex/dose), plasma and erythrocyte (RBC) ChE activities were measured during the study, while regional brain ChE activity was measured at terminal sacrifice. An additional five animals/sex each, randomly assigned to the control and high-dose groups of the main study and ChE substudy, were carried over into a four-week, treatment-free period.

TABLE 1: ANIMAL ASSIGNMENT TO STUDY GROUPS

TEST GROUP	DOSE (ppm)	MAIN STUDY[a]		ChE SUBSTUDY	
		Male	Female	Male	Female
Control	0	15	15	10	10
Low	0.5	10	10	5	5
Mid	5.0	10	10	5	5
High	50	15	15	10	10

[a] Control and high-dose groups contain 5 additional male and female animals, which were designated for the recovery (treatment-free) phase of the study

B. Diet Preparation: The high-dose test diet (50 ppm) was prepared by blending sufficient amount of ground methyl parathion (assumed to be 100% purity) with approximately 200 g of basal diet. Portions of the high-dose diet were then mixed with basal diet to prepare the 5 and 0.5 ppm test diets. Diets were prepared weekly and stored at room temperature. Preliminary formulation of the test diets were prepared one week prior to study initiation to evaluate homogeneity and stability. For determination of homogeneity, samples from the top, middle and bottom of the low- and high-dose test diets were analyzed. The preliminary test diets were further analyzed for 7- and 15-day stability at room temperature. The achieved concentration of test compound was determined at weeks 1, 4, 8, and 13.

C. Observations

1. Mortality and clinical observations: Animals were observed twice daily for moribundity and mortality and once daily for clinical signs. Detailed clinical examinations were performed in conjunction with the weekly body weight determinations.

2. Body weights: Animals were weighed at pre-study and at weekly intervals, thereafter.

3. Food consumption: Food consumption was measured at weekly intervals.

4. Ophthalmology: Ophthalmic examinations were performed at pre-study on all animals and one week prior to study termination on control and high-dose main study animals.

D. Cholinesterase Determination: Animals assigned to the ChE substudy had plasma and RBC ChE activities measured at pre-study and during weeks 4, 8, and 14 on all animals, and during week 4 of the recovery phase on designated control and high-dose animals. Regional brain (olfactory bulb, cerebellum, cortex, striatum, hippocampus, and midbrain plus stem) ChE activities were determined at the end of the main study and recovery phase. Brain sections were flash frozen and stored at -70°C until analysis. Frozen brain samples were homogenized Triton-saline (volume equal to 19 times the tissue weight) and centrifuged. Plasma, RBC, and brain supernatant fractions were assayed for ChE activity. ChE activity was measured using a Hitachi 704 Analyzer and a commercially available assay kit (BMC ReagentSet Cholinesterase Kit No. 450035), which is based on the modified Ellman method.

E. Neurobehavioral Assessment: Neurobehavioral assessment, consisting of the Functional Observational Battery (FOB) and evaluation of motor

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activity, was performed at pre-study and during weeks 4, 8, and 13 of treatment and week 4 of the recovery phase. Animals were presented to a trained technician, who was not aware of the identity of the animal's test group.

1. **Functional Observational Battery:** The following parameters were evaluated:

HOME CAGE/HAND-HELD OBSERVATIONS
- Appearance of fur
- Color of tears/deposits around eyes
- Convulsions/tremors
- Ease of handling/body tone
- Ease of removal from cage
- Excessive vocalizations
- Exophthalmus
- Lacrimation
- Palpebral closure
- Piloerection
- Respiration
- Salivation
- Writhing
- Other signs

PERFORMANCE MEASUREMENTS
- Hind/forelimb grip strengths
- Hindlimb landing foot splay
- Body temperature
- Tail flick latency

OPEN-FIELD OBSERVATIONS
- Arousal
- Circling
- Convulsions/tremors
- Gait
- Posture
- Abnormal/Stereotypic behavior
- Other signs

RESPONSE OBSERVATIONS
- Approach response
- Catalepsy withdrawal
- Olfactory response
- Pupillary reflex
- Air Righting reflex
- Touch response
- Automated auditory startle response

2. **Locomotor activity:** Motor activity was measured using automated photobeam activity recording devices. Animals were monitored individually over a 40 min session, consisting of eight 5-minute intervals.

F. Sacrifice and Pathology: Animals found dead or euthanized *in extremis* were examined grossly. During weeks 14 and 17, main study and recovery phase animals, respectively, were fasted overnight, weighed and then euthanized with an IP injection of pentobarbital. The first six main study animals, which were successfully perfusion fixed *in situ,* underwent neuropathological evaluation, the remaining animals were examined grossly. The tissues listed below were collected from the main study animals and preserved in 10% neutral-buffered formalin. Tissues from control and high-dose animals were examined microscopically, while those from intermediate dose groups were collected and examined, if necessary. Recovery phase animals were sacrificed and discarded without gross examination.

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GROSS PATHOLOGY

- Carcass
- Cervical tissues and organs
- Cranial cavity
- External body surface
- All orifices
- External surface of the brain
- Nasal cavity and parinasal sinuses
- Thoracic, abdominal and pelvic cavities and viscera

NEUROPATHOLOGY

- Muscle (Anterior tibialis & gastrocnemius)
- Brain with brainstem (Medulla/pons, cerebral cortex & cerebellar cortex)
- Cervical and lumbar dorsal root ganglia
- Gasserian ganglion
- Spinal cord (Cervical, lumbar & thoracic)
- Pituitary
- Eyes
- Peripheral nerves (Sciatic, seral & tibial)

G. Positive Controls: A positive control study (Study No.: HWA 0001-692, entitled "Neurotoxicity Study of Acrylamide (Positive Control) in Rats", dated 12 April 1994) submitted by the performing laboratory, adequately validated the FOB, motor activity and neuropathology findings.

H. Statistical Evaluations: Parametric data were first evaluated using Levene's test to determine if the variances were homogeneous. Heterogeneous data were sequentially transformed ($\log_{10}x$, x^2, $\sqrt{x}$, $1/x$, arsine, or rank) and reevaluated using Levene's test. Homogeneous data were evaluated using analysis of variance (ANOVA) and, if significant differences were observed, pair-wise comparisons were carried out using Dunnett's multiple t-test. Continuous behavioral data were analyzed by factorial analysis of variance with repeated measures. Locomotor activity data were square-root transformed before statistical analysis. Dose effects and dose × time effects were detected using univariant analysis.

IV. RESULTS

A. Analytical Chemistry (Study Table 1, pp 70-72): Test diets were analyzed for stability, homogeneity and concentration. Samples taken from the top, middle and bottom of the low- and high-dose test diets indicated that the methyl parathion was homogeneously distributed with relative standard deviations of 3.76 and 2.76%, respectively. The low- and high-dose test diets were stable for 15 days at room temperature and were both within 10% of the target concentration. Analysis of the test diets during the study showed that the achieved concentrations were within 91.1 to 128%, 94.0 to 101.5%, and 92.8 to 100.3% of the target concentrations for the low-, mid-, and high-dose test diets, respectively.

B. Clinical Signs and Mortality: All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs.

C. Body Weight and Body Weight Gain: Mean body weights and body weight gains are summarized in Table 2. The mean body weights of high-

dose males were consistently lower (4.3 to 8.4%) than concurrent controls throughout the study, none of the differences, however, achieved statistical significance. For weeks 2 through 6, high-dose females, when compared to concurrent control values, had statistically significant decreases of 6.6 to 11.4% in the mean body weights. Mean body weight gains for weeks 1 to 13 were 8.1% lower in males and 13.5% lower in females.

TABLE 2: MEAN BODY WEIGHTS AND BODY WEIGHT GAINS[a]

SEX	WEEK	DOSAGE (ppm)			
		0	0.5	5	50
Body Weights, grams					
Female	1	172	171	171	175
	2	196	193	193	183* (6.6)[b]
	3	220	214	215	196* (10.9)
	4	237	232	229	210* (11.4)
	5	246	245	243	227* (7.7)
	6	259	255	253	239* (7.7)
Body Weight Gains, grams					
Male	1-13	307	314	320	282 (8.1)
Female	1-13	133	126	133	115* (13.5)

[a] Data summarized from study Tables 3A and 3B (pp 76 to 80)
[b] Values in parentheses are the percent decrease from the concurrent control value.
* $p \leq 0.05$, compared to concurrent controls.

D. Food Consumption and Achieved Compound Intake: Mean food consumption at the high-dose level was statistically significantly lower during weeks 2 and 3 in males and weeks 1 and 2 in females (Table 3). These changes were suggestive of food palatability rather than a treatment-related effect. Overall feed consumption (Weeks 1 - 13) did not show any significant treatment related changes.

Achieved compound intake for weeks 1 to 13 are summarized in Table 4.

E. Ophthalmic Examinations: No treatment-related eye lesions were noted at the week 14 examination.

F. Cholinesterase Activities: Plasma, RBC and regional brain ChE activities are summarized in Table 5. Plasma and RBC ChE activities of high-dose males and females were statistically significantly decreased (>52%) at weeks 4, 8 and 14 of treatment. RBC ChE activity of mid-dose males was significantly decreased during Weeks 4, 8 and 14 and mid-dose females at

weeks 8 and 14. At week 14, regional brain ChE activities were all significantly decreased in high-dose males and females.

During the treatment-free recovery phase of the study, high-dose males and females showed complete recovery of plasma ChE activities, while partial recovery (but still statistically significant decreases) were noted in RBC ChE activities. ChE activities of the cerebral cortex and cerebellum of high-dose males were still slightly (but not significantly) decreased. ChE activities of the remaining brain sections of high-dose males and all brain sections of high-dose females showed some recovery but were still significantly decreased at the end of the treatment-free period.

TABLE 3: MEAN FOOD CONSUMPTION (g/animal/week) [a]

SEX	WEEK	DOSAGE (ppm)			
		0	0.5	5	50
Male	1	190	183	182	174 (-8.4)[b]
	2	207	196	197	175*(-15.5)
	3	194	185	191	174*(-10.3)
	1-13	2487	2392	2452	2310 (-7.1)
Female	1	132	130	130	118*(-10.6)
	2	145	140	138	114*(-21.4)
	3	141	139	132	125 (-11.3)
	1-13	1646	1668	1650	1676 (+1.8)

[a] Data summarized from study Table 4 (pp 82 to 83)
[b] Values in parentheses are the percent change from the concurrent control value.
* $p \leq 0.05$, compared to concurrent controls.

TABLE 4: ACHIEVED COMPOUND INTAKE (mg/kg/day) for WEEKS 1 to 13[a]

SEX	DOSAGE (ppm)		
	0.5	5	50
Male	0.029	0.295	3.02
Female	0.037	0.365	3.96

[a] Values calculated from mean weekly body weights (Table 3A, pp 76 - 77), mean weekly feed intake (Table 4 pp 82 - 83) and concentration analyses (Table 1, pg 72).

TABLE 5: CHOLINESTERASE ACTIVITY[a]

CHOLINESTERASE (U/L)	WEEK[b]	DOSAGE (ppm)							
		MALE				FEMALE			
		0	0.5	5	50	0	0.5	5	50
Plasma	Pre	472	526 (+11)[c]	528 (+12)	537 (+14)	718	694 (-3)	689 (-4)	725 (+1)
	4	440	479 (+9)	428 (-3)	148 (-66)*	1637	1625 (-1)	1427 (-13)	321 (-80)*
	8	417	502 (+20)	445 (+7)	157 (-62)*	2199	2194 (+0)	2243 (+2)	357 (-84)*
	14	449	496 (+11)	434 (+3)	175 (-61)*	2617	2639 (+1)	2453 (-6)	387 (-85)*
	17	439	...[d]	---	502 (+14)	3202	---	---	3000 (-6)
RBC	Pre	1714	1709 (+0)	1743 (+2)	1722 (+0)	1638	1688 (+3)	1743 (+6)	1730 (+6)
	4	1827	1701 (-7)	1222 (-33)*	626 (-66)*	1676	1550 (-8)	1571 (-6)	596 (-64)*
	8	1705	1693 (-1)	1378 (-19)*	815 (-52)*	2029	1810 (-11)	1541 (-24)*	769 (-62)*
	14	1688	1718 (+2)	1218 (-28)*	802 (-52)*	1739	1714 (-1)	1336 (-23)*	781 (-55)*
	17	1718	---	---	1403 (-18)*	1810	---	---	1508 (-17)*
Cerebral Cortex	14	2952	2832 (-4)	2824 (-4)	1140 (-61)*	3004	3696 (+23)	2944 (-2)	536 (-82)*
	17	2480	---	---	2240 (-10)	2992	---	---	1944 (-35)*
Cerebellum	14	2252	2308 (+2)	2312 (+3)	1396 (-38)*	2320	2388 (+3)	2276 (-2)	800 (-66)*
	17	2448	---	---	2216 (-9)	2484	---	---	2040 (-18)*
Hippocampus	14	7280	6892 (-5)	6812 (-6)	2716 (-63)*	6856	7144 (+4)	6400 (-7)	868 (-87)*
	17	6804	---	---	4996 (-27)*	6852	---	--	4020 (-41)*
Striatum	14	31700	27840 (-12)	30024 (-5)	7868 (-75)*	32388	32792 (+1)	27772 (-14)	2292 (-93)*
	17	29188	---	---	22056 (-21)*	28756	---	---	17756 (-38)*
Olfactory Bulb	14	4136	4028 (-3)	4060 (-2)	1592 (-62)*	3948	4164 (+5)	4336 (+10)	664 (-83)*
	17	4016	---	---	2956 (-26)*	3984	---	---	2624 (-34)*
Brainstem	14	4880	5555 (+14)	5372 (+10)	2204 (-55)*	5212	5276 (+1)	5152 (-1)	1152 (-78)*
	17	5492	---	---	4276 (-22)*	5496	---	---	3912 (-39)*

[a] Data summarized from study Table 6 (pp 87 to 90) and text Table 1 (pg 46)
[b] Pre = Pretreatment
[c] Values in parentheses are the percent decrease from the concurrent control value.
[d] --- = Not determined
* $p \leq 0.05$, compared to concurrent controls.

F. Neurobehavioral Results

1. FOB Findings: Treatment-related FOB findings are summarized in Table 6. A low incidence of tremors were observed in high-dose females at weeks 4 and 8 during the open field evaluations. During the righting reflex or pupillary response evaluations at week 8, one control and an additional three high-dose females had tremors. Partial and/or slow pupillary responses were noted in high-dose males and females during the weeks 4, 8 and 13 evaluation. High-dose females also had statistically significant decreases in hindlimb grip strength at weeks 4 and 13, while non-significant decreases were noted during week 8.

TABLE 6: FOB OBSERVATIONS[a]

OBSERVATION	SEX	WEEK	DOSAGE (ppm)			
			0	0.5	5	50
Tremors[b]	Female	4	0/10	0/10	0/10	2/10
		8	1/10	0/10	0/10	4/10
		13	1/10	1/10	0/10	0/10
Pupillary Response Partial and/or Slow Constriction[c]	Male	4	0/10	0/10	0/10	1/10
		8	0/10	2/10	0/10	3/10
		13	1/10	0/10	1/10	3/10
	Female	4	0/10	0/10	0/10	5/10
		8	0/10	1/10	1/10	9/10
		13	0/10	0/10	0/10	4/10
Hindlimb Grip Strength	Female	4	690	683	701	533*
		8	874	965	914	739
		13	1029	1010	936	838*

[a] Data summarized from study Tables 8D (pg 124), 9E (pg 152), 9G (pg 156), 9H (pg 158) and 10D (pg 166).
[b] Includes tremors observed during righting reflex, pupil response or olfactory response evaluations.
[c] Includes responses observed during pupillary response assessment and observed during other response evaluations.
* $p \leq 0.05$, compared to concurrent controls.

2. Motor Activity: No treatment-related changes in locomotor activity were observed at the 4-, 8-, and 13-week evaluations.

G. Sacrifice and Pathology

1. Gross pathology: No treatment-related gross pathological changes were observed in either the perfused or non-perfused animals.

2. Neuropathology: Degenerative lesions were observed in the peripheral nerves of high-dose males and females (Table 7). These lesions were not suggestive of a treatment-related effect since the incidences of the lesions was low and also observed in control animals.

TABLE 7: INCIDENCE OF NEUROPATHOLOGICAL LESIONS[a]

OBSERVATION	SEX	DOSAGE (ppm)			
		0	0.5	5	50
Axonal Degeneration					
Dorsal Root Fiber	Male	0/10	0/10	0/10	1/10
	Female	1/10	0/10	0/10	1/10
Ventral Root Fiber	Male	0/10	0/10	0/10	2/10
	Female	1/10	0/10	0/10	1/10
Sciatic Nerve	Male	1/10	0/10	0/10	1/10
	Female	1/10	0/10	0/10	1/10
Tibial Nerve	Male	2/10	0/10	0/10	0/10
Sural Nerve	Female	0/10	0/10	0/10	1/10

[a] Data summarized from study Table 15 (pg 191).

V. DISCUSSION and CONCLUSIONS: Methyl parathion was administered to groups of Crl:CD BR (Sprague-Dawley) male and female rats for 13 weeks at dietary concentrations of 0 (basal diet), 0.5, 5 or 50 ppm (equivalent to 0, 0.029, 0.295 or 3.02 mg/kg/day, males; 0, 0.37, 0.365, or 3.96 mg/kg/day, females). Neurobehavioral evaluations (10 animals/sex/dose) were carried out at pre-study and weeks 4, 8 and 13; plasma, RBC and regional brain (week 14 only) ChE activities were evaluated on 5 animals/sex/dose at pre-study and weeks 4, 8 and 14. Additional control and high-dose animals (5 animals/sex) in the main study and ChE substudy were carried over into a treatment-free (basal diet) recovery phase of the study. At the end of the 4-week recovery phase, neurobehavioral and ChE evaluations were carried out.

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