1-21-94

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.:4581-292

From: Lucy D. Markarian, Biologist 5/12/93
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

To: Dennis Edwards, PM 19
Insecticide-Rodenticide Branch
Registration Division (7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

E 1/21/94

Applicant: Atochem North America
3 Parkway, Room 619
Philadelphia, Pa 19102

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Methyl Parathion:O,O-Dimethyl O-p-nitrophenyl Phosphorothioate	20.9 %
Related Isomers	1.1 %
Inert Ingredient(s):	78.0 %
Total:	100.0 %

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BACKGROUND

Atochem North America has submitted five new studies in support of their product Penncap-M under EPA 4582-292. This is a microencapsulated insecticide containing methyl parathion. Previously five tests had been submitted and reviewed as of 9/23/91. At that time acute dermal and inhalation toxicity studies were found to be supplementary data, and a sensitization test had been requested. This submission of new tests contains all but an inhalation study. This is expected to be submitted in the near future. Aerosolizing the encapsulated product has been a problem. At this time the product is registered as a restricted pesticide with the signal word WARNING. Atochem would like this to be changed to CAUTION.

RECOMMENDATION

The submitted acute dermal, eye irritation, dermal irritation, and dermal sensitization tests are considered core minimum data. The acute oral toxicity test is considered to be supplementary data.

The registrant must either accept the results of the formerly submitted acute oral test, or submit a new test that assures the homogeneity of the test material, uses no dilutions unless absolutely necessary, and uses animals in an acceptable age range. In the event the results of the new study differ significantly from the study submitted and accepted earlier, the difference must be explained. E

In the past the signal word WARNING was used. It is not known what this was based on. There is one reference to dermal toxicity at 1200 mg in interagency correspondence found in the file. There were no specific tests that were referenced for the acute dermal results except the ones presented and reviewed on 9/23/91. The active ingredient is on record to have high acute toxicity (cholinergic effects). By the inhalation route, toxicity potential is not only high, but rapid as well. It is considered to be a hazardous waste.

As claimed by the registrant this product is encapsulated and consequently expected to be less toxic than other methyl parathion formulations. The previously submitted oral test conducted with the encapsulated product bears this out. Oral LD_{50} is reported to be at 20 mg/kg in male rats and 62 mg/kg in females (Farm chemicals Handbook, 1990) versus 600 mg/kg in the previously submitted test. with the encapsulated product. In the submitted dermal test LD_{50} is 2500 mg/kg. The published dermal LD_{50} is 491 mg/kg for the active ingredient. At the present we do not have any inhalation data on the encapsulated product. The active ingredient, methyl parathion has an LC_{50} of 0.135 mg/L according to published data. E E E

The rating of the tests is discussed below.

Acute Oral Toxicity - Supplementary

1.The test material was in suspension. No effort was made to keep the suspension homogeneous during dilution and intubation. If the test material was not kept homogeneous, there is no assurance that the individual doses were accurate.

2.No explanation is given for the need for dilution. When the test material is in liquid form it is expected that it will be administered as received. This tests the impact of the undiluted test material on the test model. Any ingestion of the formulation is expected to be in undiluted form. The test material was diluted by weighing 15 grams of test material (liquid) and making the volume up to 30 ml. This is a 50 % dilution w/v. PRS fails to see why this was necessary when the undiluted test material had a specific gravity of approximately 1, and each 200 g rat would have received 1 ml of test material. This is measurable by an ordinary syringe.

3. Animal ages ranged from 6 to 12 weeks. While it is claimed that the weights did not vary more than 20 %, this much variation in age is not desirable or acceptable . It is concluded that some of the test animals were twice as old as the others. Rats reach puberty between 40 and 60 days and some of them may not have been mature at 6 weeks. Ideally Sprague Dawley strain should weigh 200-300 g when tested. Some of the animals were less than 200 grams. When an older animal shows less than normal gains in weight (weighs about the same as an animal two or more weeks younger), it may be an indication of less than perfect health and should not be inducted into the study.

Acute Dermal Toxicity- Core minimum

The homogeneity of the test material is not verified.

Eye Irritation- Core minimum

1. The source of light, or if magnification was used is not reported. The guidelines indicate that these are to be reported.

2.The corneal findings were not confirmed with fluorescein dye. This is not a requirement, but adds confidence to the reported results.

3. It is not indicated how the homogeneity of the test material was maintained for accurate dosing.

Dermal Irritation - Core minimum

The homogeneity of the test material is not verified.

Dermal Sensitization - Core Minimum

PRS finds the product to be a sensitizer. The results from the test group are compared to the results from the vehicle control or naive control groups. There was absolutely no reaction at any of the sites induced with vehicle and challenged and rechallenged with the test material and the second vehicle. When compared with the 4/20 positive readings at the primary challenge , and 2/20 positive readings at rechallenge with a lower concentration and in acetone, it shows the product to be a sensitizer. Incidence and severity indices are not very meaningful, but in this case, compared to 0 index from the vehicle control group, even that shows sensitization potential. The results from the test group should not be compared to the positive control group at any time to show positive or negative potential for sensitization. The positive control group is to demonstrate the laboratory's ability to induce sensitization, as well as the possibility of inducing sensitization in the guinea pigs.

PRS does not see the need for a rechallenge with a lower concentration. Especially since the pre rechallenge screening did not find 90 % in acetone to be the highest non irritating concentration. It was in effect completely non irritating with a score of 0 for 4/4 sites. The fact that there were 2/20 positive responses and many more (8/20) ± scores indicates that the animals were sensitized.

There should have been naive controls for the rechallenge.

Rechallenge should not be at a lower concentration when no irritation is observed in the naive or vehicle control groups. Generally rechallenge is at the same concentration or higher than the primary challenge. In this case it should have been at 100 %.

The positive control group should be challenged at a lower concentration. Induction and challenge were at the same concentration, but in different vehicles. Positive control tests are expected to be conducted using the same principles as the test groups. What is applicable to the test group is applicable to any control group, otherwise the purpose of the control group is nullified. In this test the laboratory did not show the ability to perform an adequate test judging by the positive control group. Induction and elicitation with DNCB were at irritating concentrations. Irritation at induction is acceptable; however, elicitation has to be at the highest nonirritationg concentration. These values for DNCB are established and available in published literature.
With the exception of the rechallenge, the test group was conducted correctly.

LABELING

The precautionary label will be recommended when all the outstanding data is submitted.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager:19 Reviewer: L. Markarian
MRID No.: 425849-01 Report Date:10/30/92
Testing Facility:Pharmacon Research Int.
Report No.PH 402-ANA-001-92
Author(s):Victor T. Mallory
Species:Rat, Sprague Dawley
Age:6 - 12 weeks
Weight:dose range 164-208 g, limit test 181-242 g
Source:Charles River Laboratories, Inc., Wilmington, MA
Test Material:Penncap-M, batch EGC-31C2-20,
yellow aqueous suspension
Quality Assurance (40 CFR §160.12):Included

Conclusion:

1. The estimated LD_{50} is > 5000 mg/kg
3. Tox. Category: Classification:Supplementary

Procedure (Deviations from §81-1):

A range finding study was made using 3 dose levels. No animals died at 5000 mg/kg. A limit test was performed at 5000 mg/kg. The test material was diluted to be administered at 10 ml/kg (v/v in deionized water. It is not indicated if the suspension was stirred during dilution or when withdrawn with syringe or how the suspension was kept homogeneous. Fasted animals were intubated with the diluted suspension. Observations were at 1 and 4 hrs after intubation and daily thereafter. Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Dosage mg/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
5000	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

There was no mortality.Signs of toxicity included decreased activity 10/10 diarrhea 10/10, poor grooming 3/5 F,abnormal gait and stance 3/5 F, chromadocryorrhea 1/5 F, tremors 2/5 F, and elevated gait 2/5 F. All were normal after day 6. Acceptable gains in body weight were noted at 7 and 14 days
Necropsy revealed mottled kidneys in 6/10. No other gross pathology was observed.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager:19 Reviewer: L. Markarian
MRID No.: 425948-01 Report Date:10/22/92
Testing Laboratory:Pharmacon Research, Int.
Report No.:PH 422-ANA-004-92
Author(s):Victor T. Mallory
Species:Rabbit, New Zealand White
Weight:2.4 - 2.9 K
Source:Hazleton Research Products, Denver PA
Test Material:Penncap-M Batch EGC-31C2-20,
Yellow aqueous suspension
Quality Assurance (40 CFR §160.12):Included

Summary:

1. The estimated LD_{50} is > 2500 mg/kg

2. Tox. Category: III Classification:core minimum

Procedure (Deviation From §81-2):

Undiluted test material was applied to the shaved skin of the animals on an approximately 10 % of the body surface.The site was covered with gauze dressing and the trunks of the animals were wrapped in dental dam. At 24 hrs the wrappings were removed and the sites washed with water and gauze. Observations were daily for 14 days. Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Reported Mortality

DOSAGE mg/kg	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2500	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:

No mortality or signs of toxicity were observed. there was no dermal irritation. Necropsy revealed no abnormalities.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager:19 **Reviewer:** L. Markarian
MRID No.: 425849-02 **Report Date:**10/22/92
Testing Laboratory: Pharmacon Research, Int.
Report No.: PH421-ANA-001-92
Author(s): Victor T. Mallory
Species: Rabbit, New Zealand White
Sex: Male and female
Weight:2.5 - 3.0 K
Source: Hazleton Research Products, Denver PA
Dosage:0.1 ml
Test Material: Penncap-M batch EGC-31C2-20
Yellow aqueous suspension
Quality Assurance (40 CFR §160.12): Included

Summary:

1. **Toxicity Category:**IV

2. **Classification:** Core minimum

Procedure (Deviations From §81-4):

Undiluted test material was instilled in the conjunctival sacs of six pre examined eyes. Observations were at 1, 24, 48, and 72 hrs according to Draize.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	0/6	0/6	0/6	0/6				
Iris	0/6	0/6	0/6	0/6				
Conjunctivae								
Redness	0/6	0/6	0/6	0/6				
Chemosis	0/6	0/6	0/6	0/6				
Discharge	-	-	-	-				

Comments:

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager:19 Reviewer: L. Markarian
MRID No.: 425849-03 Report Date:10/22/92
Testing Laboratory:Pharmacon Research, Int.
Report No.:PH 420-ANA-001-92
Author(s):Victor T. Mallory
Species:Rabbit, New Zealand White
Age:young adult
Sex:Male
Weight:2.8 - 2.9
Dosage:0.5 ml
Test Material:Penncap-M batch EGC-31C2-20
Yellow aqueous suspension
Quality Assurance (40 CFR §160.12):Included

Summary:

1. **The Primary Irritation Index =0**

2. **Toxicity Category:IV**

3. **Classification:Core minimum**

Procedure (Deviations From §81-5):
Undiluted test material was applied to the clipped intact skin of the rabbits. The sites were covered with gauze and dental dam. At 4 hrs the wrappings were removed and the sites wiped wit gauze and water. Evaluations were at 1, 24, 48 and 72 hours according to Draize.

Results:

No irritation was observed at any interval at any site

Special Comments:

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager:19 **Reviewer:** L. Markarian
MRID No.: 425849 **Report Date:**11/2/92
Testing Laboratory: Pharmacon Research, Int.
Report No.:PH 424-ANA-002-92
Author(s): Susan D. Armondi
Species: Guinea pig, Hartley
Weight:300 - 377 g
Source: Buckberg Lab Animals, Tompkins Cove, NY
Test Material: Penncap-M Batch EGC-31C2-20
Yellow aqueous suspension
Positive Control Material:DNCB
Quality Assurance (40 CFR §160.12): Included

Method: Buehler

Summary:

1. **This Product is a dermal sensitizer.**

2. **Classification:**Core minimum

Procedure (Deviation From §81-6):

A pre test screening was made for the definition of the induction and elicitation concentrations. Four guinea pigs and four concentrations were used: 100 % and v/v dilutions at 50, 10, and 1% in deionized water. At 100 % 1/4 sites showed ± reaction. No other reaction was observed at any site. Induction and primary challenge were made at 100 %. There were 20 animals (10 M & 10 F) in the test group. 10 animals were used as controls that were induced with deionized water and challenged with the test material. 5 animals were used as positive control, induced with 0.3 % DNCB in ethanol and challenged with 0.3 % DNCB in acetone.
A rechallenge was made with 90 % test material in acetone. vehicle control animals were rechallenged with acetone and 90 % test material in acetone. There were no naive controls for the rechallenge.
The test and control materials were applied to the clipped skin of the guinea pigs using Hill Top chambers in 0.3 ml aliquots. The guinea pigs were restrained and rubber dam was used to establish good contact with the skin. At 6 hrs the patches were removed and the sites were wiped clean of any residue. There were three inductions, made 1 week apart.
Challenge was two weeks after the last induction. Challenge applications were at naive sites applied in similar way as the inductions. Rechallenge was made a week after the primary challenge at a naive site in similar manner. The vehicle controls were rechallenged at this time with acetone and 90 % test material. The rechallenge was at the request of the registrant. A prechallenge screening was made using four guinea pigs and four concentrations. The dilutions were made at 60, 70, 80, and 90 % using acetone. No

reaction was observed at any site or dilution. Rechallenge was at 90 % in acetone
Evaluations were at 24 and 48 hrs after induction and challenges according to Buehler.

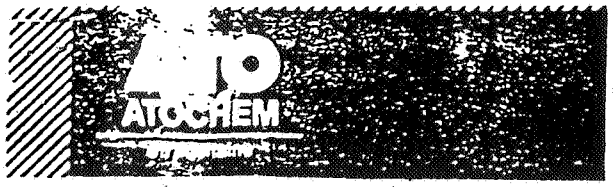
Results:

	Test		Vehicle Control		Positive Control	
First induction	24	48	24	48	24	48
Male	0/10	0/10	0/5	0/5	1/3 ±	1/3 ±
Female	0/10	0/10	0/5	0/5	2/2 ±	2/2 ±
Second Induction						
Male	0/10	0/10	0/5	0/5	2/3 1	1/3 1
					1/3 2	1/3 2
						1/3 3
Female	0/10	0/10	0/5	0/5	2/2 1	2/2 1
Third Induction						
Male	0/10	1/10 ±	0/5	0/5	1/3 2	1/3 2
					2/3 3	2/3 3
Female	3/10 ±	3/10 ±	0/5	0/5	1/2 2	1/2 3
					1/2 2	1/2 3
Primary Challenge	100 % test material				0.3 % DNCB in Acetone	
Male	5/10 ±	2/10 ±	0/5	0/5	3/3 3	1/3 1
		2/10 1				1/3 2
		1/10 2				1/3 3
Female	2/10 ±	3/10 ±	0/5	0/5	1/2 2	2/2 3
	3/10 ±	1/10 1			1/2 3	
Rechallenge	90 % test material in acetone					
Male	4/10 ±	3/10 ±	0/5	0/5		
		1/10 1				
Female	3/10 ±	5/10 ±	0/5	0/5		
	1/10 1					

The laboratory has calculated incidence and severity based on these results and concluded that the formulation is not a sensitizer. PRS finds the product to be a sensitizer.

Tox Chem No: 053501 Methyl Parathion Current Date: 5/11/93
Laboratory:Pharmacon Research International, Inc., Waverly, PA

S T U D Y	M A T E R I A L	MRID NO	R E S U L T S	TOX CAT	CORE GRADE
Acute Oral Limit Test(Rats) PH 402-ANA-001-92 11/30/92	Penncap-M EGC-31C2-20	425849-01			Supplementary
Acute Dermal Limit Test(Rabbits) PH 422-ANA-004-92 10/22/92	" " " "	425948-01	LD_{50} > 2500 mg/kg	III	Minimum
Eye Irritation in Rabbits PH 421-ANA-001-92 10/22/92	" " " "	425849-02	Nonirritating	IV	Minimum
Dermal Irritation in Rabbits PH 421-ANA-001-92 10/22/92	" " " "	425849-02	Nonirritating	IV	Minimum
Dermal Sensitization Guinea Pigs PH 424-ANA-002-92 11/2/92	" " " "	425849-04	← POSITIVE [redacted]		Minimum



RESTRICTED USE PESTICIDE

Due to very high acute toxicity to humans [illegible]
For retail sale to and use only by certified applicators or persons under their direct supervision and only for those uses covered by the certified applicator's certification. Direct supervision for this product is defined as the certified applicator being physically present during application, mixing, loading, repair and cleaning of application equipment. Commercial certified applicators must also ensure that all persons involved in these activities are informed of the precautionary statements.

PENNCAP-M®

MICROENCAPSULATED INSECTICIDE

ACCEPTED
JUL [illegible] 1991
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 4581-292

ACTIVE INGREDIENTS:	
O,O-Dimethyl O-p-nitrophenyl phosphorothioate*	20.9%
Related Isomers	1.1%
INERT INGREDIENTS	78.0%
TOTAL	100.0%

*Methyl Parathion (Contains 2 pounds Methyl Parathion and Related Isomers per Gallon) U.S. Patent Nos. 3,429,827, 3,577,515, 3,959,464

KEEP OUT OF REACH OF CHILDREN

AVISO WARNING

PRECAUCION AL USUARIO:

Si usted no lee ingles, no use este producto hasta que la etiqueta haya sido explicado ampliamente.

STATEMENT OF PRACTICAL TREATMENT

IF SWALLOWED, induce vomiting immediately by giving two glasses of water and sticking finger down throat. Call a physician. Never give anything by mouth to an unconscious person.

IF ON SKIN, immediately wash with soap and water and flush with plenty of water.

IF IN EYES, immediately flush eyes with plenty of water for at least 15 minutes.

Refer to back panel for Precautionary and First Aid Statements and Note to Physician.

EPA Registration No. 4581-292 EPA Establishment No. 4581-TX-1

Net Contents: ____ U.S. Gallons/____ Liters

Sold by:
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Philadelphia, PA 19102

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