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

011048

MAY 16 1994

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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Parathion, Acute oral neurotoxicity study in rats

TO: Larry Schnaubelt PM 72  
Reregistration Branch  
Special Review and Reregistration Division (H7508C)

FROM: *[Signature]* 4/15/94  
Robert P. Zenzian Ph.D.  
Senior Pharmacologist  
Toxicology Branch I  
Health Effects Division (H7509C)

THROUGH: Karl Baetcke Ph.D.  
Chief  
Toxicology Branch I  
Health Effects Division (H7509C) *[Signature]* 5/13/94

Compound; Parathion *Coswell 637* MRID; 431179-01

Registration #: 057501 Registrant; Chem Nova DP Barcode; D199873

Action Requested

Review the following study:

Citation  
Acute neurotoxicity study of ethyl parathion in rats, D.J. Minnema, Hazleton  
Washington, HWA 2688-100, Feb 3, 1994, MRID 431179-01

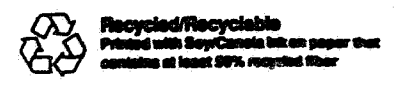
Core Classification Acceptable

Conclusions

Single oral dose of 0, 0.025, 2.5 & 10.0 mg/kg males and 0, 0.025, 0.5 & 2.5 mg/kg females. 2 deaths males 10.0 mg/kg. Significant depression ( $p > 0.05$ ) plasma, RBC and brain (6 areas) cholinesterase activity males 10.0 and females 2.5 mg/kg 4 hours post dose. 50 to 80% of concurrent controls. Incomplete recovery 14 days post dose, significant depression ( $p > 0.0$ ) male RBC and brainstem. Functional observational battery, signs indicative cholinesterase toxicity 4 hours post dose males 10 and females 2.5 mg/kg. Full recovery day 7. No histopathological lesions in the nervous system 14 days post dose.

Attachments

19/29



Data Evaluation Report

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Compound Parathion

Citation

Acute neurotoxicity study of ethyl parathion in rats, D.J. Minnema, Hazleton Washington, HWA 2688-100, Feb 3, 1994, MRID 431179-01

Reviewed by *R.P. Zendzian* 4/5/94  
Robert P. Zendzian PhD  
Senior Pharmacologist

Core Classification Acceptable

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Materials

Ethyl parathion  
Batch No 79818-01  
brown liquid  
purity 86.2%  
from Cheminova Agro A/S

Vehicle/control  
Duke's<sup>®</sup> Corn Oil  
Lot no 2B25 17:59

Test animals  
Male and female Sprague-Dawley Crl:CD<sup>®</sup>BR rats  
approximately 4 weeks old  
from Charles River Laboratories  
Raleigh NC

Experimental design

Group	Dose mg/kg	Number of Animals			
		Neurobehavioral		Cholinesterase	
		Male	Female	Male	Female
1	0	10	10	10	10
2	0.025	10	10	5	5
3	0.5	0	10	0	5
4	2.5	10	13	5	12
5	10.0	13	0	12	0

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Animals designated for neurobehavioral testing were dosed at approximately seven weeks of age and animals designated for cholinesterase determinations were dosed at approximately eight weeks of age. A single oral dose.

Dosing formulations were prepared in corn oil so that the designated dose was administered orally in 2 milliliter of solution per killogram body weight. Formulations were prepared separately for dosing the neurobehavioral and cholinesterase animals. Samples were analyzed for parathion content.

Animals were observed for mortality and moribundity twice daily and a thorough physical examination conducted at each weighing interval. Body weights were obtained at randomization, prior to treatment, day 0, day 7 and day 14,

Cholinesterase

The animals designated for cholinesterase determination were sampled according to the following schedule.

Table 1. Schedule of cholinesterase samples. Blood samples for cholinesterase activity were taken 2 days prior to dosing. Blood and brain were taken for cholinesterase activity on day zero, four after dosing, and on day 14. The latter animals were those previously sampled on day -2.

Dose mg/kg	Number of Animals						
	Male			Dosing Day	Female		
	-2	0	14		-2	0	14
0		5				5	
0	5	5 >----->			5	5 >----->	
0.025		5				5	
0.5						5	
2.5		5				5	
2.5					5	5 >----->	
10.0		5					
10.0		5	5 >----->				

Blood samples were analyzed for plasma and RBC activity. The brain was removed, divided into six regions and each analyzed for cholinesterase activity. Brain regions were olfactory bulbs, cerebellum, cortex, straitum, hippocampus and midbrain plus brainstem.

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### Neurobehavioral

"A battery of behavioral tests and observations, referred to as the Functional Observational Battery (FOB), designed to measure various aspects of sensory and motor functions, was conducted on the first 10 or 13 (Group 4 females and Group 5 males) animals/group/sex prior to initiation of dosing, 4 hours after dosing and at least 1 and 2 weeks after dosing. The 4-hour-postdose time interval was provided by the Sponsor and, according to the Sponsor, represented the time of peak neurobehavioral activity of the test material. The FOB was performed during the dark cycle at approximately the same time of the day at each interval. With the exception of the performance measures, all neurobehavioral assessments were conducted under red-light conditions. A detailed description of the criteria for each observation is presented in the following pages." See appendix I pages 23-27 from the report.

### Termination

"On the day of scheduled necropsy (at least 15 days after dosing), all animals designated for neurobehavioral observations were weighed and given an intraperitoneal injection of sodium pentobarbital. A whole body perfusion was performed on six rats/sex/group." All of the remaining rats were necropsied. The following tissues from each perfused animal were collected and preserved.

Anterior tibialis muscles  
brain with brainstem (medulla/pons, cerebellar cortex and cerebral cortex)  
cervical dorsal root and ventral root fibers  
cervical spinal cord  
cervical dorsal root ganglia  
eyes with a portion of the optic nerve  
gasserian ganglion  
gastrocnemius muscles  
lumbar dorsal root and ventral root fibers  
lumbar spinal cord  
lumbar dorsal root ganglia  
macroscopic lesions  
mid-thoracic spinal cord  
pituitary  
sciatic nerve  
sural nerve  
tibial nerve

### Histopathology

"With the exception of the proximal sciatic, sural and tibial nerves, all preserved tissues from the perfused animals in the control (Group 1 male and female rats) and high-dose

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animals (Group 5 male and group 4 female rats) were impeded in paraffin, sectioned at 5u, mounted and stained with hematoxylin and eosin. The proximal sciatic, sural and tibial nerves were embedded in plastic (glycol methacrylate), cross-sectioned at 1 u, stained with toluidine blue O, and examined microscopically from all perfused animals in the control and high-dose groups (Group 5 male and Group 4 female rats). In addition, longitudinal sections of the peripheral nerves were embeded in paraffin, sectioned at 5 u, stained with luxol fast blue, and counter stained with periodic acid-Schiff."

Results

Two high dose (10 mg/kg) males died the day of dosing. Signs indicative of choinesterase poisoning, hypoactivity, labored respiration, rough coat, chromodacryorrha, urine stains, muscle fasciculations, tremors and salivation, were observed in the remaining males on the day of dosing and continued for 13 days-post dose for one to two males. Similar signs were observed in one high dose (2.5 mg/kg) female on the day of dosing. A significant decrease in weight relative to control was observed in the high dose males (10 mg/kg) on day 7 post dose but not on day 14. No effect on body weight was observed in the females.

Results of cholinesterase determinations are presented in Table 5 from the report. Results as percent of concurrent control have been calculated by the reviewer. A dose of 2.5 mg/kg parathion produced significant depression in plasma and RBC cholinesterase activity ( $p > 0.05$ ) 4 hours post dose in both sexes. Recovery, partial to full, was observed at 14 days post dose, but the RBC activity in the males at 10 mg/kg remained significantly depressed ( $p > 0.05$ ).

In effect on the brain, the female was more sensitive then the male at four hours post dose. A dose of 2.5 mg/kg (HDT) in the female produced a significant reduction of activity ( $p > 0.05$ ) in all six brain areas tested but no apparent effect was observed in the males at this dose. A significant reduction of brain activity ( $p > 0.05$ ) was observed at 10 mg/kg (HDT) in the males. Brain activity, in both sexes, showed a variable but incomplete degree of recovery by day 14 post dose. However, only the male brainstem showed significant depression ( $p > 0.05$ ).

Mild changes in FOB compared to pretreatment and concurrent controls were observed at 4 hours post dose which could be attributed to treatment in the males at 10 mg/kg (HDT) and the females at 2.5 mg/kg (HDT). All treated animals were normal at 7 and 14 days post dose. See appendix II.

No treatment related effects were observed at histopathological examination.

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Pages 6 through 13 are not included.

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Tox Chem No. Parathion

File Last Updated

Current Date

EPA  
MRID

Study/Lab/Study #/Date  
Acute neurotoxicity,  
Rat; Hazleton Wash, ;  
IWA 2688-100; 2/3/94

Material  
tech 86.2%

MRID  
No.  
431179-01

Results:  
LD50, LC50, PIS, NOEL, LEL  
Single oral dose of 0, 0.025, 2.5 &  
10.0 mg/kg males and 0, 0.025, 0.5 &  
2.5 mg/kg females. 2 deaths males 10.0  
mg/kg. Significant depression (p>0.05)  
plasma, RBC and brain (6 areas) cholin-  
esterase activity males 10.0 and females  
2.5 mg/kg 4 hours post dose. 50 to 80%  
of concurrent controls. Incomplete  
recovery 14 days post dose, significant  
depression (p>0.0) male RBC and  
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toxicity 4 hours post dose males 10 and  
females 2.5 mg/kg. Full recovery day 7.  
No histopathological lesions in the  
nervous system 14 days post dose.

TOX  
Category  
N/A

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