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

MEMORANDUM

DATE: 11/20/81

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Monitor 4 Liquid Insecticide: Amended Registration to Add Sprinkler Irrigation of Potatoes--A Resubmission.
EPA Reg. No. 3215-280. Accession Nos. 242410 and 242411.
TOX Chem No. 378A

FROM: Krystyna K. Locke
Toxicology Branch/HED (TS-769) Krystyna K. Locke 11/10/81

TO: William Miller, PM Team No. 69458
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch/HED (TS-769) Budd 11/16/81

THRU: William L. Burnam, Acting Branch Chief
Toxicology Branch/HED (TS-769)

Action Requested:

Incremental risk assessment.

Recommendation:

Toxicology Branch recommends that the proposed use of Monitor 4 Liquid Insecticide be approved for the following reasons:

1. This submission has already been reviewed by Toxicology Branch but has been rejected because of the deficiencies in two acute studies, oral and dermal, conducted with Monitor 4 (J. Doherty; 4/10/78). These deficiencies have now been resolved.

2. Monitor 4 is already registered for use on potatoes and a tolerance of 0.1 ppm has already been established for Monitor (methamidophos) residues in or on potatoes. Residues of Monitor in potatoes treated by sprinkler irrigation are not expected to exceed this existing tolerance (L. M. Bradley, RCB; 8/13/80).

3. The proposed use of Monitor 4 will add no new residues to the human diet. In other words, the Theoretical Maximal Residue Contribution (TMRC) will remain unchanged.

4. Although serious gaps exist in the toxicity data baseline for Monitor, due to the recent invalidation of studies conducted by IBT, these gaps do not affect Toxicology Branch's recommendations because of 2. and 3.

5. The invalid studies are gradually being replaced by the new studies. Three studies (acute dermal LD50 with Monitor 4, and teratology and acute delayed neurotoxicity with Technical Monitor) have been submitted with the current request for amended registration of Monitor 4 Liquid Insecticide.

   The following results were obtained:

   a. Acute dermal LD50 (rabbit): 987 mg/kg (male) and 515 mg/kg (female)
      Core Classification of Study: Guideline.

   b. Teratology (rabbit): Monitor was not teratogenic or embryotoxic at the 2.5 mg/kg level (highest tested).
      Core Classification of Study: Minimum.

   c. Acute delayed neurotoxicity (hen): No signs of delayed neurotoxicity and no spinal cord lesions were observed at the 50.63 mg/kg level (highest tested).
      Core Classification of Study: Guideline.

   Detailed reviews of these studies accompany this evaluation.

Evaluation:

1. The Agricultural Chemical Division of Mobay Chemical Corporation requested a label amendment for Monitor 4 Liquid Insecticide in order to include irrigation application for potatoes. This formulation contains 40% of O,S-dimethyl phosphoramidothioate (methamidophos), an active ingredient. All of the inerts in the formulation have been cleared under Sec. 180.1001(c). The proposed application rate for spinkler irrigation is the same as the registered rate (0.75-0.1 lb. a.i./acre). The PHI is 14 days. According to RCB (Lynn M. Bradlely; 8/13/80), residues of Monitor in potatoes treated by sprinkler irrigation are not expected to exceed the existing tolerance of 0.1 ppm. RCB recommended the proposed label amendment.

2. The toxicity data in the original submission were evaluated by Toxicology Branch, but the proposed label amendment was denied because two acute studies, oral and dermal, were considered unacceptable (John Doherty; 4/10/78). According to the reviewer, "The rabbit acute dermal and rat acute oral LD50 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 LD50 test will be Core Minimum, but the dermal LD50 test will be Core Supplementary and have to be repeated to support labelling."

   In the case of the acute dermal study, the standard deviations were about 50% and the report did not contain data on the survivors, body weights and major necropsy findings.

The report on these studies has currently been submitted to Toxicology Branch for evaluation under the Registration Standards process. Judging by the numbering system employed, these studies were apparently conducted by Mobay Chemical Corporation in 1971. The acute dermal LD50 study has been replaced by one conducted on 7/10/79 (Nos. 79ADL04 and 67995; review attached).

3. Study desirable but lacking for the purpose of this action: primary dermal irritation study. The available study (rabbit; No. 70-189; 12/16/71) was conducted with 50 mg of Monitor 4 and not with the required 500 mg. Monitor 4 was nonirritating at that exposure level (PIS = 0.125).

Attachments:

OPP:HED:TOX: K.LOCKE:sb 11/9/81 X71511 #m6

Acute Dermal Toxicity of Monitor 4 to Rabbits. D. Nelson; Stanley Research Center, Mobay Chemical Corporation.

Raptima R. Loche (review); 11/10/81

Study Nos. 79 ADL 04; 67995

Date of Study: July 10, 1979

EPA Accession No. 242411; TOX Chem. No. 378A

This study was started on 5/1/79 and was completed on 6/20/79.

Summary

1. With one exception (females, 442 mg/kg level), toxic signs were seen in male and female rabbits at all dosages tested.

2. At the termination of the study, males at the 304 mg/kg level (lowest tested) and all of the females gained weight. The remaining males gained only about 1/14, or less, of the weight attained by other rabbits.

3. Gross microscopic changes, attributed to Monitor 4, were seen only in those animals which died before the termination of the study.

4. Toxicity category of Monitor 4: II

   LD50 (mg/kg): 987 (male; abraded skin)
   : 516 (female; abraded skin)

5. Classification of the study: Core-Guideline.

Evaluation

Experimental Procedures:

Monitor 4 (42.7% a.i.) was applied to the abraded backs of male and female New Zealand rabbits at the following levels: 304, 597, 1170 and 2293 mg/kg (males) and 304, 442, 477, 515, 554, 749 and 1170 mg/kg (females). The rabbbits weighted 1.97-2.92 kg; 8 rabbits (4 male and 4 female) per dose were used; the exposure time was 24 hours; and the observation period was 14 days. All rabbits were examined for gross lesions at the time of death or at the day 14 sacrifice.

Results:

1. Mortality: All of the males died at the highest level tested and all of the females died at the three highest levels tested. Deaths occurred within 21-26 hours post treatment.

2. Weight: On day 7 after treatment, the average weight loss for the males was 11 and 10% for the 597 and 1170 mg/kg levels, respectively. The remaining males and most of the females gained weight (2.4-5.7%). At the time of sacrifice (day 14), males at the 304 mg/kg level (lowest tested) and all of the females weighed 10-15% more than they did on day zero. The lower was the dosage, the higher was the weight gain. The remaining males gained only about 1/14, or less, of the weight attained by other rabbits.

3. Toxic Symptoms: Signs of toxicity were seen in nearly all of the male and female rabbits, and at all levels of Monitor 4 tested. These were: diarrhea, salivation, ataxia, tremors, decreased activity, dyspnea, unthrifty appearance and constricted pupils.

4. Gross Microscopic Findings: Animals that died. In males, pulmonary congestion was present in 3 animals, an intussusception in the small intestine in one animal, and serosal hemorrhages in 2 animals. In females, pulmonary congestion occurred in 3 animals, serosal intestinal hemorrhages in 2 animals, and a necrosis in the duodemal portion of the small intestine in 1 animal. One female (at the 515 mg/kg level) has a postmortem rupture of the stomach and diaphragm which were caused by thinning of the stomach wall and by mucosal atrophy. The intestinal changes in both male and female rabbits were attributed to the dermal application of Monitor 4. No male rabbits died at the 304 mg/kg level (lowest tested) and no female rabbits died at the 304, 442 and 477 mg/kg levels.

5. Gross Microscopic Changes: Animals sacrificed at 14 days. These data are reported for individual animals. No gross lesions were found in male and female rabbits which were sacrificed at the termination of the study.

6. LD50 and 95% Confidence Limits:

Male	987 (590-1655) mg/kg
Female	516 (493-539) mg/kg

7. Toxicity Category: II
   Core Classification: Guideline

Typing Error:

On page 3 under Results, 2-nd paragraph, there is a statement that "Weight gains were seen on all levels except weight loss on day 7 at 500 mg/kg". There was no 500 mg/kg level. The correct figure is 515 mg/kg.

SRA 5172 (Methamidophos): Studies of Embryotoxic and Teratogenic Effects on Rabbits Following Oral Administration

L. Machemer; Bayer A. G., Institute Für Toxikologie, Wuppertal-Elberfeld, West Germany. Submitted by Mobay Chemical Corporation (Chemagro). Study Numbers 8410 (Bayer A. G.); 67990 (Chemagro).

Date of Study: 5/31/79 Raptyma R. Loche (reviewer); 11/10/81
EPA Accession No. 242411
TOX Chem No. 378A

This study was conducted from June to September, 1978.

Summary

1. Monitor was not embryotoxic or teratogenic at the 2.5 mg/kg level (highest level tested).

2. Treatment of female rabbits with Monitor (0.1, 0.5 and 2.5 mg/kg body weight) during the gestation days 6-18 did not affect their appearance and behavior, or caused death.

3. Monitor was maternally toxic at all levels tested. Although not strictly dose-related, there was a 53-63% decrease in the weight gain of the dams during the treatment period. At the conclusion of the experiment (gestation day 29), the average weight of the experimental animals was about 47-48% of the weight attained by the controls.

Classification of this study: Core-Minimum

Evaluation

Experimental Procedures:

Himalayan rabbits weighing 2.0-2.5 kg, 15 per dose level, received daily 0.1, 0.5 or 2.5 mg of SRA 5172/kg of body weight from gestation day 6 through 18 (gestation day zero: the day on which copulation occurred). SRA 5172 (methamidophos) is the active ingredient of TAMARON (MONITOR). The test material was MONITOR Technical containing 62% of methamidophos and was dated 11/11/77. The test material was given by oral intubation, in 0.5% aqueous Cremophor emulsion, using 5 ml of the emulsion/kg of body weight. The control groups received the same volume of emulsion. On gestation day 29, the fetuses were removed from the dams by cesarean section. The following examinations were performed at that time:

1. Determination of the number of implantations, living and dead fetuses or embryos, and stunted fetuses (those weighing less than 25 g).

2. Determination of the sex of all fetuses, the weight of each litter, the average placenta weight per litter.

3. Inspection of all fetuses for external malformations and alterations.

4. Necropsy of all fetuses and evaluation of the abdominal and thoracic organs.

5. Examination of the fetuses for brain malformations after separation of the heads, fixation and cross-sectioning.

6. Examination of the fetuses for skeletal defects after staining with alizarin red S.

The number of fetuses examined ranged from 69 to 91 per dosage. The crown-rump measurements of living pups were not made. The dams were observed daily for general appearance, behavior and mortality. They were weighed on gestation day zero, daily during the treatment period, and before sacrifice.

The following methods were used to test data for statistical significance: the U test of Wilcoxon-Mann-Whitney; the Chi-square test; the Chi-square test (correction of Yates); or the exact test of Fischer.

The male rabbits were not treated with Monitor. Himalayan rabbits were used in this study because their embryos/fetuses are very sensitive to the toxic effects of thalidomide (2 references are cited in support of this statement). The highest dose of 2.5 mg/kg/day was selected because, in a preliminary experiment with 3 female rabbits, the oral dose of 5 mg/kg (administered 13 times) produced a weight loss and caused diarrhea in one rabbit.

The aqueous Cremophor emulsion in which Monitor was administered is not characterized chemically. The test material was not apparently analyzed for methamidophos content and the impurities before being used in the study.

Results:

Effects on the Dams:

1. Treatment of female rabbits with SRA 5172 (methamidophos/Monitor; 0.1, 0.5 and 2.5 mg/kg) did not affect their appearancce and behavior, or caused death. The following symptoms and one death were not apparently treatment-related:

    a. Temporary diarrhea in one animal and temporary constipation in another animal, both at the 0.1 mg/kg level.

b. Loss of abdominal hair at the termination of the experiment, at the 2.5 mg/kg level.

c. One rabbit died of a superlative cystitis on gestation day 9, at the 0.5 mg/kg level.

d. In the control group, one rabbit died of respiratory problems on gestation day 8 and another rabbit developed keratoconjunctivitis at the termination of the experiment.

2. Although not strictly dose-related, there was a decrease in the weight gain of the dams at all levels tested. During the 13 days of treatment with Monitor, the controls gained an average of 96.5 g, whereas the experimental animals gained only 35.3-45.3 g or 36.58-46.94% of the weight gain attained by the controls. Considering the entire gestation period, the average weight gain for the controls was 231.2 g and for the experimental animals, 108.6-110.7 g or 46.97-47.88% of the weight gain attained by the controls. The differences were statistically significant for the 0.1 mg/kg group ($p < 0.05$) and the 2.5 mg/kg group ($p < 0.01$). The reduced weight gain was not caused by a small litter size or a lower fetus weight. No information was provided on the food consumption of the animals.

3. All of the fertilized females in the experimental groups and 13/14 in the control group were pregnant at the time of cesarean section.

Effects on the Development of Embryos and Fetuses:

1. Monitor, at all levels tested, had no effect on the number of implantations, resorptions (includes aborted fetuses) and stunted fetuses, fetal deaths, sex distribution, and fetal and placental weights. These data are summarized below for the controls and the 2.5 mg/kg level (highest tested).

Parameter Tested	Averages Controls	2.5 mg/kg Level
No. of implantations	6.6	6.1
No. of resorptions	0.9	0.2
Stunted fetuses	0.0	0.07
Fetal deaths	5.7	5.9
Sex distribution: males	2.6	3.0
: females	3.1	2.9
Fetal weight (g)	38.90	38.86
Placental weight (g)	4.54	4.47

2. There were no fetuses with retarded skeletal development at the 0.1 and 0.5 mg/kg levels. One fetus with skeletal retardations was found in the control group (Sternum) and one in the 2.5 mg/kg group (pubic bone).

3. The following individual malformations were found:

Dose mg/kg	Dam No.	No. of Malformed Fetuses	Malformations
0 (Control Group)	-	-	None
0.1	1111	1	Fused ribs, scoliosis
	1123	1	Ascites, pulmonary hypoplasia, cardiac hyperplasia, enlarged brain ventricles
	1151	1	Acranius, thoracoschisis, deformation of the exteemities
0.5	1128	1	Open eye, cheilognathopalatoschisis*, micrognathia, defect of the body wall.
2.5	1141	1	Bifurcation of the gall bladder

* Cleft in the lip, upper jaw and palate.

These malformations, non-uniform in type, were considered spontaneous rather than treatment-related. The fact that no malformations were found in the control group was attributed to chance. According to the historical data, malformations occurred spontaneously with a frequency of 1.31% in the rabbit strain used in this study (42 of 3215 control fetuses; range in 41 control groups: 0 to 6.66%). After discussing these data with Dr. Louis Kasza, Pathologist, HED/TB, this reviewer agrees that the reported malformations were not apparently caused by Monitor.

Acute Delayed Neurotoxicity Study on Monitor Technical. S. M. Kruckenberg, B. W. Fenwick, S. M. Brown, L. J. Kassebaum and R. K. Nilson; Kansas State University. Submitted by Mobay Chemical Corporation.

Study Nos. 79 ANH01; 68037 Krystyna R. Locke (review); 11/10/81

Date of Study: 7/29/79

EPA Accession No.: 242411

TOX Chem. No. 378A

This study was started on May 1 and was completed on July 29, 1979.

SUMMARY

1. Acute oral LD50 and 95% confidence interval: 29.75 (23.1-38.1) mg/kg of body weight; adult hen. Test material: Monitor Technical (74% a.i.).

2. Monitor, in the presence of atropine sulfate (50 mg/kg of body weight), did not cause delayed neurotoxicity or spinal cord lesions in hens at the 50.63 mg/kg level (highest tested), with or without redosing.

3. Monitor, in the absence of atropine sulfate, did not cause delayed neurotoxicity or spinal cord lesions at the 33.75 mg/kg level, with or without redosing. Only 3 hens were redosed in this test.

4. Triorthocresol phosphate (TOCP; positive control), 500 mg/kg of body weight, administered orally in the presence of atropine sulfate (50 mg/kg of body weight), caused severe leg paralysis and moderate to marked neuronal degeneration in 7 out of 10 hens tested. Three hens did not develop visible signs of neurotoxicity but showed slight to moderate degeneration of neurons during the histological examination.

5. Atropine sulfate (50 mg/kg of body weight), given intramuscularly, was not totally successful in preventing deaths from the acute toxic effects of Monitor. Two out of 10 test hens and 4 out of 12 test hens died at the 30 mg/kg and 50.63 mg/kg level of Monitor, respectively.

6. Classification of Study: Core-Guideline

EVALUATION

Experimental Procedures:

In order to study delayed neurotoxicity of Monitor, an acute oral LD50 was first determined. Technical Monitor (74% a.i.), 10, 15, 22.5, 33.75, 50.63 and 75.94 mg/kg of body weight, was administered to 6 hens per level. All the hens that survived this portion of the study (10, 15 and 22.5 mg/kg levels) were observed for symptoms of delayed neurotoxicity for 17-31 days. The three survivors from the 33.75 mg/kg group were redosed with the same level of Monitor after the first 21-day observation period. The observation period after redosing was 24 days.

Ten hens which did not participate in the LD50 experiment received 30 mg/kg of Monitor orally and 50 mg/kg of atropine sulfate intramuscularly. Another 12 hens received 50.63 mg/kg of Monitor and 50 mg/kg of atropine sulfate. At the end of the first 21-day observation period, the hens were again given their respective doses of Monitor and atropine sulfate, and were again observed for 21 days. The two levels of Monitor given in the presence of atropine sulfate and the 33.75 mg/kg level given without atropine were all higher than the LD50 determined in this study.

Concurrently with the Monitor treatment, 10 hens were dosed orally with 500 mg/kg of triorthocresol phosphate (TOCP) for a positive control. TOCP was administered in the presence of 50 mg/kg atropine sulfate (given intramuscularly) and the hens were observed for 36 days. Eight hens were held untreated as controls for 44 days.

The KSU White Leghorn hens, 9-18 months old, were used in this study. The test subtances were administered by gastric intubation without fasting, in a volume of water which equalled to 1% of the hen's weight. The following parameters were studied:

a. Daily observations for signs of toxicity.

b. Weight and food intake measurements (done every third day).

c. Gross necropsy on all test and control hens.

d. Histopathology of the following regions of the spinal cord: cervical, thoracic, lumbo-sacral and peripheral nerve. A total of 29 hens were examined as follows:

Test Group	Number Examined
Controls	7*
TOCP + Atropine	9
30 mg/kg Monitor + Atropine	6*
33.75 mg/kg Monitor	3
50.63 mg/kg Monitor + Atropine	4*

* Selected randomly.

Results:

1. Oral LD50 Determination:

The acute oral LD50 for Technical Monitor (74% a.i.) was 29.75 mg/kg (adult hens). No toxic symptoms and no deaths occurred at the 10 and 15 mg/kg levels. Deaths and signs of poisoning were observed at the remaining levels (22.5, 33.75, 50.63 and 75.94 mg/kg). The higher was the dosage, the sooner toxic symptoms appeared and the faster the death occurred. The acute signs of poisoning were: muscular weakness, unsteadiness (leg weakness), diarrhea, excessive salivation, anorexia, lateral and sternal recumbency, dyspnea, and cyanotic combs and wattles shortly before death. Death was caused by respiratory paralysis. All of the hens died in the 50.63 mg/kg and the 75.94 mg/kg groups. At the 50.63 mg/kg level, 5 hens died within 15-49 hours after treatment whereas one hen lived for 6 days after treatment. At the 75.94 mg/kg level, all of the hens died within 2 hours after treatment. As is shown below, body weights at the conclusion of the experiment did not generally reflect food intake.

Monitor Technical mg/kg	Food Intake Status*	Body Weight Status*
10	Unchanged	111 g gain
15	7.5 g decrease	Unchanged
22.5	34.5 g decrease	135 g loss

* Differences between day 0 and the day of sacrifice (averages per hen), calculated by this reviewer.

2. Control Group:

No signs of toxicity were seen in this group and no neuronal degeneration was detected in 7 out of 8 test hens which were examined histologically. At the conclusion of the experiment, these hens ate an average of 4 g less and weighed an average of 83 g less per bird than they did on day zero.

3. TOCP-Treated Group:

Seven of the 10 hens in this group developed leg weakness which progressed to paralysis and the hens were unable to sit or move. One hen died on day 26 after treatment, after several days of being in a morbid condition and finally becoming laterally recumbent. This hen was not examined histologically because of postmortem autolysis. Three hens failed to develop signs of neurotoxicity for 36 days (termination of the test), but had slight (1 hen) and moderate (2 hens) neuronal lesions. Spinal cord tissues from the 6 hens with signs of delayed neurotoxicity showed moderate (1 hen) and marked (5 hens) degeneration of neurons. The histological lesions correspond, therefore, fairly well with the clinical signs of neurotoxicity. However, the absence of neurotoxic symptoms in 3 hens with slight to moderate spinal cord lesions suggests that changes at the cellular level precede visible signs of neurotoxicity.

At the conclusion of this experiment, these hen ate an average of 20 g less and weighed an average of 219 g less per bird than they did on day zero.

4. Hens Treated Twice With Monitor (delayed neurotoxicity):

None of the 13 surviving hens in the 30, 33.75 and 50.63 mg/kg groups had delayed neurotoxic symptoms or spinal cord lesions. Atropine, 50 mg/kg given intramuscularly, was not totally successful in protecting the hens from the acute toxic effects of Monitor. There were 2 deaths at the 30 mg/kg level (1 after redosing) and 4 deaths at the 50.63 mg/kg level (all before redosing). There were no deaths in the 33.75 mg/kg group, the 3 survivors from the LD50 determination part of the study. These hens were redosed but received no atropine. As is shown below, body weights at the conclusion of the experiment did not reflect food intake.

Monitor Technical mg/kg	Food Intake Status*	Body Weight Status*
30 + A	Unchanged	114 g loss
33.75	55 g decrease	20 g gain
50.63 + A	8 g increase	125 g loss

* Differences between day 0 and the day of sacrifice (averages per hen), calculated by this reviewer. A = atropine sulfate

The results of the histological examination of the 29 hens are tabulated individuaally and also represented graphically in a 172-page report entitled "NERVOUS SYSTEM HISTOPATHOLOGY REPORT" (which is a part of this submission).

Unclarities:

1. It is stated on page 2 under "III. Rationale of Dosage Levels Used" (last sentence at the bottom on the page) that "Six hens were held untreated for the lengh of the study as controls." The correct number of hens in the control group is 8.

2. The asterisk should be removed from numbers A-39, A-36 and A-12 (Table 2C, p. 18). These 3 hens were the only survivors in the 33.75 mg/kg group and were, therefore, the only ones left to be redosed on the observation day 21 and then examined histologically at the conclusion of the study. It is, therefore, incorrect to say that these hens were "randomly selected for histological studies".

OPP:HED:TOX: K.LOCKE:sb 10/30/81 X71511 #m5