11-6-72

11157
001716

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Date: November 6, 1972

Reference: EUP 1410 (Vydate) The petitioner is requesting a temporary tolerance for residues of the insecticide methyl N',N'-dimethyl-N[(methylcarbamoyl) oxy]-1-thiooxamimidate in or on the r.a.c. peanuts at 0.2 ppm.

Subject:

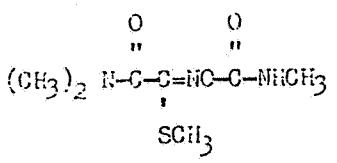
To: Dr. Drew W. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 3G1316

E. I. duPont deNemours
Wilmington, Delaware 19898

This insecticide is to be used in the eight major peanut growing states with a total of 155 acres under test with 1560 lbs Vydate being used.

Formula:



Toxicity data submitted

Acute and Sub Acute (*-summarized data only)

LD_{50}* - Rats (M) using 90% active material - 5.4 mg/kg

LD_{50}* - Rats using 24.7% soln in DMF mg/kg

	Active Ingredient	Mixture
Male	4	16
Female	2.8	11

Subacute oral* - Using 99% technical as a 0.05% solution in acetone + peanut oil five times a week for two weeks. Six of 6 animals survived 10 daily doses of 2.4 mg/kg with no apparent cumulative toxicity. Gross manifestations were slight pallor and salivation after dosing on the first 2 days and mild inflammation of the stomach at sacrifice. No other histopathologic signs were noted.

001716

(a) ALD and Delayed Paralysis (234-70) – The test material as a 1% suspension was administered in single doses directly into the crops of hens approximately 1 year old. A few minutes prior to dosing with the test compound, the chickens, except those used to determine the ALD, received IM injections of 0.5 mg/kg atropine. The ALD was found to be 40 mg/kg. The delayed paralysis test demonstrated the following signs: After administration of 20 and 40 mg/kg of test material with IM injection of 0.5 mg/kg atropine there was sudden depression, lethargy, ruffed feathers, slight regurgitation difficulty, ataxia, and incoordination. After 12 hours no clinical signs of abnormality were observed, egg production was normal. There were no compound-related histopathological changes reported. Mortality ratio was 0/5 for both 20 mg and 40 mg/kg test levels.

Eye Irritation test 263-68, 278-69) – Four albino rabbits were administered 10 mg into the right conjunctival sac and two were similarly treated with an equivalent amount of the material dissolved in propylene glycol. One eye of each pair exposed to powder or solution was washed for one minute with tap water 20 seconds after contact; the other eye was the control. Observations were made at 15 minutes, 1, 2, 3, and 4 hours, and at 1, 2, 3 and 7 days. It was found that the compound produced marked pupillary constriction, usually with minor iritic congestion in both washed and unwashed eyes. Conjunctival irritation was generally mild and corneal injury was not observed. Complete recovery occurred within 2 to 7 days. Prompt washing after dosing with the powder reduced the duration of pupillary constriction but did not obviously decrease ocular reactions in those treated with the propylene glycol solution.

In test HL 378069 0.1 ml of the formulation in DMF was instilled into the right conjunctival sac of each of six male albino rabbits, six other rabbits were dosed similarly with 0.1 ml of a 25% suspension of dust in distilled water. Systemic effects that were observed were characteristic of anticholinesterase activity; this included pupillary constriction, chewing and licking motion, salivation, fasciculations, reduced muscular coordination and hyperpnea. DMF formulation symptoms caused by the water suspension

In a similar study DMF formulations with test material concentrations of 20%, 16% and 12% were used and compared with 0.1 ml of a 25% dust suspension in distilled water. It was found that the 25% water suspension was less toxic than an equivalent concentration in DMF. This test was to show that Vydate was absorbed through the eye to give systemic effects similar to cholinesterase inhibition, but was less toxic than Systox at the same level.

Acute Skin Absorption Tests (282-70, 102-70, 103-70 and 123-69) In tests 282-70, 102-70 and 103-70 albino rabbits were used as test animals. In test 282-70 single rabbits were tested with the test material in decreasing doses of 0.6% of dose for the previous rabbit. The test material was applied as a paste in hydrophilic ointment to both clipped intact and clipped abraded

skin and allowed to remain in-situ for 24 hours. The wrappings were then removed, areas of exposure were washed with water, and the rabbits observed for recovery period of 14 days. The ALD varied considerably, depending upon the conditions of exposure. The range was from 60 mg/kg to 5000 mg/kg. The following table shows these variations:

% Test Material	Solvent	Skin	ALD mg/kg
25	Hydro. Oint.	Intact	5,000
		Abraded	130
50	Water	Intact	2,250
		Abraded	90
25	Prop. Glyc.	Intact	130
		Abraded	60

Clinical signs in the rabbits were typical of those produced by chemical with anticholinesterase activity.

Test 162-70 was another test to evaluate the skin as a route for entry of the insecticide into the body. Six rabbits per dose were treated with the insecticide after being clipped and the skin abraded. The test material was applied and allowed to remain for 24 hours at which time the area was cleaned with soap and water. Survivors of the treatment were then observed for 14 days. The LD50 on a commodity basis was 2160 mg/kg.

Test 103-70 was similar to the above test except that the material was applied to clipped intact skin as a paste in hydrophilic ointment. Levels used were 5,000, 1,500 and 450 mg/kg - ALD was found to be 5000 mg/kg.

Test 123-69 used undiluted liquid applied through a layer of gauze to the skin of the clipped trunk of male albino rabbits. Five different formulations were tested, the ALD of INX-1179-161 and IND-1410-10 were 300 and 450 mg/kg respectively. The ALDs of INX-1179-162, IND-1410-11 and INT-1642-45 where dimethylformamide was the solvent were 3400, 3400, and 2250 mg/kg respectively. It is apparent that the toxicity of these compounds depends upon the solvent and its fat solubility and/or non-polarity.

In the skin irritation and sensitization tests (146-68) male guinea pigs were used. The test compound was used as a suspension in propylene glycol or in 1:1 acetone - dioxane containing 13% guinea pig fat (f.a.d.). For the irritation test applications of 0.05 ml were lightly rubbed into the shaved intact and abraded skin. In the test for skin sensitization, a series of exposures were given over a three-

001716

week interval: Three of seven animals started on a series of nine applications of 25% material in propylene glycol to abraded skin completed the series, four of the five animals scheduled for four intradermal injections (each 0.1 ml of 1.0% solution in propylene glycol) completed the treatments. After a 2 week rest period, the material was applied again. The conclusions of this test were that Vydate produced negligible irritation and no sensitization in skin tests with guinea pigs. However, it caused severe systemic effects particularly after application to abraded skin.

Fifteen-exposure Dermal stud (235-70)

Fifteen male and 15 female rabbits were divided into 3 groups of 5 male and 5 female. One group acted as the control, one had abraded skin and one had intact skin. The dose application was 193 mg/kg for 6 hours a day for 15 days.

Results of this study show a decline in weight during the first stages of treatment which was probably due to stress of confinement and low food consumption. There was a slight diarrhea and neuro-muscular weakness in the hind quarters plus the normal signs of cholinesterase inhibition. There were random anatomical lesions in the liver, kidney, brain, G.I. tract, respiratory tract, testes and spleen in both the test and control animals. In summary, they stated that these animals showed no cumulation systemic effects attributable to the test material.

Acute Dust inhalation test (280-69)

Male rats were exposed (head only) to an aerosol of the test material for up to 11 hours. Particle size was reported to be 0.2μ but the samples taken were through a filter so this would have acted as a sizing device. Following exposure the surviving rats were placed in regular housing cages and observed for 14 days. The pathological summary submitted stated there were no gross effects attributable to exposure. However, microscopically there was mild congestion in the heart, lungs, liver, kidney and thymus in the survivor of the 0.077 mg/L exposure. The reported LC_{50} was 0.064 mg/L, this level would be equivalent to approximately 1.12 mg total or 4.48 mg/kg body wt.

In experiment 281-69 a test similar to the previous test was made using higher concentration with only a 1 hour exposure time. In this test, six male and 6 female rats were used per exposure. The LC_{50} for the test material was calculated to be as follows:

Male = 0.17 mg/L ≈ approximately 2.97 mg/kg
Female = 0.12 mg/L ≈ approximately 2.10 mg/kg

001716

Test number 282-69 was another one hour inhalation study using a liquid formulation instead of the dust as in the previous two tests. The survivors of the exposure were pale and incoordinated with pulmonary congestion on the first day; corneal opacity, hyperemia, hypersensitivity to touch, thickened ears and facial alopec, all recovered during the 14 day recovery period. The LC_{50} are as follows:

Male = 0.67 mg/L / 11.84 mg/kg
Female = 0.68 mg/L / 11.28 mg/kg

Antidote Studies 57-70, 322-69 and 282-69

In two studies rats were given 2X the oral LD50 of 5.4 mg/kg to test the effectiveness of the antidote. In study 57-70 both PAM (100 mg/kg) and Atropine Sulfate (50 mg/kg) were tested. In test 322-69 only Atropine Sulfate (50 mg/kg) was tried. In both tests the Atropine sulfate gave complete recovery. The PAM gave only 80% recovery. In the third test (282-69), performed by Hazelton Laboratories, monkeys were given the insecticide according to the following schedule:

Monkey #	Sex	Insecticide mg/kg
996-K	F	5
	2nd dose 9 days later	25
3-J	F	20
	2nd dose 9 days later	25
10-J	F	25
11-J	M	40

After dosing, the animals were observed until death occurred. In the antidotal study 6 rhesus monkeys were given the oral lethal dose of 25 mg/kg of insecticide followed by 10 mg/kg atropine. The antidote was withheld until the animals exhibited signs of toxicity. Results showed that atropine (10 mg/kg) given orally or intavenously, would protect monkeys against the lethal effect of 25 mg/kg of the insecticide.

Cholinesterase Activity (18-70)

In 2 trials (20 rats each) ChE activity in rats was tested. A dose of 4.85 mg/kg per animal of insecticide was given, in one group of 10, 5 mg/kg atropine was given Ip and the peripheral blood was taken from the tail vein of each rat at 5 minutes, 4 hours and 24 hours. This same procedure was duplicated in the 2nd trial. ChE activity was measured by the colorimetric method of Ellman (1961). The sublethal dose caused decreased ChE activity of the whole blood. When atropine was administered the magnitude of the depression was decreased and the return to normal was more rapid (i.e. by 9 hrs. for treated, 24 hrs. untreated).

5

001716

Teratogenic study in rats (5-71)

One hundred thirty seven pregnant rats were divided into 5 groups, one group acted as the control and received the regular purina lab chow with 1% corn oil. The remaining groups each received this basic diet plus 50 ppm, 100 ppm, 150 ppm and 300 ppm of the test material. These diets were given on the 6th day of gestation through the 15th day. All animals were sacrificed by CHCl3 on day 20 and fetuses removed by cesarian section.

Results of this test were depressed weight gain in the dams at 100 ppm and at 300 ppm; this was the result of decreased food intake. No gross changes were observed in the tissues and organs of the pregnant rats. There was no significant difference between the test animals and controls in implantation sites resorptions and live fetuses. There was no effect on embryonal development as judged by crown-rump length and weight or any fetal anomalies. Some fetuses from each litter were cleared with Alizarin Red S to measure skeletal effects, others were fixed with Bouin's fluid to detect visceral and soft tissue anomalies.

Subacute Studies

13 Week Oral Administration in Dogs - Four groups of 4 male and 4 female beagles were given the test insecticide at levels of 0, 50, 100 and 150 ppm respectively. These diets were fed for 13 consecutive weeks. Clinical laboratory studies were performed initially and at 4 and 13 weeks. Hematological studies included: Hct, Hgb, RBC, WBC and differential count. Blood chemistry studies included: blood sugar, BUN, SP, bilirubin, albumin, Na, K, bromsulphalein liver function test, cl, CO_2, Ca, SGPT, AP, SGOT, and serum electrophoresis. Urine analyses included: Sp gr, pH, sugar, acetone, protein, bilirubin, and microscopic examination of the sediment. No blood or brain ChE determinations were made.

At termination all dogs were necropsied and weights of thyroid, heart, liver, spleen, kidneys, adrenals, and testes with epididymis recorded. Microscopic examinations were made of the thyroid, heart, liver, gall bladder, spleen, kidney, adrenal, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, testes, ovary, bone marrow, and unusual lesions of the 0 and 150 ppm levels.

Results of this study showed no significant changes with regard to any of the parameters listed above.

No effect level > 150 ppm based upon systemic toxicity.

90 Day Feeding Study in Rats (303-69)

Sixty-four male and sixty-four female rats were divided equally into 4 groups and given the insecticide orally at 0, 50, 100 and 500 ppm respectively. After 91-95 days of continuous feeding all but 6 male and 6 female rats in each group were sacrificed. Clinical laboratory studies, Hematological studies and Urine analyses were similar to the above 13 week study with no ChE determinations being made.

Results showed that the animals on the 500 ppm level started to fasciculate after being on the diet for 2 days. At 4 days they exhibited ruffed fur, mild diarrhea, bulging eyes, lacrimation, and loss of weight. Animals fed 100 ppm showed no clinical signs except depressed rate of weight gain. The 50 ppm group exhibited no clinical signs of toxicity. In the urine analyses the 100 ppm group had a significant increase in occult blood. The 150 ppm group had an increase in both the occult blood and urine protein. Incorporated into this study was a reproduction study of one generation and 2 litters at the same dose levels. There was a 20% decrease in weanling weights which was significant at p .001. This would indicate that a no-effect level was demonstrated. However, the females also had a decreased weight gain due to reduced food intake. This would result in a reduced milk production. The no-effect level could therefore be assessed at 50 ppm.

Three Generation Reproduction Study.

Sixty-four male and sixty-four female weanling albino rats were divided into 4 equal groups of 16 male and 16 females and fed the following diet:

Group	Diet
1	Purina Lab Chow + 1% Corn oil
2	" " " " + 50 ppm Vydate
3	Purina Lab Chow + 1% Corn oil + 100 ppm Vydate
4	Purina Lab Chow + 1% Corn oil + 150 ppm Vydate

After 12 weeks of feeding, the females were housed separately and exposed to each of 3 males (Fo) from the same feeding group for a period of 5 days, this mating produced the F_{1A} litter. After an interval of approximately 1 week after delivery the Fo animals were mated a second time to produce the F_{1B} litter; the F_{1A} litter had been sacrificed. The F_{1B} litter was then mated to produce the F_{2A} and F_{2B}. This process was repeated until the F_{3A} and F_{3B} litters

had been produced.

Results show no significant difference between the control and 50 ppm test group throughout the entire reproduction study with respect to the various indices and average weanling body weight. In the 100 and 150 ppm groups the weanling body weights and the viability and lactation indices appeared to be somewhat lower. This study points out as in the previous abbreviated reproduction study that the lower weanling body weights was due to an adverse nutritional effect rather than a toxic one. The petitioner reported that the histopathological evaluation of the pups from litter F_{3B} was not completed as yet. No-effect level 150 ppm.

Chronic Feeding Studies

2 Year Rat - A 2 year feeding study was made using 420 albino rats receiving 0, 50, 100, and 150 ppm of an adequate nutritional diet. The study was started using levels of 0, 50, 100, and 500 ppm but the animals at the 500 ppm level became severely toxic consequently the level was lowered to 150 ppm. The study was designed the same as the 90 day and 13 week studies with the same hematological, biochemical and histopathological parameters being made. In addition ChE activity was measured by the pH-Stat and colorimetric method on blood taken from the tail vein and heart of 10 male and 10 female rats from each of the control and 150 ppm groups after 4 and 8 days and after 1, 6, 12, and 24 months of feeding. At the 1 and 6 month examinations the 100 ppm group was also examined. Aliesterase activity was also tested from these rats after 1, 12 and 24 months.

No clinical signs of toxicity were observed at the 50 ppm level; at 100 and 150 ppm there was a decrease in rate of weight gain with no other clinical signs of toxicity. Significant ChE inhibition occurred only at the 500 ppm level. ChE activity averages for the males and females at the 0, 100, and 150 ppm levels are as follows:

Levels		4 days	8 days	1 mo	6 mos.	12 mos.	24 mos.
0	Males	8.8	6.8	6.5	6.6	9.0	7.1
100	"	—	—	6.8	7.4	—	—
150	"	9.3	4.3	6.8	6.5	9.3	7.3
0	Females	8.8	7.5	7.9	8.1	8.5	7.2
100	""	—	6.3	7.7	7.7	—	—
150	"	7.0	7.0	6.9	7.1	6.8	8.3

[redacted]

8

It can be seen from these data that there was a decrease in ChE activity at the 150 ppm level in the males at 8 days but returned to normal by 1 month. However, a portion of this decrease may be due to technique since the controls also had a 2 unit decrease in the same time.

There was a decrease in the organ weights but it was postulated that these lower organ weights, observed after 2 years of feeding 150 ppm were merely due to the lower food intake and lower body weight.

During the 2 year feeding study animals were taken out of the main feeding study to complete another 3 generation reproduction study. The study was designed as the previous reproduction study. All the parameters measured (same as previous reproduction test) were negative to any significant changes that could be attributable to the test material. This test included pathologic changes as well as gross and microscopic changes.

2 Year Dog Study

Four males and 4 female beagle dogs per group were fed 0, 50, 100, and 150 ppm for 2 years. Hematological, biochemical (blood) and urinary examinations on each dog were conducted before the start of the trial and at 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months of feeding, no ChE tests were made. These parameters included the following:

Hematology: Erythrocyte count, hemoglobin concentration, hematocrit, total and differential leucocyte count.

Biochemistry: Glucose, urea-nitrogen, cholesterol, alkaline phosphatase activity, glutamic-pyruvic transaminase activity, total protein and albumin-globulin ratio. Cholinesterase and aliesterase activity was measured once before the test began, and after one, six, twelve, and twenty-four months of feeding Vydate.

Urine Analysis: Quantitative measure of volume, osmolality, and protein; semi-quantitative test for urobilinogen; tests for sugar, acetone, bilirubin and blood; color, appearance and pH noted; microscopic examination of sediment from an aliquot of each specimen.

001716

After approximately 1 year of continuous feeding 1 male and 1 female from the control group and 150 ppm group were sacrificed for examination. All the surviving dogs were necropsied at termination. Tissues examined microscopically were brain, heart, lung, liver, spleen, kidney, testis, stomach, thyroid, adrenal, pituitary, pancreas, prostate, urinary bladder, epididymis, fallopian tubes, uterus, ovary, duodenum, cecum, colon, skeletal muscle, peripheral nerve, bone marrow, eyes, thoracic aorta, mammary gland, esophagus, gall bladder, spinal cord, trachea, thymus, salivary gland and tonsil.

Results of these tests indicate no significant difference at the 100 ppm level for either the rat or the dog. In the rat there was a slight depression of ChE activity at 150 ppm but this was only a temporary condition. In the dog, according to the summary submitted there was a suggestion of liver involvement at the 150 ppm level. No other pathological or histological signs were found. No-effect level 100 ppm.

Wildlife Studies

Studies were made on the toxicity of Vydate to Coturnix Quail, Bluegill, Goldfish, and Rainbow trout. Following are the LD_{50} for these:

Coturnix Quail	- LD_{50} 4.64 mg/kg
Bluegill	- LC_{50} 5.6 mg/kg
Goldfish	- LC_{50} 27.5 mg/kg
Rainbow trout	- LC_{50} 4.2 mg/kg

Coturnix Quail were also fed Vydate at levels of 0, 70 ppm, 140 ppm and 210 ppm. The birds were fed the test diet for 1 day followed by the control diet for 2 days. This cycle was repeated 10 times, resulting is a 30-day feeding study. No signs of compound effect were reported.

10

001716

Conclusions and Recommendations

It is apparent that the no effect level for this insecticide is 100 ppm in both the dog and the rat 2 year feeding study based upon systemic toxicity. At this level the ADI would be 3.0 mg/kg for a 60 kg man.

The requested level at 0.2 ppm on peanuts would not present a toxicological hazard to the public. TB therefore recommends this temporary tolerance be granted.

Robert P. Schmidt, D.V.M.
Toxicology Branch
Pesticides Tolerances Division

cc: JCCummings
FRD/EPA
Atlanta Branch (CLewis)
Perrine Branch
Division Reading File
Branch Reading File
PP# 3G1316

R/D Init:CHWilliams 11/6/72
RPSchmidt:dtb 11/8/72
Init:CHWilliams