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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Methamidophos (Monitor): 82-5b Subchronic Neurotoxicity Screening Study and Related Data

DP Barcode No. D202454 (main study)
D199019 (related data)
Submission No. S463940 (main study)
S457625 (related data)

Rereg. Case No. 0043 Case No. 819351
EPA ID No. 101201 P.C. Code No. 101201
CAS Registry No. 10265-92-6 Tox. Chem. No. 378 A

FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 4/4/95
Section I, Toxicology Branch I
Health Effects Division (7509C)

TO: Larry Schnaubelt / Robert Richards, PM Team No. 72
Reregistration Branch
Special Review and Reregistration Division (7598W)

THRU: Roger Gardner, Section Head Roger Gardner 4-26-95 KKL 4/26/95
Section I, Toxicology Branch I
Health Effects Division (7509C)

Section I, Toxicology Branch I/HED has completed an evaluation of the following studies:

82-5b A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Methamidophos (MONITOR®) in Fischer 344 Rats. L.P. Sheets and B.F. Hamilton; Miles, Inc., Agricultural Division, Stilwell, Kansas; Study Numbers: 106351 and 92-472-RE; Study completion date: April 13, 1994.
MRID No. 43197901

81-8 SS and 82-5b Historical Control and Method Validation Studies in Rats for the Acute and Subchronic Neurotoxicity Screening Battery. L.P. Sheets, B.P. Stuart and S.G. Lake; Miles, Inc., Agricultural Division, Stilwell, Kansas; Report No. 103979; Date of Report: March 31, 1993.
MRID No. 42770301

In the main study (MRID No.43197901), Methamidophos was administered in the diet for 13 weeks to male and female Fischer 344

rats. The nominal concentrations of Methamidophos (a.i.) used were 0, 1, 12 and 60 ppm (the analytical concentrations were 0, 1, 12 and 59 ppm a.i., respectively). The following treatment-related effects were observed: **(1) In the low-dose group:** Inhibition of brain and plasma cholinesterase activities; **(2) In the mid-dose group:** Increased incidence of urine stains (F), reduction in motor and locomotor activities, decreased body weight gain (F), and inhibition of cholinesterase activities in brain, plasma and erythrocytes; and **(3) In the high-dose group:** muscle fasciculations, increased reactivity, perianal and urine stains, red and clear lacrimation, reduction in motor and locomotor activities, decreased forelimb grip strength, tremors (M), sluggishness (F), decreased body weight gain, and inhibition of cholinesterase activities in brain, plasma and erythrocytes.

Based on the above findings, the **NOEL for neurotoxicity** is 1 ppm (0.067 mg/kg/day for males and 0.074 mg/kg/day for females). The **LOEL for neurotoxicity** is 12 ppm (0.789 mg/kg/day for males and 0.899 mg/kg/day for females). The **NOELs and LOELs for the inhibition of cholinesterase activities**, for both sexes, are as follows: Erythrocytes: NOEL = 1 ppm and LOEL = 12 ppm; plasma and brain: NOEL = < 1 ppm (LDT) and LOEL = 1 ppm. The analytical concentration of Methamidophos used in the high-dose group, 59 ppm, was equivalent to 4.26 mg/kg/day for males and 4.94 mg/kg/day for females.

This study is classified as **Core Minimum** and satisfies the guideline requirement for a subchronic neurotoxicity screening study (82-5b).

The second submission (MRID No. 42770301) was not reviewed separately. Only the historical control and method validation data for the subchronic neurotoxicity screening battery were reviewed and the findings included in the evaluation of the main study (MRID No. 43197901).

Krystyna K. Locke 4/4/95

Primary Review by: Krystyna K. Locke, Toxicologist
Section I, Toxicology Branch I/HED

Roger Gardner 5-26-95

Secondary Review by: Roger L. Gardner, Section Head
Section I, Toxicology Branch I/HED

DATA EVALUAATION RECORD

STUDY TYPE: 82-5b Subchronic Neurotoxicity Screening Battery

EPA IDENTIFICATION NUMBERS:

MRID No. 43197901
DP Barcode No. D202454
Submission No. S463940
P.C. Code No. 101201
CAS Registry No. 10265-92-6

Rereg. Case No. 0043
Case No. 819351
I.D. No. 101201
Tox. Chem. No. 378 A

TEST MATERIAL: Methamidophos Technical (O,S-Dimethyl phosphoramidothioate); Purity: 75.6-75.8%; Batch No. 0-06-7009; Clear, colorless liquid, stored at freezer conditions. The chemical identity and structure of Methamidophos was confirmed by nuclear magnetic resonance and mass spectroscopy prior to study initiation.

SYNONYM(S): Monitor

SPONSOR: Miles Inc., Agricultural Division, Kansas City, MO

STUDY NUMBERS: 106351 and 92-472-RE

TESTING FACILITY: Miles Inc., Agricultural Division, Toxicology, Stilwell, Kansas

TITLE OF REPORT: A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Methamidophos (MONITOR®) in Fischer 344 Rats

AUTHORS: L.P. Sheets and B.F. Hamilton

STUDY COMPLETION DATE: April 13, 1994

EXECUTIVE SUMMARY: In a subchronic neurotoxicity screening study (MRID 43197901), technical grade Methamidophos (76 % a.i.) was administered in the diet for 13 weeks to 8-week old male and female Fischer 344 rats (18/sex/group). The nominal concentrations of Methamidophos used were 0, 1, 12 and 60 ppm a.i. (the analytical concentrations were 0, 1, 12 and 59 ppm a.i., respectively) and were based on the results of subchronic and chronic feeding studies referenced in the review. These doses were equivalent to 0, 0.067, 0.787 and 4.26 mg a.i./kg/day, respectively (males) and 0, 0.074, 0.899 and 4.94 mg a.i./kg/day, respectively (females). Twelve rats/sex/dose were used for neurobehavioral evaluation,

with half used for neuropathology. The remaining rats (6/sex/dose) were used for determinations of cholinesterase activity in plasma, erythrocytes and brain.

Relative to the controls, there was an increased incidence of urine stains in the mid-dose females during most of the study. Treatment-related clinical signs, observed in most of the high-dose males and females during most of the study, included muscle fasciculations, increased reactivity, perianal and urine stains, and red and clear lacrimation. Other treatment-related effects were: **(1)** Reduction in motor and locomotor activities in both sexes, in the mid-dose (17-32%) and high-dose (26-57%) groups; **(2)** Decreased forelimb grip strength in both sexes, in the high-dose group only (14-31%); **(3)** Tremors, in the high-dose males; **(4)** Reduced activity (sluggish arousal during open field observation), in the high-dose females; **(5)** Decreased body weight gain in the mid-dose females (10%) and high-dose males (11%) and females (17%); and **(6)** Inhibition of cholinesterase activities in erythrocytes (70-98%) in the mid-dose and high-dose groups, and in plasma (17-91%) and brain (6-86%) at all dose levels.

Based on the above findings, **the NOEL for neurotoxicity is 1 ppm (0.067 mg/kg/day for males and 0.074 mg/kg/day for females). The LOEL for neurotoxicity is 12 ppm (0.787 mg/kg/day for males and 0.899 mg/kg/day for females). The NOELs and LOELs for inhibition of cholinesterase activities, for both sexes, are as follows: Erythrocytes: NOEL = 1 ppm and LOEL = 12 ppm; Plasma and brain: NOEL = < 1 ppm (LDT) and LOEL = 1 ppm. This study is classified as Core-Minimum and satisfies the guideline requirement for a subchronic neurotoxicity screen (82-5b).**

EXPERIMENTAL PROCEDURES:

This study was started on January 11, 1993 and terminated on April 15, 1993.

Young adult male and female Fischer 344 rats, 18/sex/dose, received Methamidophos in the diet for 13 weeks at the following analytically-confirmed concentrations: 0, 1, 12 and 59 ppm (nominal concentrations were 0, 1, 12 and 60 ppm, respectively). Twelve rats/sex/dose were used for neurobehavioral evaluation, with half used for neuropathology. The remaining rats (6/sex/dose) were use as satellite animals for determinations of cholinesterase activity. The doses of Methamidophos used in this study were based on the results obtained in the following studies (referenced in Attachment I of this review): **(1)** 13-week study in which Methamidophos was tested at dietary levels of 0, 2, 6, 20 and 60 ppm (1970; MRID 00014155); **(2)** two-year chronic toxicity/carcinogenicity study, in which Methamidophos concentrations of 0, 2, 6, 18 and 54 ppm were tested (1984; MRID 00148452); and **(3)** an 8-week dietary feeding/cholinesterase study in which Methami-

dophos doses of 0, 0.5, 1, 2 and 4 ppm were used (1991; MRID 41867201). **In the current study, the rats were:**

(1) Obtained from Sasco, Inc., Madison, Wisconsin;
(2) Acclimated for one week prior to placement on the study;

(3) Eight weeks old at the time of treatment;

(4) Housed individually in suspended stainless steel wire-mesh cages, at temperature of 18-26°C, relative humidity of 40-70% and 12-hour light/dark cycle;

(5) Assigned to groups on the weight basis, using software from INSTEM Computer Systems, Stone, Staffordshire, U.K.

(6) Identified by cage cards and tail tattoos; and

(7) Fed unrestricted amounts of food (Purina Mills Rodent Lab Chow 5001-4 in "etts" form) and tap water. Corn oil was used as the vehicle for the test compound at 1% by weight of the diet.

The following parameters were examined:

(1) Clinical observations: at least once daily. Detailed physical examinations for clinical signs of toxicity were carried out and recorded each week.

(2) Body weight and food consumption: weekly. Rats were also weighed on the day of sacrifice for terminal body weight measurements.

(3) Motor/locomotor activity (figure-eight maze): one week prior to treatment and during weeks 4, 8 and 13. Rats were examined individually for 90-minute sessions and during each 10-minute interval. These tests were conducted according to the procedures listed in Attachment I of this review (references 9, 10 and 11). Studies with untreated rats and with rats treated with reference substances that increase (triadimefon) and decrease (chlorpromazine) motor activity established the sensitivity, reliability and validity of these test procedures.

(4) Functional observational battery (FOB) [home cage observations, observations during handling, open field observations, reflex/physiological observations, landing foot splay and grip strength]: at the same time intervals as motor activity. These tests were conducted according to the procedures listed in Attachment I of this review (references 5, 7, 8 and 9). Studies were also conducted with acrylamide, carbaryl and untreated rats to establish

the sensitivity, reliability and validity of these test procedures.

(5) Ophthalmology: before treatment and during week 12, for all rats. The following ocular functions/structures were examined: pupillary reflex (using a penlight or a transilluminator); eyelids, conjunctiva, cornea, aqueous humor and lens (with a slit lamp microscope); and vitreous humor, retina, choroid and optic disc (using an indirect opthalmoscope and and a condensing lens). Rats with ophthalmological abnormalities that could interfere with the interpretation of the study results were not assinged to the study.

(6) Cholinesterase activity (satellite group; 6 rats/sex/dose; nonfasted): prior to treatment and during weeks 4 and 13, in plasma and erythrocytes; and at the termina-termination of the study, in brain, according to the procedures listed in Attachment I of this review (references [1-6]). Cholinesterase activity was measured using a modification of the Ellman procedure. In this modification, 6,6'dithiodinicotinic acid was used as a coupling agent rather than the Ellman regent 5,5'-dithiobis-2-nitrobenzoic acid, in order to avoid hemoglobin interference. Clinical biochemical and hematological parameters, other than cholinesterase activities, were not measured.

(7) Gross necropsy was performed on one half of the group used for neurobehavioral evaluation. These rats, the first 6 males and 6 females at each dose level, were deeply anesthetized with sodium pentobarbital and then perfused through the left ventricle with sodium nitrite. The perfused rats were weighed and then fixed *in situ* with Universal fixative (4% w/v glutaraldehyde and 4% w/v formaldehyde) in phosphate buffer. The necropsy involved an examination of all organs, body cavities, cut surfaces and external orifices and surfaces. The following tissues/organs were removed from each rat and post-fixed with 10% buffered formalin: entire brain, spinal cord, both eyes with optic nerves, peripheral nerves (sciatic, tibial and sural), gasserian ganglion, gastrocnemius muscle and tail (physical identifier). The brain was weighed prior to placement in formalin and the brain/body ratio calculated.

The remaining rats (6/sex/dose from the neurobehavioral group and 6/sex/dose from the satellite group) were sacrificed by CO_2 asphyxiation without perfusion, necropsy or collection of tissues. Only brain tissue (whole brain) was collected from each of the satellite group rats for the determination of cholinesterase activity.

(8) Histopathology: The following tissues from the perfused control and high-dose male and female groups (60 ppm) were further processed for microscopic examination: brain (olfactory region, forebrain, midbrain, pons, medulla oblongata and cerebellum) and spinal cord (cross- and longitudinal sections from the cervical, thoracic and lumbar regions) were embedded in paraffin and stained with Hematoxylin and Eosin. Dorsal root ganglia, cauda equina, gasserian ganglion, eyes, optic nerves, gastrocnemius muscle, and additional tissue from the hippocampus and cerebellar cortex were embedded in glycol methacrylate and stained with Modified Lee's. Peripheral nerve tissues were embedded in Epon and stained with Toluidine Blue. Additional sections from each region of the brain and spinal cord were stained with Luxol Fast Blue/Cresyl Violet and Sevier-Munger stains. Previous studies with trimethyltin and acrylamide established the sensitivity and reliability of these procedures for detecting lesions in peripheral nerves and central nervous system (Reference 9 in Attachment I of this review). Since treatment-related lesions were not observed in the high-dose group, tissues from other groups were not examined.

Statistical analyses were performed as is detailed in Attachment II of this review. The procedures referenced numerically in this section are fully referenced in Attachment I.

RESULTS:

Actual Intake of Methamidophos (a.i.)

Based on body weight, food consumption and diet analysis data, the mean intake of Methamidophos by rats in the 0, 1, 12 and 60 ppm groups was as follows:

Males: 0, 0.067, 0.787 and 4.26 mg/kg/day, respectively.
Females: 0, 0.074, 0.899 and 4.94 mg/kg/day, respectively.

Concentration of Methamidophos in Diets

The mean concentrations of Methamidophos in diets fed to the 1, 12 and 60 ppm (nominal values) groups were 0.986, 11.6 and 58.6 ppm, respectively; or 1, 12, and 59 ppm, respectively (analytical values). The diets were assayed for Methamidophos concentration during the test weeks 1, 5, 9 and 14.

Homogeneity of Methamidophos in Diets

Methamidophos was homogeneously distributed in diets. The

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distribution of Methamidophos in diets was determined for the low-dose (1 ppm) and high-dose (60 ppm) groups. Three samples were taken from areas of a mixing bowl designated as top, middle and bottom. The mean concentration, standard deviation (SD) and coefficient of variation (CV) were then determined for 9 samples from each dose group. The mean concentration of Methamidophos in the 1 ppm diet was 1.02 ppm (102% of nominal; SD=0.9 ppm; CV= 9.1%). The mean concentration of Methamidophos in the 60 ppm diet was 58 ppm (96.7% of nominal; SD= 5.6 ppm; CV=9.7%).

Stability of Methamidophos in Diets

Methamidophos mixed in rat diets at nominal concentrations of 1 or 60 ppm was stable for a minimum of 14 days at room temperature (about 22°C) and for 28 days at freezer (-23°C) storage. Diet containing 12 ppm of Methamidophos was not studied for stability.

Clinical Observations and Mortality

Treatment-related clinical signs were not observed in the low-dose and mid-dose males. Relative to the controls, there was an increased incidence of urine stains in the mid-dose females (4/12 vs 10/12) during most of the study. Treatment-related clinical signs, observed in the high-dose males and females, included muscle fasciculations, increased reactivity, perianal and urine stains, and red and clear lacrimation. Most of these signs occurred in most of the rats during most of the study. According to the authors of this study, all treatment-related clinical signs were associated with cholinergic toxicity. There were no unscheduled deaths. The incidence of clinical signs and their duration are in Attachment III of this review.

Body Weight

Relative to the control values, body weight gains of male and female rats in the low-dose group and of male rats in the mid-dose group were not affected by treatment. The remaining rats (mid-dose females and high-dose males and females) gained less weight than did the controls throughout the study, but the differences were statistically insignificant. Considering the initial body weights (Day 0) and those on Day 91 for each group, males in the control, low-dose, mid-dose and high-dose groups gained 139, 146, 144 and 124 g, respectively. The corresponding weight gains for the female groups were 60, 58, 54 and 50 g, respectively. Therefore, relative to the control values, male rats in the high-dose group and female rats in the mid-dose and high-dose groups gained 11%, 10% and 17%, respectively, less weight than did the controls. Although these decreased weight gains were statistically insignificant, they appeared to be treatment-related.

Food Consumption

Compared with the controls, Methamidophos had no effect on food consumption of the low-dose and mid-dose male and female rats. However, the mean daily food consumption of the high-dose males and females was 7.1% and 9.5%, respectively, greater than that of the control rats during the study. The mean food consumption of the control, low-dose, mid-dose and high-dose male rats was 67.8, 68.0, 67.8 and 72.6 g/kg body weight/day, respectively. The corresponding values for the female rats were 77.1, 75.4, 77.5 and 84.4 g/kg body weight/day, respectively.

Motor/Locomotor Activities

Compared with the controls, motor and locomotor activities were not affected by Methamidophos in the low-dose male and female groups, but were reduced significantly in both sexes, in the mid-dose and high-dose groups. Males and females in the high-dose group had reduced activities during weeks 4, 8 and 13 (when tests were conducted), with no evidence of cumulative toxicity beyond week 8. The reduction in activities in the mid-dose group was observed only during week 4 (for females) and week 8 (for males). The motor and locomotor activities, expressed as percent difference from control, are summarized in Attachment IV of this review.

Functional Observational Battery (FOB)

Treatment-related effects were not observed in the low-dose male and female groups, but were observed in both sexes, in the mid-dose and high-dose groups. Male rats in the mid-dose and high-dose groups had perianal and urine stains. Other effects observed only in the high-dose males were muscle fasciculations, tremors and decreased forelimb grip strength. Female rats in the mid-dose and high-dose groups had muscle fasciculations and an increased incidence of urine stains, whereas decreased forelimb grip strength and a higher incidence of reduced activity (sluggish arousal during open field observation) were also observed in the high-dose females. A higher incidence of reduced activity was noted only during the last test (week 13), wheras the other toxic (cholinergic) signs were observed in males and females throughout the treatment period. The results of the grip strength test are in Attachment V of this review and the other results are summarized below.

Methamidophos (ppm)		0	1	12	60
Finding		Percent of Rats Affected			
Stains: Perianal	(M)	...	...	8	25-42
	(F)	...	...	...	...
Urine	(M)	...	...	8	8-34
	(F)	8	8	41-75	67-100
Muscle Fasciculations					
Males		...	...	...	16-92
Females		...	...	25	83-100
Tremors	(M)	...	...	...	8
	(F)	...	...	...	...
Arousal- Sluggish					
Males		83	67	58	92
Females		25	17	25	67

This table is based on Table 5, pages 50-75, of the submitted report (MRID 43197901). Twelve rats/sex/dose were used in these tests.

... Finding not observed (M) = Males (F) = Females

Ophthalmology

Ophthalmological findings were reported for 12 males and 12 females from each group (neurobehavioral group) and included corneal opacity, corneal scars, chromodacryorrhea and periocular alopecia. Relative to the control values, there was an increased incidence of corneal opacity and corneal scars (females only) in the high-dose group, whereas the other findings were not dose-related. These data are summarized below.

Methamidophos (ppm)	0	1	12	60
Finding#	Percent of Rats Affected			
Corneal opacity				
Males	58	58	33	75
Females	33	33	33	75
Corneal scar				
Males	...	...	...	...
Females	...	...	...	16
Chromodacryorrhea				
Males	16	25	8	...
Females	...	25	16	...
Periocular alopecia				
Males	25	25	8	...
Females	...	16	...	...

This table is based on TABLE OP1K-SUM, pages 334 and 335, of the submitted report (MRID 43197901). # Observed during week 12, the only time when ophthalmological examination was performed.

... Finding not observed

Although the increased incidence of corneal opacity and scars in the high-dose group was not statistically significant, it appeared to be treatment-related. According to B.F. Hamilton, principal pathologist in this study and author of the PATHOLOGY REPORT, all ophthalmological findings observed were incidental and not related to administration of Methamidophos. According to this pathologist, corneal opacity was part of a common, spontaneous corneal dystrophy in Fischer 344 rats (references [8,9] in Attachment I of this review).

Cholinesterase Activities

Determination of plasma and erythrocyte cholinesterase (PChE and RChE, respectively) activities on day 6 before treatment indicated that there were no significant differences between control rats and rats allocated to the treatment groups.

Relative to the control values, statistically significant decreases in RChE, PChE and brain cholinesterase (BChE) activities were observed in the mid-dose and high-dose Methamidophos-treated groups. There were also statistically significant inhibitions of BChE activity in the males at week 13 and of PChE activity in the the females at week 4, in the low-dose group, but were considered in this submission as biologically insignificant.

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According to B.F. Hamilton, principal pathologist for this study, inhibitions of RChE, PChE and BChE activities <20% were regarded as biologically insignificant. The cholinesterase inhibition data are summarized below.

Percent Inhibition Relative to the Control Values

Nominal Dose # (ppm)	Week 4 (Day 24)		Week 13 (Day 86)		
	RChE	PChE	RChE	PChE	BChE
MALE RATS					
1	1	7	7	26	6*
12	70*	44*	76*	41*	58*
60	79*	79*	97*	74*	84*
FEMALE RATS					
1	0	17*	9	6	6
12	77*	64*	70*	60*	60*
60	98*	91*	95*	90*	86*

The above table is based on TABLE CHE1-SUM, pages 340-345, and on TABLE CHE2-SUM, pages 346-348, of the submitted report (MRID 43197901). These tables contain cholinesterase activities and constitute Attachment VI of this review.

Analytical doses were 1, 12 and 59 ppm, respectively. These doses were equivalent to 0.067, 0.787 and 4.26 mg of Methamidophos/kg/day, respectively, for males. The corresponding values for the females were 0.074, 0.899 and 4.94 mg/kg/day, respectively.

* Statistically different from control: $p \leq 0.05$. Based on N=6/sex/dose.

Gross Necropsy

There were no gross lesions in perfused rats of either sex which were attributed to treatment with Methamidophos. Darkening of the lumbar cauda aquina areas of the spinal cord in one control female was considered an incidental finding. For each of the remaining rats, "All findings normal" was recorded in the Necropsy History Report (pages 412-419 of the submission; MRID 43197901). One half of the rats used for neurobehavioral evalua-

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tion (6/sex/dose) were necropsied at the termination of the study.

Brain Weights and Brain/Terminal Body Weight Ratios

These data were obtained for the 6 rats/sex/dose which were necropsied. There were no significant differences in terminal body weight or brain weight (absolute or ralative) between control and treated rats of either sex. These data are in Attachment VII of this review.

Histopathology

Treatment-related effects were not observed in the tissues examined: neural tissues and skeletal muscle. Microscopic changes, generally minimal and regarded as common spontaneous alterations in the Fischer 344 rats (references [8, 9, 10] in Attachment I of this review) were: **(1)** Degeneration of scattered individual nerve fibers in the brain, spinal cord and spinal nerve roots; **(2)** Axonal swelling in the medulla oblongata and spinal cord; **(3)** Ocular microgranulomas; and **(4)** Corneal mineralization. These data are summarized below.

Methamidophos (ppm)	0		60#	
	Males	Females	Males	Females
Number examined	6	6	6	6
Lesion	Number of Organs / Tissues Affected			
Degeneration, Nerve Fiber:				
Midbrain	...	...	1	...
Brain (pons)	...	...	1	...
Cerebellum	6	5	6	6
Optic nerve	...	...	1	...
Spinal cord:				
Cauda equina	...	1	...	1
Cervical	3	4	5	3
Lumbar	2	1	1	2
Thoracic	2	5	3	3
Spinal nerve roots	...	1	...	...
Axonal Swelling:				
Medulla oblongata	4	2	6	3
Cerebellum	...	...	...	1
Spinal cord:				
Cervical	...	...	1	1
Lumbar	1	1	2	1

Continued on next page

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Methamidophos (ppm)	0		60#	
	Males	Females	Males	Females
Number examined	6	6	6	6
Lesion	Number of Organs / Tissues Affected			
Axonal Swelling:				
Spinal cord:				
Thoracic	...	...	...	2
Ocular Microgranulomas:	4	5	6	3
Corneal Mineralization:	3	4	3	5

This table is based on TABLE MP1-SUM, MICROPATHOLOGY SUMMARY (Incidence and Lesion Grade), pages 371-376, of the submitted report (MRID 43197901).

Nominal dose. The analytical dose for both sexes was 59 ppm.

... Zero (0) incidence.

None of the findings observed in the high-dose group were significantly different from those observed in the controls ($p \leq 0.05$). Because treatment-related findings were not observed in the high-dose group, the low-dose and mid-dose groups were not examined histologically.

COMMENTS:

Review of the final report and supporting data indicated that the design and conduct of the study were adequate to assess the neurotoxic potential of Methamidophos in the rat. However, hematological and clinical chemistry determinations, other than cholinesterase activities, were not performed.

The study authors did not consider cholinergic effects to be neurotoxicity and regarded the highest dose of Methamidophos tested, 59 ppm (equivalent to 4.26 mg/kg for males and 4.94 mg/kg for females), as a neurotoxic NOEL. Toxicology Branch I/HED considered cholinergic signs to represent neurotoxicity and, therefore, designated the lowest dose of Methamidophos tested, 1 ppm (equivalent to 0.067 mg/kg for males and 0.074 mg/kg for females) as a neurotoxic NOEL.

The principal pathologist for this study, Dr. B.F. Hamilton, regarded cholinesterase activity inhibitions < 20% in brain, erythrocytes and plasma as biologically insignificant. Based on this premise, he concluded that 1 ppm of Methamidophos (0.067 mg/kg for males and 0.074 mg/kg for females) was an overall NOEL for cholinesterase inhibition. Toxicology Branch I/HED disagees with this conclusion in the case of cholinesterase activities in brain and plasma (erythrocyte cholinesterase activity was not inhibited in the 1 ppm group). Because, following treatment, cholinesterase activity was determined only twice in plasma and only once in brain, it is difficult to conclude unequivocally that an inhibition is (or is not) biologically insignificant. For this reason, Toxicology Branch/HED concluded that the NOEL for brain and plasma cholinesterase inhibition was < 1 ppm and the LOEL was 1 ppm. The LOEL = 1 ppm is in agreement with the LOEL established in another subchronic (56-day) feeding/cholinesterase study (MRID No. 41867201) with the same strain of rats and conducted by the same testing facility (in 1990). In that study, the LOEL for the inhibition of brain and plasma cholinesterase activities was 0.07 mg of Methamidophos/kg for the male rats and 0.06 mg of Methamidophos/kg for the female rats.

The following statement were included in the submission:

(1) No Claim of Data Confidentiality, signed and dated 4/13/94;
(2) Good Laboratory Practice Compliance, signed and dated as above; and
(3) Quality Assurance, showing that this study was inspected 38 times between 12/12/92 (Animal Shipment Receipt and Examination) and 3/11/94 (Final Report Review).

Methamidophos tox. review # 011530

Page_____ is not included in this copy.

Pages 16 through 43 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__X__ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

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