TR-977

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: April 10, 1978

SUBJECT: Pesticide Registration#3125-280 Caswell#378A 000977

FROM: John Doherty
Toxicology Branch

TO: Franklin Gee
Product Manager #16

Registrant: MOBAY Chemical Co
Chemagro Agricultural Division
Kansas City, Mo. 64120

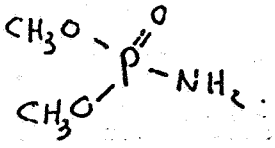
Product: MONITOR(R)4

Active Ingredient:

O,S-dimethyl phosphoramidothioate ---------- 40%

Inert [redacted] ---- 60%

Structure:



Synonymn: Tamaron

CFR 180.315 has set tolerances of 0.1 to 1.0 ppm on various agricultural commodities.

Action Requested: Amendment to registration related to use of this chemical.

Remarks and Recommmendations

1) Toxicology Branch cannot approve amending this registration until the following acceptable studies are submitted using the formulation of MONITOR(4) as test material.

   i) rat acute oral LD_{50}
   ii) rabbit acute dermal LD_{50}

2) The rabbit acute dermal and rat acute oral LD_{50} studies were judged CORE invalid because no identification of the lab that performed the test or date the test was given was provided.

   If this information is provided then the oral LD_{50} test will be CORE minimum, but the dermal LD_{50} test will be CORE supplementary and have to be repeated to support labelling (see review).

1-76

EPA FORM 1320-6 (REV. 3-76)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

000977

The dermal toxicity in presently category II but the standard deviations were about 50%. Thus there is a reasonable possibility that the label should conform to category I and the precautionary statements revised.

3) Many studies supporting the tolerances for MONITOR were supported by data from Industrial Biotest (see Quaife memo).

4) The teratogenesis study was judged to be CORE supplementary. Two incidences of clubhand occurred in the animals treated with 0.3 mg/kg of test material. The teratogenesis hazard of this chemical is not clarified.

5) MONITOR was updated and the tolerances checked. It was found that assuming that the NEL was 1.5 ppm (90-day dog ChE study) and using a safety factor of 10, the PADI was not exceeded.

6) The oral toxicity is sufficient to classify the product as a Category I toxicant. Therefore a front panel precautionary statement is required.

Summary of Acute Toxicity

Test	Results	TOX CAT.	Core-Guidelines
Rat Acute Oral LD_{50}	m-17.8(12.6-25)mg/kg f-20.0(13.4-298)mg/kg	(I) ? ←	Invalid Invalid
Rabbit Acute Dermal LD_{50}	285.6(188-432)mg/kg	(II) ? ←	Invalid
Inhalation LC_{50} (1)	>3.28 mg/L	III	Minimum
Eye Inhalation (rabbit)	not irritating	III	Minimum over
Skin Irritation (rabbit)	not irritating	?	Minimum

(1) Industrial Biotest, N 968, February 11, 1972.

Review of Skin Irritation Study

Chemagro Research Department, 70-189, December 16, 1971.

50 mg of MONITOR(R) was applied to two areas of the shaved backs of 6 rabbits. One area was abraded by scrubbing with a nail brush. The other area was not abraded. Due to the toxicity of the material only 50 mg were applied and not the 500 mg as required. The areas were covered for 24 hours and the treated areas examined for erythema, edema and necrosis.

Results, only very slight erythema and edema were noted and this occurred in only 1 of the six rabbits. The single irritation score was .75 and the average for six rabbits was .125.

This study is CORE minimum. Although less than the required amount was used, it can be concluded that it poses an irritation hazard that is less than the toxicity hazard (lethal). Appropriate label instructions for a compound that is toxic by the dermal route are included on the label.

000977

The missing information has been obtained during the Registration Standards review:

Testing lab. — Chemagro
Report # 31646 ; 12/16/71
Test material: Monitor 4 (40% a.i.) ; used 0.1 ml
Results: slight redness and chemosis in 2/4 rabbits during the 24-48 hrs post treatment.
No irritation at 72 hrs post treatment.

R. Locke ; 9/23/81

Review of Inhalation Study

000977

Industrial Bio-Test, N 968, February 11, 1972.

5 male and 5 female rats were exposed to an aerosol of 8.0 percent aqueous solution of Monitor (4 lbs/gal). This was equivalent to a concentration of 41 mg/Li of air or 3.28 mg of Monitor /L of air.

Results: No deaths occurred. All the rats exhibited tremors and exophthalmus during the exposure period. Necropsy revealed slight hyperemia of the lungs in eight of these animals. Body weight gain over the 14 day period was normal.

CORE minimum. An LC_{50} was not determined, but sufficient data to classify this formulation as a Category III toxicant were.

Review of Oral LD_{50}

No letterhead identifies the laboratory. The report was taken from 239-2404 and accompanied a letter of June 16, 1972 by W.L.B. The report is numbered 31986.

Groups of 4 males and 4 females Sprague-Dawley rats weighing 200-250 gms were used. The male rats were exposed to doses of /.5, 15, 30 and 60 mg/kg and groups of female rats were exposed to 10, 20, 40 and 80 mg/kg. The rats were observed for 14 days.

Results: The LD_{50} for male rats was calculated to be 17.8 (12.6 to 25.2) mg/kg (greater than 20%).

The LD_{50} for female rats was calculated to be 20.0 (13.4 to 29.8) mg/kg (greater than 20%).

CORE INVALID. Sufficient data is obtained to classify this formulation into Category I. No comments were made on the general health of the surviving animals, nor was necropsy performed. The lab and the test data are not identified.

Review of Dermal LD_{50}

Report No. 31986 (see under Review of Oral LD_{50})

Undiluted formulation Monitor 4 was applied to the backs of New Zealand rabbits. These animals were shaved but not abraded. After 24 hours the material was removed and the area washed with soap and water.

Results: mal LD_{50} = 285.6 (188.5 to 432.8), much greater than 20%
female LD_{50} = 285.6 (189.5 to 432.8), much greater than 20%
(in mg/kg

CORE Invalid The standard erro is about 50% and the LD_{50}'s were calculated to be near the borderline for classification into Category I. Also, the backs of the rabbits were supposed to have been abraded. An additional test must be presented to evaluate the dermal toxicity. This report should contain data on the surviving animals, body weight gain, and major necropsy findings.

4

000977

Review of Delayed Neurotoxicity Study

Industiral Bio-Test, J9546, May 27, 1971.

A total of 30 hens (laying) were divided into groups of 10. One group as positive control and two groups treated with Monitor (technical). The test materials were fed in a standard laboratory diet for 30 days. The dosage level was reported as 0.3 and 3.0 mg/kg of Monitor and 50 mg/kg of TOCP (positive control).

Results: (1) A severe body weight loss was noted in the TOCP treated hens. Body weight loss was also noted in the 3.0 mg/kg Monitor hens. Food Consumption for the TOCP treated hens was severely decreased, but for the Monitor treated hens it was considered normal. This reviewer notes that the 3.0 mg/kg hens consumed much less than the 0.3 mg/kg hens in the Monitor study. (2) None of the hens in the Monitor groups died. 2 of the TOCP treated hens died. All of the TOCP treated hens exhibited ataxia by test day 17. (3) Microscopic examination of representative sections of the peripheral and control nervous system of both the positive control (TOCP) and Monitor (3.0 mg/kg) hens revealed no abnormalities which could be attributed to the test material or test procedure. The use of a special myelin sheath stain (solochrome cyanin) revealed no evidence of demyelination.

This study is CORE Supplementary and does not resolve the question of Monitor being capable of causing delayed neurotoxic effects. The dose of Monitor administered was supposed to be an LD_{50} and given by gavage. No rational was presented for the doses used, nor was the route of administeration (by diet) justified. Positive controls did not show evidence of demyelination.

Review of Neurotoxicity Study with 75% Monitor

Industrial Bio-Test, J6480, November 12, 1968.

An acute oral LD_{50} was determined using hens (Legho) and found to be 27.5 mg/kg (22.5 to 33.6).

Three groups of six hens each were utilized in the neurotoxicity study. The groups consisted of untreated controls, test group receiving 27.5 mg/kg, and positive control birds receiving 500 mg/kg of TOCP. Birds in the Monitor Group were given a second 27.5 mg/kg dose after 21 days of observation. Dosage was by gavage.

Results: 2 of the Monitor and 2 of the TOCP treated birds died within the 42 days. Weight loss was evident in the TOCP treated group only.

Reactions to Monitor subsided in 4 days and no ataxia developed. Ataxia developed in the TOCP treated hens 14 days after dose administration.

Core Minimum. Microscopic and histological examinations were not reported. There is an inconsistancy in the text. It is stated that 4 birds were used for the positive controls, but the table list six birds.

5

000977

Review of Teratogenesis (Rabbits)

Industrial Biotest, J9515, November 18, 1971.

Rabbit does were treated with Monitor Technical at 0.1 mg/kg/day (17 does), or 0.3 mg/kg/day (23 does), or Thalidomide (37.5 mg/kg.day, 27 does) on days 6 through 18 of gestation.

Results: These levels of MONITOR ha[illegible] no observable or reported effects on the does, nor was fetal mortality, incidences of resorption or abortions affected by treatment with MONITOR.

Two of the 63 pups in the group treated with MONITOR (0.3 mg/kg) developed talipomanus (club hand). This was not observed in any of the other progeny.

Core Supplementary. No justification for these low doses of MONITOR in given. The dose is supposed to have some observable effects in the doe. Since two clear cut cases of talipomanus developed at the highest test dose used, higher doses should be tried. Core guidelines now require teratology studies in 2 species of animals.

S.E.W. 5/1/78

6