UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: February 21, 1980

SUBJECT: EPA Reg.#1016-EUP-LE; LARVIN 500 Thiodicarb Insecticide for Cotton and Soybeans; PP#9G2152, application for temporary tolerances for residues of thiodicarb and its metabolites in or on cottonseed at 0.4 ppm, soybean seed at 0.1 ppm and soybean straw at 0.02 ppm. CASWELL#900AA; Acc.#099223, 099224

FROM: William Dykstra
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TO: Charles Mitchell
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& Residue Chemistry Branch
(TS-769)

Recommendations:

1. The EUP and temporary tolerances are not toxicologically supported for the following reasons:

   (a) A NOEL for fetotoxicity in the rat teratology was not established. This study needs to be repeated at lower doses.

   (b) The acute delayed neurotoxicity study showed that technical Larvin produced marginal delayed neurotoxic signs in 8 of the 38 animals after 21 days. The eight hens were sacrificed at 21 days, rather than redosed which is recommended, and the remaining 30 hens were redosed and observed for an additional 21 days. Although the redosed birds displayed no delayed neurotoxic signs, the possibility that Larvin technical may be a delayed neurotoxic agent necessitates that this study be repeated according to EPA guidelines.

   (c) The mouse teratology study is required to have signatures of the IRDC personnel who conducted the experiment.

2. The label for Larvin 500 should include in the precautionary labeling "May Cause Skin Sensitization".

3. The remaining toxicology studies submitted were acceptable.

(CONFIDENTIAL)
Larvin 500 Thiodicarb Insecticide

Ingredient	Percent Weight
Larvin [redacted]	46.3
[redacted]	[redacted]
	100.00

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Inerts cleared under 40 CFR 180.1001.

Review:

A. LARVIN Thiodicarb Insecticide Technical

1. Acute Oral Toxicity Study in Male and Female Rats (Hazelton Project No. 400-613, Dec. 13, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

Groups of twenty Sprague-Dawley rats (10M + 10F) received dosages of 50, 88.92, 158.11, 281.17 and 500 mg/kg of test material. Observation for 14 days.

Results: LD50 = 398 (256-620) mg/kg; Males
LD50 = 248 (120-511) mg/kg; Females
LD50 = 325 (204-516) mg/kg; Both Sexes

Toxic Signs: tremors, depression, urine stains, soft feces, salivation, slight depression, rough coat, red stains around nose and/or eyes, ataxia, prostation, and hunching.

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Body Weight: Survivors gained weight.

Necropsy: Dark red discoloration of the lungs, compound and yellowish fluid in the stomach and intestine, and air in the stomach.

Classification: Core-Minimum Data

Toxicity Category II: WARNING

2. Acute Dermal Administration in Rabbits (Hazelton Project No. 400-614, Dec. 17, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

Five groups of twelve rabbits (6M + 6F) received doses of 0 (saline), 1.59, 2.51, 3.98 and 6.31 gm/kg BW of test material on the fur-clipped skin (one-half of the rabbits were further abraded) under an impervious cuff for 24 hours. Observations for 14 days.

Results: No deaths, LD50 > 6.31 gm/kg

Toxic Signs: Slight to moderate ataxia, soft feces, open sores and/or scabs.

Dermal Irritation: Slight to moderate erythema.

Body Weight: Survivors gained weight.

Necropsy: Surface pitting of kidneys, dark red areas in lungs.

Histopathology: Minimal or slight focal acanthosis, focal hyperkeratosis and sub-epidermal pleocellular inflammatory infiltrate.

Classification: Core-Minimum Data

Toxicity Category III: CAUTION

3. Primary Skin Irritation Study in Rabbits (Hazelton Project No. 400-617, Nov. 23, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

0.5 gm of test material was applied to intact and abraded skin sites on the fur clipped trunk of 6 NZW rabbits under an impervious cuff for 24 hours. Observation and scoring at 24 and 72 hours after exposure.

Results: P.I. = 0.0; No erythema, edema or other dermal effects were observed at 24 or 72 hours.

Classification: Core-Guideline Data Toxicity Category IV: CAUTION

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4. Acute Eye Irritation Study in Rabbits (Hazelton Project No. 400-616; Nov. 23, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

44 mg (0.1 ml) of test material was instilled into the left eye of each of nine NZW rabbits with the untreated right eye serving as the negative control. In six rabbits (3/sex), the treated eye was not rinsed; in three rabbits (one male and two female), the treated eye was flushed for one minute with lukewarm water 20-30 seconds after instillation of the compound. Observation with 2% sodium fluorescein was done prior to testing and at 24, 48 and 72 hours, and 4 and 7 days.

Results: Corneal opacity and conjunctival redness, chemosis and discharge were observed in the washed and unwashed eyes of the test rabbits. All lesions were observed to clear by Day 7.

Classification: Core-Guideline Data

Toxicity Category II: WARNING

5. Pilot Teratology Study in Rats (IRDC No. 369-028, Sept. 10, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

Pregnant Charles River CD COBS rats were used in this pilot study to determine dosage levels of UC51762 for a teratology study. Groups of five pregnant rats received dosage levels of 0, 20, 40, 80, 120 and 160 mg/kg/day by gavage as a single daily dose on gestation day 6 through 19 at a constant volume of 10 ml/kg. A control group received the vehicle only, 0.5% methocel, on a comparable regimen. During gestation the females were observed daily for mortality and clinical signs of toxicity. Uterine examinations were performed on all females on gestation day 20 and the location of viable and non-viable fetuses, early and late resorptions and the number of total implantations and corpora lutea were recorded.

Results: There were no biologically meaningful differences in appearance, behavior or uterine examination data in the 20 mg/kg/day dosage group when compared to the control group.

This group showed a reduction in mean maternal body weight gain when compared to the control group. Two rats in the 40 mg/kg/day dosage group died, three rats in the 80 mg/kg/day dosage group died and all of the rats in each of the 120 and 160 mg/kg/day dosage groups died.

Conclusion: Due to high maternal toxicity, a dosage level of 40 mg/kg/day is considered excessive for a teratology study.

Classification: Supplementary Data

✓ 6. Teratology Study in Rats (IRDC No. 369-029, Dec. 28, 1979)

Test Material: Larvin Insecticide (UC51762) technical.

Group of 25 pregnant Charles River COBS CD rats were used to determine the teratogenic potential of UC51762. Dosage levels at 0, 10, 20, and 30 mg/kg/day were administered orally by gavage at a single daily dose on days 6 through 19 of gestation at a constant volume of 10 ml/kg. The control group received the vehicle, 0.5% aqueous methocel, on a comparable regimen at a volume of 10 ml/kg. Cesarean sections were performed on all dams on gestation day 20.

Results: Biologically meaningful differences in appearance and/or behavior were noted in all treatment groups when compared to the control group. Matting of the haircoat in the region of the mouth, forelimbs and ventral surface, and dry red matter, primarily around the eyes and nose, occurred in the treatment groups in a dose-related pattern.

Inactivity, tremoring and a clear oral discharge recurred as a post-dose response throughout the entire treatment period in the 20 and 30 mg/kg/day dosage groups. These observations were present approximately one to four hours after dosing. They were not present at subsequent dosing the following day. Hair loss, primarily on the forelimbs and ventral surface, was noted in all groups although an increase was apparent in the 30 mg/kg/day dosage group. Survival was 100% in all groups. At sacrifice hydronephrosis was noted in a control animal, Dam #21625.

A dose-related reduction in mean maternal body weight gain occurred over the entire treatment period. A mean maternal body loss occurred in the 20 and 30 mg/kg/day dosage groups during the first three days of treatment. The mean number of viable fetuses, early resorptions, post-implantation loss, total implantations, corpora lutea, and the fetal sex distribution in the 10 and 20 mg/kg/day dosage groups were comparable to the control group. Nonviable fetuses were absent from all groups and late resorptions (a total of 2) occurred only in the 30 mg/kg/day dosage group.

Although mean post-implantation loss appeared to be increased in the 30 mg/kg/day dosage group when compared to control group. Dam #21681 and 13 early resorptions.

The increase in mean post-impantation loss was primarily due to this one dam. A decrease was noted in the mean number of total implantations in the 30 mg/kg/day dosage group, however, since implantation occurs prior to treatment, this was not considered to be treatment related.

A statistically significant dose-related decrease in mean fetal body weight was noted in all treatment groups.

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There were no biologically meaningful differences in the number of litters or fetuses with malformations in any of the treatment groups when compared to the control group, however, dose-related increases occurred in the number of litters and fetuses with developmental variations (specifically, unossification of the hyoid, sternebrae #5 and/or #6 and other sternebrae). Other increases in the number of litters and fetuses with developmental variations were noted in the 20 and 30 mg/kg/day dosage groups when compared to the control group.

Conclusion: The test material produced signs of maternal and fetal toxicity as evidenced by dose-related decreases in mean maternal body weight gain and mean fetal body weight and dose-related increases in reduced fetal ossification. The test material was not teratogenic when administered to pregnant rats at dosages up to 30 mg/kg/day. However, the NOEL for fetotoxicity was not established in the study.

7. Pilot Teratology Study in Mice (IRDC#369-030, Aug. 29, 1979)

Test Material: UC51762 technical

A pilot study using pregnant Charles River CD®-1 mice was performed to determine dosage levels of UC51762 for a teratology study. Forty females were assigned to a control group and seven treatment groups consisting of five mice each. The test article was administered orally by gavage as a single daily dose on days 6 through 16 of gestation at dosage levels of 20, 60, 100, 150, 200, 300 and 400 mg/kg/day at a constant volume of 5 ml/kg. The control group received the vehicle only, 0.5% Methocel®, on a comparable regimen at a volume of 5 ml/kg.day. During gestation, the females were observed daily for mortality and clinical signs of toxicity. On gestation day 17, all surviving females were sacrificed and the location of viable and nonviable fetuses, early and late resorptions and the number of total implantations and corpora lutea were recorded. There were no biologically meaningful differences in appearance or behavior in the 20-, 60- and 100- mg/kg/day dosage groups when compared to the control group. All surviving mice in the 150-, 200- and 400- mg/kg/day dosage groups showed no adverse effects to treatment. Two mice in the 150- mg/kg/day dosage group, one mouse in the 200- mg/kg/day dosage group, all mice in the 300- mg/kg/day dosage group and four mice in the 400- mg/kg/day dosage group died. At necropsy, the cause of death was not determined for any of these mice. There were no biologically meaningful differences in mean maternal body weight gains or in the mean number of viable fetuses, early or late resorptions, post-implantation loss, total implantations or corpora lutea in the 20-, 60-, 100-, 150- and 200- mg/kg/day dosage groups when compared to the control group. The one surviving mouse in the 400- mg/kg/day dosage group was gravid.

A dosage level greater than 200 mg/kg/day for a teratology study would produce excessive maternal toxicity.

Classification: Supplementary Data

8. Teratology Study in Mice (IRDC Draft No. 369-031; no date and unsigned report)

Test Material: UC51762 technical

Groups of 25 pregnant Charles River CD-1 mice were used to determine the teratogenic potential of UC51762. Dosage levels of 50, 100, and 200 mg/kg/day were administered orally by gavage as a single daily dose on gestation days 6 through 16 at a constant volume of 5 ml/kg/day. The control group animals received the vehicle only, 0.5% methocel, at a volume of 5 ml/kg/day on a comparable regimen. Cesarean sections were performed on all surviving females on gestation day 17.

Results: No biologically meaningful differences were found in the treated groups when compared to the control group in appearance and behavior, mean maternal body weight gain, mean number of viable fetuses, post-implantation loss, total implantations, and corpora lutea per dam, or in the number of fetuses and litters with malformations and developmental and genetic variations. Toxicity was evident only in the 200 mg/kg/day treatment group as seen by six deaths occurring on the first two days of test material administration. Upon necropsy, all six mice had lung congestion. No teratogenic response was present when UC51762 was administered at a dosage level of 200 mg/kg/day or less.

Conclusion: The NOEL for maternal toxicity is 100 mg/kg/day, UC51762 is not teratogenic or fetotoxic at 200 mg/kg/day or less.

Classification: Core-Minimum Data

9. Approximate Acute Oral Toxicity (LD50) in Hens and Estimation of Efficacy of Atropine Prophylaxis vs. a greater than LD50 dose (FDRL No. 6064, 12/22/78)

Adult white leghorn hens between 10 and 14 months of age (1.0-2.5 kg BW) received by gavage doses of UC51762 and observed for a minimum of 5 days.

Results: LD50 = 582 mg/kg

The efficacy of atropine sulfate prophylaxis against an LD75 (830 mg/kg) dose was seen to be sufficient to warrant recommendation of a reduction in the size of test group in the subsequent Delayed Neurotoxicity Study from 40 to 22 animals.

Classification: Core-Minimum Data

10. Evaluation of UC51762 #40-488 as a Potential Delayed Neurotoxic Agent following Oral Administration to Hens protected by Atropine Sulfate (FDRL No. 6065; June 14, 1979)

The experimental design of the delayed neurotoxicity evaluation was as follow:

Group	No. of Birds	Material	Dose level**
A	10	Vehicle (corn oil)	- (1.89 ml/kg)
B	10	TOCP (corn oil)	750 mg/kg
C	40	UC51762 #40-488 (in corn oil)	660 mg/kg (LD50)
		Atropine (aqeuous solution)	14.2 mg/kg

**Dosing on 2/5/79 at 1.89 ml/kg

Observations concerning pharmacologic and toxicologic effect were recorded daily. Body weights were recorded prior to dosing (fasted) and bi-weekly thereafter. Food consumption was recorded bi-weekly. Prior to initiation and daily thereafter, each animal was given a neurological evaluation as follows:

Each animal was observed walking for several minutes after being stimulated. Special attention was paid to developing abnormalities of gait and the ability to alter direction of walking/running.

The following scale was used to evaluate the neurologic condition:

0 - normal

2 - slight or doubtful neurotoxic signs

8 - positive paralytic signs

12 - advanced paralytic signs

16 - death

slight or doubtful signs: included leg weakness

positive paralytic signs: included lack of coordination, loss of balance, and a tendency to fall back on ramp due to severe leg weakness.

Advanced paralytic signs: included inability to walk, hyperextension, ataxia, complete prostation, and morbidity.

Those birds which died during the first 5 days after dosing were considered to have died from acute anti-cholinergic effects and, therefore, not subjected to gross autopsy in this assay for delayed neurotoxic effect.

On day 21, all birds from the positive control group as well as seven fron the test group which displayed a questionable or marginal neurotoxic effect, and one test group bird displaying a seemingly positive effect, were sacrificed. Anesthesia was induced with approximately 25 mg/kg sodium pentobarbital, and followed by in situ systemic perfusion using 10% neutral buffered formalin. Fixative was introduced into the left ventricle and drained from either the vena cava or the right atrium.

The entire brain and spinal cord as well as most of the sciatic nerve, were then removed. Tissues were embeded in paraffin and histological slides were prepared and stained with hematoxylin and eosin. Pathological examination was carried out by the study director in conjunction with the FDRL Pathology staff.

Sections prepared included the cervical, thoraxic, and lumbosacral regions of the spinal cord, and the sciatic nerve. Particular attention was given to the identification and counting of swollen axons in cord sections. Sections of cervical cord received the most time of examination, and the recording of findings was as number of swollen axons per cross sections of cervical spinal cord.

(Option A)

On day 22, in that "signs of marginal value or questionable significance" [3] had been observed, Option A was carried out. (See Protocol, Appendix I).

The positive control group, "B", was sacrificed in toto, as described above. Several birds from the test group which displayed these marginal or questionable signs were also sacrificed in order that tissue from these animals be avialable for examination. A total of 10 birds were sacrificed at this point.

The positive control group was replaced with eight naive birds, receiving animal numbers 6065161-6065168, and redosing was conducted as follows:

(February 27, 1979)

Group	No. of Birds	Material	Dose Level*** (mg/kg)
A	10	vehicle (corn oil)	-
B	8	TOCP (in corn oil)	750
C	30	UC51762 #40-488 (in corn oil)	660 (LD_{60})[4]
		Atropine (aqueous solution)	14.2

***Dosing on 2/27/79 at 1.89 ml/kg.

Observations, body weights and food consumption were recorded as described above for the first dosing session. Neurologic evaluations were again made and recorded daily through day 42 of study (20th day after Option A was carried out).

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(3) 40 CFR 163. 81-7 (b) (7).

(4) See FDRL Study #6064.

All remaining birds were sacrificed after 42 days of study. All vehicle control and TOCP treated birds, as well as 10 remaining birds randomly selected from the test group, were sacrificed by in situ systemic perfusion of 10% neutral buffered formalin after anesthesia with sodium pentobarbital. These birds were submitted to gross necropsy and tissues were taken, fixed in formalin, and histologically prepared, as above. The balance of the test group birds were sacrificed by overdose of pentobarbital and submitted to gross necropsy as above. Tissues were fixed in formalin and have been retained by FDRL.

Statistical Analysis

Statistical analyses of applicable data (body weights, food consumption, neurologic evaluation scores, and pathology score data) were conducted using an Analysis of Variance with one way classification such that the probability of committing a Type I error was equal to or less than 5% ($p \leq 0.05$). Differences were identified using the Least Significant Difference (LSD) test.

Results:

Body Weights

It may be seen that during the period immediately following the first dosing (initial through day three), a loss of weight was noted in both the positive control and the test group, while a gain in weight was seen in the vehicle control group. This depression in body weight continued to display significance through day seven, when the animals began to recover. After this initial effect on body weight was overcome, animals in the test group began to gain weight at a regular pace, surpassing their original fasted weights at day 10. Birds in the positive control attained the level of their fasted pre-dose weights and maintained this level through sacrifice.

Following the re-dosing session, test birds again displayed an initial depression of body weight but recovery was evident by day 13 post re-dosing. Positive control birds did not display a significant weight loss during the period following the second round of dosing. Vehicle controls again showed a steady increase in body weight throughout the period following the second dosing session.

Food Consumption

Animals in both the positive control and test groups displayed depressions in food consumption during the period immediately following dose. After this, the animals recovered and ate comparable or greater amounts than the vehicle control group.

Following re-dosing, both positive control and test animals again displayed depressed food consumption levels. They both again recovered; however the positive control values again became significantly depressed as the effects of displayed neurotoxicity worsened.

Neurologic Evaluations

Following administration of UC51762 #40-488, test birds displayed an initial severe neurotoxic incapacitaiton lasting, in some birds, for as long as six days. With this exception, neither the positive control nor test group displayed any significant deviation from the vehicle during the first two weeks.

Beginning on day eleven, however, both the positive control and the test groups began to display increasing neurotoxic evaluation scores. The test group never displayed a significant value during this period of days eleven through twenty-one, as compared to vehicle control. The positive control group's scores were significantly different from vehicle control group's from day 16 through day 21.

The test group's behavioral scores indicated a marginal yet questionable level of delayed neurotoxicity, as evidenced by mean neurological evaluation scores ranging from 0.16 ± 0.09 to 0.47 ± 0.14.

In accordance with protocol, "Option A" was carried out on day 22, with all 10 vehicle control birds, 8 naive birds which received the positive control, and 31 of the 38 surviving test group birds being re-dosed, after fasting. The other eight test group birds, whose scores indicated the marginal behavioral reaction, were sacrificed so that tissues would be available.

Immediately following the second dosing, birds in all three groups displayed varying degrees of behavioral toxicity, yet no group displayed significant differences from vehicle controls. After peaking at 2 to 4 days after dosing, all groups' scores began to decline. The positive control group, however, again began to display significance on day 30 (day 11 post re-dosing) and continued as such through termination. No vehicle control or test group birds showed any score other than zero (normal) after the eleventh day post re-dose.

Observations

Following initial observations of normalcy in all cases, generally observations paralleled neurologic evaluation scores in all birds on study.

In most cases, a neurological evaluation score of "2" was associated with an observation of slight in incoordination or weak legs.

Observations of incoordination, weak, or "down on hocks" were associated often with scores of "8", while a "12" was often associated with the observation that the animal was alert, but litle else.

Gross Necropsy Observations

No observations of any significance were noted during autopsies in any group.

Two birds in the positive control were seen to have mottled lungs and one was noted as dark. Diarrhea was noted for several test group birds as well as dark livers for several others. Loss of feathers was noted for many birds across all groups, but this is not uncommon for birds housed under these conditions, and this would not be through to be a test effect.

Microscopic Findings

Microscopic observation of tissue sections revealed no tendency for the test material to produce the type of lesion, i.e. swollen axons, notably in the cervical region of the spinal cord, associated with typical delayed neurotoxins.

The mean number of swollen axons per cross section of cervical spincal cord were counted. This counting indicated a background level of 0.08 ± 0.04 (vehicle control), yet 5.3 ± 0.05 swollen axons per section were counted in the positive control (TOCP).

Of the eight birds sacrificed after 21 days, a mean number of swollen axons of 0.32 ± 0.1 was noted. The greatest number of these swollen axons was seen in only one animal, 6065152 (2.1 ± 0.6 swollen axons per section). All others displayed few or no swollen axons.

At termination, the mean number of swollen axons noted in the ten randomly selected test group animals was $0.02 = 0.01$.

Conclusion:

UC51762 #40-488 displayed a potential for delayed neurotoxicity which was manifested as marginal symptoms up to 21 days in 8 birds. These clinical signs were not apparent in the redosed test animals after 42 days. This conclusion was made after consultation with our pathologist, Dr. L. Kasza, on 2/20/80.

Classification: Core-Minimum Data

B. LARVIN 500 INSECTICIDE Formulated (UC51762)

11. Acute Oral Toxicity Study in Male and Female Rats (Hazelton Project No. 400-613, Dec. 13, 1979)

Test Material: Larvin 500 Insecticide

Five groups of twenty Sprague-Dawley rats (10M + 10F) were dosed with 50, 88.92, 158.11, 281.17 and 500 mg/kg of test material. Observations for 14 days.

Results: LD_{50} = 298 (193-404) mg/kg; males
LD_{50} = 142(100-202) mg/kg; females
LD_{50} = 192 (150-245) mg/kg; both sexes

Toxic Signs: Depression, tremors, urine stains, salivation, soft feces, red stains on nose and/or eyes, rough coat, prostation, lacrimation, hunching and ataxia.

Body Weight: Survivors gained weight.

Necropsy: Dark red discoloration of the lungs, compound and yellow fluid in the stomach and intestine, air in stomach, browish-yellow fluid in the intestine.

Classification: Core-Minimum Data

Toxicity Category II: WARNING

12. Acute Dermal Administration in Rabbits (Hazelton Project No. 400-614, Dec. 17, 1979)

Test Material: LARVIN 500 Insecticide

Four groups of 12 and 20 (group receiving 2.04 gm/kg) NZW rabbits (6 or 10/sex) received dosages of 0 (distilled water), 1.23, 1.58 and 2.04 gm/kg of test material on the intact skin (one-half of the animals were further abraded) of the fur clipped trunk under an impervious cuff for 24 hours. Observation for 14 days.

Results: Three deaths during the course of the study, two in group 3 and one in group 4. LD_{50} > 2.04 gm/kg

Toxic Signs: Slight to moderate depression, marked anorexia, soft feces.

Dermal Irritation: Very slight erythema in all groups with minimal incidence of edema.

Necropsy: Epidermal scaling, alterations of kidney and stomach mucosa.

Histopathology: Diffuse acanthosis, hyperkeratosis, necrotic cell debris on the epidermal surface and occasional incidences of epidermal necrosis.

Classification: Core-Minimum Data

Toxicity Category III: CAUTION

13. Acute Inhalation Toxicity Study in Rats (Hazelton Project No. 400-615, Nov. 30, 1979)

Test Material: Larvin (UC51762 Technical Dust)

One group of 5 male and 5 female rats was exposed for 4 hours to a nominal concentration of 5.31 mg/L of air of test material. The mean gravimetric concentration of airborne solids was 0.32 mg/L of air. A second group was exposed to air alone. Observation was for 14 days.

Results: No deaths; LC50 > 5.31 mg/L (nominal)
LC50 > 0.32 mg/L (gravimetric)

Toxic Signs: Body tremors, eye discharge, gasping, urine stained fur.

Body Weight: Survivors lost weight.

Necropsy: Not remarkable.

Classification: Core-Minimum Data

Toxicity Category II: WARNING

14. STATUS REPORT
ACUTE INHALATION (RAT) OF UC 51762 4F FORMULATION

Tests have been conducted at the Hazelton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia under supervision by Dr. William B. Coate, Director of Inhalation Toxicology Department.

Test 1. Five male and five female rats were exposed for four hours to a nominal concentration of 5 mg/liter of air of UC 51762. Delivery of the formulation (a micronized suspension in an aqueous carrier) was made with a needle atomizer. The resultant gravimetric (respirable) concentration was low (0.022 mg/liter) probably as a result of particle classification and the test was repeated.

Toxic signs were preening, sneezing, mastication, salivation and some weight loss (regained in 14 days holding period).

No deaths occurred.

No exposure-related gross pathology was seen.

No histopathology found in lungs, liver or kidneys.

Test 2. Five male and five female rats were exposed for four hours to a nominal concentration of 7 mg/liter of air (total generated suspension volume of chamber airflow in 4 hours = 14 mg/liter); gravimetric chamber concentration of 0.084 mg/liter. Delivery of the formulation was made with a Vaponefrin nebulizer. The gravimetric measurements (filter contents) have been confirmed by chemical analyses.

Toxic signs were the same as noted in Test 1.

No death occurred.

No exposure-related gross pathology was seen.

Histopathology is in progress and will be completed by February 5, 1980.

Classification: Supplementary Data

15. Primary Skin Irritation in Rabbits (Hazelton Project No. 400-617, Nov. 23, 1979)

Test Material: Larvin 500 Insecticide

0.5 gm of test material was applied to intact and abraded skin sites on the fur clipped trunks of 6 NZW rabbits for 24 hours under an impervious cuff. Observation and scoring at 24 and 72 hours after exposure.

Results: P.I. = 0.0, no irritation

Classification: Core-Minimum Data

Toxicity Category IV: CAUTION

16. Acute Eye Irritation Study in Rabbits (Hazelton Project No. 400-616; Nov. 23, 1979)

Test Material: Larvin 500 Insecticide

0.1 ml of test material was instilled into the left eye of nine NZW rabbits with the untreated right eye serving as the control. In six rabbits (3/sex), the treated eye was not rinsed; in three rabbits (2M + 1F), the treated eye was flushed for one minute with lukewarm water 20-30 seconds after instillation of the compound. Observation and scoring at 24, 48, 72 hours and 4 and 7 days. The left eye of each rabbit was examined with 2% sodium fluorescein 24 hours prior to instillation and at each observation period following instillation.

Results: No corneal opacity or iritis was observed in the washed or unwashed treated eye of the test rabbits. Conjunctival redness and chemosis were observed in both washed and unwashed treated eyes in test rabbits. All lesions were observed to clear by day 7.

Classification: Core-Minimum Data

Toxicity Category III: CAUTION

17. Dermal Sensitization Potential in the Guinea Pig (Carnegie-Mellon Institute of Research, Report#42-61, June 22, 1979)

Test Material: UC51762 technical purified grade

The potential of the test material to produce dermal sensitization was examined in 15 male albino guinea pigs and compared with two known sensitizers, ethylenediamine and formalin (10 guinea pigs/each chemical) using the modified Landsteiner procedure.

Ten interdermal injections using 0.1% suspension or dilutions of the samples in saline were followed by a 14-day incubation period and a challenge injection.

Results: One guinea pig died after receiving 2 "sensitizing" doses of UC51762 and one was killed because of poor health and abnormal weight loss after receiving 3 "sensitizing" doses of ethylenediamine. The death of these guinea pigs was not considered treatment related since all the other animals showed normal weight gain and good health.

UC51762-Technical Purified Grade:

The results, indicate that 6/14 (43%) and 3/14 (21%) animals reacted positively (grades of 25 or higher) 24 and 48 hours after the challenge injection, respectively. The median grades for all 14 animals were 13 and 18.5 at 24 and 48 hours, respectively, both being lower than the "final" grade of 25 which indicated no sensitizing potential. The individual and median scores following the sensitizing doses indicate that the dermal responses increased slightly after the fourth injection. Thus, under the conditions of our modified Landsteiner Test, UC51762-Technical Purified Grade had a minimal sensitizing potential for guinea pigs.

Ethylenediamine:

The results indicates that 7/9 (78%) and 2/9 (22%) animals reached positively after the challenge injection at 24 and 48 hours, respectively. The median grades for all 9 animals were 41 and 25 at 24 and 48 hours, respectively. The individual and median scores for the sensitizing doses demonstrate that the dermal responses increased slightly during the "sensitizing" period. Thus, under the conditions of our modified Landsteiner Test, ethylenediamine had a mild sensitizing potential for guinea pigs.

100% Neutral Buffered Formalin:

The results, indicate that 0/4 (0%) of the animals reacted positively after the challenge injection at both 24 and 48 hours. The median grades for all 4 animals were 0 at 24 and 48 hours. The individual and median scores for the sensitizing doses indicate the dermal responses changed very little after each successive injection. Thus, under the conditions of our modified Landsteiner Test, 10% neutral buffered formalin had no sensitizing potential for these 4 guinea pigs.

Discussion and Conclusions

In this study, UC51762 (Technical grade) produced weak sensitization reactions in guinea pigs as compared to the reactions produced by UC51762-75WP and UC51762-4F (CHF Project Report 42-26). It is possible that other chemical agents in these formulations may enhance the sensitizing potential of the UC51762. Since the positive control compound ethylenediamine (EDA) elicited a somewhat weaker response in this study than in the previous one, we have compared the median scores of the UC51762-treated animals with those of the positive control animals in both studies. The results are shown below:

	Median Score		Ratio - UC51762/EDA	
	24 hrs.	48 hrs.	24 hrs.	48 hrs.
UC51762-75WP	108	84	1.5	1.2
UC51762-4F	70	70	1.0	1.0
EDA Control	72	68	-	-
UC51762-Technical	13	18.5	0.3	0.7
EDA Control	41	25	-	-

This comparison reveals that, in spite of the reduced response to EDA in the second study, the responses induced by UC51762-Technical Grade were not as severe as those induced by either formulation.

Classification: Core-Minimum Data

18. Dermal Sensitization Potential in the Guinea Pig (Carnegie-Mellon Institute of Research, Special Report#42-26, March 28, 1976)

Test Materials: UC51762-4F (44% UC51762)

UC51762-75WP (75% wettable power)

The potential of two formulations of UC51762 to produce dermal sensitization was examined in male albino guinea pigs and compared with responses to two known sensitzers, ethylenediamine and formalin, nine intradermal injections using 0.1% suspensions or dilutions of the sample in saline were followed by a 15-day incubation period and a challenge injection.

Results:

UC51762-75WP produced moderate sensitization, whereas UC51762-4F was a mild to moderate sensitizer. In this test, formalin produced no sensitization, but ethylenediamine did elicit a mild to moderate response. The table in item #17 shows the quantitative response of the materials.

Classification: Core-Minimum Data

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19. Skin Sensitization in Guinea Pigs (CDC Research Study No. CDC-UC-003-79, July 12, 1979)

Test Material: UC51762, 99+%

The test material was studied for Guinea Pig Kin Sensitization according to the Code of Federal Regulations. The method employed was modified from the method of Buehler and the method of Draize. Ten young adult male White Hartley Guinea Pigs were clipped free of hair over the back, prior to the study, and at least once a week during the induction phase. A 0.5 ml aliquot of the test material was then applied by gentle inunction to an area of the back, left of midline, and allowed to air dry for 5 to 15 minutes. The back was then covered with a gauze pad and held in place with hypoallergenic adhensive tape. The patch was removed after 24 hours. The applications were made three times weekly for three weeks or a total of 9 applications at the same site. Following a 17 day rest period in which no applications were made, the animals were reclipped and twice challenged at the original induction site and a virgin site, with the same volume and concentration of material for a 24 hour period.

The challenges were made on Days 37 and 39 and readings were taken on Days 38, 40, and 43, according to the Method of Draize. A gross necropsy was performed on all animals at the end of the study.

Results: There were no skin changes seen in the skin during the induction and challenge periods. Necropsy was unremarkable.

Classification: Core-Minimum Data

20. Skin Sensitization in Guinea Pigs (CDC Study No. CDC-UC-004-79; July 12, 1979)

Test Material: UC51762-4F

UC51762-4F was studied for Guinea Pig Skin Sensitization according to the Code of Federal Regulations. The method employed was modified from the method of Buchler and the method of Draize as described in item #19.

Results: There were no skin changes seen in the ten guinea pigs during the challenge period. There were no detectable gross lesions found at necropsy.

Classification: Core-Minimum Data

21. Clinical Safety Evaluation of Larvin UC51762 Powder and Larvin 500 Flowable (FDRL OE No. 2177, Nov. 14, 1979)

PURPOSE

The purpose of the test was to determine the irritation and sensitization potential of the test products after repeated application under occlusion to skin of human subjects.

EXPERIMENTAL DESIGN

Panel Selection

Panel A - 30 subjects, 7 male and 23 female, ranging in age from 15 to 63 years comprised Panel A.

Panel B - 35 subjects, 5 male and 30 female, ranging in age between 15 and 64 years comprised Panel B.

The selection of the panelists was based on the following criteria:

a. Willingness to participate in the study.
b. Dependability and ability to read and understand instructions.
c. Absence of any physical or dermatological condition which would preclude application of the test material.
d. Reading, understanding and signing an informed consent contract (In the case of minors, parental consent was obtained).

Test Materials

The test materials used in the study were provided by Union Carbide. They were received on July 2, 1979 and were as follows:

Product Code	Name	Description
51762	Larvin 500	light yellow thick liquid
51762	Larvin	light yellow powder*

Method

The 10 Repeat Insult Patch Test was conducted as follows:

Induction Phase:

About 0.2 ml of each test product was placed on a 2 cm square of Webril® non woven cotton fabric affixed to Dermicel (Johnson & Johnson) cloth tape. This patch was covered with strips of Blenderm (3M) tape to form an occlusive patch after it has been applied to the inner aspect of the arm or the back of each volunteer.

* = the powder 51762 was moistened with distilled water before application to the patch.

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The subjects removed the patches 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48 hour rest periods followed the Saturday removal. Each site was scored by a trained examiner just prior to the next patch application. This procedure was repeated until 10 applications of the test materials had been made.

If a subject developed a positive reaction of at least a 2+ during the induction phase, the patch was applied to a fresh new site for the next application. If a 2+ reaction occurred in the new site, no further applications were made. However, the subjects were challenged with the test materials.

Challenge Phase:

Ten to fourteen days after application of the last induction patch, the challenge patch was applied to the original contact site and to a fresh, adjacent site. The sites were scored at 24 and 48 hours after application. The panelists were asked to report any delayed reactions, which might have occurred after the last reading of the challenge, to the laboratory.

0 = no reaction 1+ = erythema
2+ = erythema and papules (mild edema)
3+ = erythema, papules (mild edema) and vesicles
4+ = erythema, papules, marked edema and vesicles

RESULTS AND CONCLUSIONS

Individual test data are presented in the Tables. Fifty-five subjects completed; ten subjects did not complete the test for personal reasons and not because of adverse reactions to the test products.

NOTE: Subject no. 26 showed delayed reactions after the 8th induction patch to several products being tested including the two Larvin samples. No further exposures were made for the remainder of the induction period, and at the challenge only virgin sites were patched, since erythema was still present in the original sites. Subject 26 was in Panel A.

Sample 1. Larvin 500 Flowable

When tested as described, Larvin 500 Flowable elicited reactions from 11 subjects. During the induction phase, reactions were observed in 10 subjects; however, only subject 7 (Panel A) and 22 and 32 (Panel B) reacted with significant reactions. Subject 7 reacted with erythema and mild edema (2+) after the 7th induction patch and again immediately after the next phase. Subject 22 reacted with a strong (4+) reaction after the 8th induction patch, and subject 32 reacted with erythema and mild edema (2+) after the 8th induction patch and again after two applications on the fresh patch site.

At the challenge, 7 subjects reacted: Subjects 7, 10, 11, 14, 18 adn 26 (all in Panel A) and subject 32 (Panel B). The reactions consisted of only erythema or of erythema and mild edema (2+). Most of the subjects reacted at both original and virgin challenge sites, (see note about subjects 26 above).

It appears, therefore, that Larvin 500 Flowable is not a significant irritant as tested. However, it appears that it may be capable of inducing mild sensitizaton in human subjects when tested as described earlier.

Sample 2. Larvin 51672 Powder

When tested as described earlier, Larvin 51672 Powder elicited dermal responses from 10 subjects. Six of these subjects reacted during the induction period; nos. 11, 27 and 30 (Panel A) with transient erythema (1+) after one of the induction patches, and nos. 7 (panel A), 5 and 32 (Panel B) with erythema and mild edema after one or two of the induction patches.

At the challenge, subjects 10, 14 (Panel A) and subjects 5 and 6 (Panel B) reacted with erythema (1+), and nos. 7 and 26 (Panel A) reacted with reacted with erythema and mild edema at both patch sites (see note about subject 26 above).

It appears, therefore, that Larvin 51762 Powder is not a significant irritant as tested. However, it appears that it may be capable of inducing mild sensitization in human subjects when tested as outlined above.

Classification: Core-Minimum Data

TOX/HED:th:Initial CFRICK:2-21-80

per C. Frick 2/25/80

W. Kirk Sutter 3/4/80

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