4-18-90

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 773-LL
Clinafarm EC (enilconazole)

FROM: Lucy D. Markarian 4/18/90 = 4/18/90
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

TO: Lewis/Fairfax (PM 21)
Fungicide - Herbicide Branch
Registration Division (H75-05C)

APPLICANT: Pitman-Moore
P.O.Box 207
Terre Haute, IN 47808

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Imazalil: 1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy) ethyl)-1H-imidazole	13.76%
Inert Ingredient(s):	86.24%
Total	100.0%

BACKGROUND: The data submitted by the applicant in support of Enilconazole on 1/20/85 was reviewed by HED. The HED review classified the procedures as core minimum, and assigned the following categories: Acute oral (III) Acute Dermal (III) Primary Eye irritation (I), and Primary skin irritation (IV). The data submitted for acute inhalation toxicity and dermal sensitization were classified as supplementary; therefore unacceptable. It was recommended that the applicant submit new acute inhalation toxicity and dermal sensitization data (1/29/85) The applicant questioned the FHA/PRS review of 3/11/88. It was reviewed again by MLW (9/7/88) The MLW review concurred with the HED review, and again recommended new tests.

Fresh data was submitted by the applicant for acute Inhalation Toxicity and dermal sensitization on 1/25/90. MRID numbers used are 414308-01 and 414308-02.

RECOMMENDATION:

1- The new data is classified as core minimum for both inhalation toxicity and dermal sensitization and considered acceptable by RSB/PPS.

2- The data was classified as core minimum:

a- Acute inhalation study - because particle size determination was from a single concentration, Some of the gross pathological data was discarded, and there were sex differences that the applicant did not consider significant.

b- Dermal Sensitization - because inspite of the fact that valid data was obtained the modified Buehler protocol was not followed accurately

3- Current Acute Toxicity Profile:

	Category				
Acute Oral	III	Review Source: MLW 11/20/85	Acute Inhalation study	III	Current Review
Acute Dermal	III		Dermal sensitization study	not a contact sensitizer	
Primary Dermal Irritation	IV				
Acute Eye Irritation	I				

4- No additional Toxicity data is required to support Enilconazole

LABELING: The hazard indication signal is Danger

1. Since the product is Tox Catagory I due to eye irritation, it hits the trigger for Restricted use product and should be so labelled unless the PM team feels that alternative labelling language effects the hazard.

2. Revise Precautionary statement as follows:

Corrosive, causes irreversible eye damage. Harmful or fatal if swallowed. Harmful if absorbed Through skin or inhaled. Avoid breathing spray mist and contact with skin. Do not get in eyes, wear goggles or face shield. Wash Thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

3. Revise Statement of Practicle Treatment as follows:

If in eyes: Hold eyelids open and flush with steady gentle stream of water for 15 minutes. Call physician.

Goggles & face shield are readily available and used by applicators in industrial application. Plus lots of TOX I eye irritation product warnings, systems not restrictive use

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21)
Reviewer: L.D. Markarian
MRID No.: 414309-01
Report Date: 4/13/90
Testing Laboratory: International Research & Development Corp. Report No. 131-003
Author(s): C. E. Ulrich
Species: Rat, Sprague Dawley
Sex: 30 male, 30 Female (5/sex/Group) Weight: Mean ♂ 228-284g, ♀ 162-201g
Source: Charles Rives, Portage, Michigan
Test Material: Enilconazole (Clinafarm 15% Ec) Lot 2216-32
Quality Assurance (40 CFR §160.12): included

Summary:

1. LC_{50} (mg/kg): Males = —; Females = —; Combined = 3.1 mg/L 95% Confidence 2.9-3.4mg
2. The estimated LC_{50} is —
3. Mean Concentration: —
4. Tox. Category: III. Classification: Core minimum

Procedure (~~Deviations From §81-3~~): Groups of 5 male and 5 female rats were subjected to four hour exposures to different levels of test material. Treated animals were observed during exposure, at five hours (post exposure) and twice daily there after for mortality and signs of toxicity. Body weights were taken at 0, 7, and 14 days and upon death.

~~Results~~:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
4.1	5/5	5/5	10/10
4.0	5/5	3/5	8/10
2.9	2/5	0/5	2/10
2.9	4/5	1/5	5/10
1.6	0/5	0/5	0/10
0.19	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings~~:

Procedure Continued Exposure was in 54L Glass and Stainless steel chamber. Aerosol was generated using a positive displacement pump, heated to approximately 80°C, metered to a pneumatic atomizer (Spraying Systems Co. Type J Body No 2050 liquid nozzle, No 64 air nozzle) Additional compressed air was metered to the atomization chamber to dilute aerosols as required. Nominal Concentrations

were determined by deviding weight of the Test material used by total volume of air passed Through the chamber. Actual concentrations were measured using HPLC and gravimetrically. Particle size distribution was measured by 8 stage Cascade impactor (Andersen). Stage 4 had 63.4% cumulative micron 2.1 or less and stage 5 had 25.3% cumulative micron 1.05 or less at chamber atmosphere approximately at 28.3 L/min

Group Number	Mortality	Nominal Concentration	Gravimetric Analysis	HPLC Analysis	Equivalent Aerodynamic Diameter(mmm)	Geometric Standard Deviation
I	10/10	13.0	4.1	4.1	1.9	1.78
IV	8/10	8.1	3.8	4.0	1.6	1.90
V	2/10	6.6	3.0	2.9	1.6	1.85
VI	5/10	5.9	3.0	2.9	1.6	1.88
II	0/10	3.1	1.6	1.6	1.6	1.81
III	0/10	1.2	0.17	0.19	1.6	1.82

Symptomology and Gross Necropsy Findings

Toxic manifestations included Ataxia (Group I only) Respiratory distress of varying degrees, increased salivation, red brown material around eyes, nose and mouth (Except group III) urine stained abdomens (Except group III). Incidence of signs of Toxicity were fewest in the lower Two dose levels

Mean body weight gain for males in groups II and III were lower Than expected, but mean body weight gain for The females in the same groups were comparable To historical control data.

Necropsy revealed pulmonary edema in groups IV, V, VI in 7, 2, 3 animals respectively

In addition Two animals That died during exposure in group III showed very dark livers

There were no observable gross pathologicaly signs in groups II and III

No gross necropsy results were available for group I.

Rationale for the classification of the acute inhalation Toxicity study as core minimum is That:

1. Particle size was not determined for each concentration. Just a sample from Group IV is given

2. Gross pathological data for Group I was inadvertently discarded

3. There appears to be a sex difference in mortality. The females in the median dose range appear less sensitive Than the males. mortality at 4.0 mg/L is 5/5 for males and 3/5 for females, but more prominantly at 2.9 mg/L, at two separate runs it is 2/5 and 4/5 for males and 0/5 and 1/5 for females. The applicant has considered These results not significantly different and calculated LC_{50} on combined mortality only. They also cited The fact That The dose-response curve was too steep to calculate LC_{50} separately for males and females.

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

Product Manager: (21)
MRID No.: 414309-02
Testing Laboratory: Biosearch Inc. Philadelphia, Pa
Author(s): Donna M. Daniels
Species: Guinea Pig (Hartley)
Sex: Unspecified
Source: Buckshire Corp. Perkasie, Pa
Test Material: Enilconazole (Climatarm 15% EC)
Positive Control Material: 1-Chloro 2,4 Dinitrobenzene (DNCB)
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 4/16/90
Report No. 89-6556A

Weight: Test 416-560g, Positive Control 391-540g

Method: Modified Buehler

Summary:

1. This product ~~is~~ / (is not a dermal sensitizer.)
2. Classification: Core Minimum

Procedure (~~Deviation From §81-6~~): Prior to initiation of the study a Primary irritation assay was done on four Guinea Pigs at 50, 25, 10 and 5% V/V dilutions in deionized water. The highest minimal irritating level for induction and a non irritating level were found to be 25 and 10% respectively.

Results: For induction all applications were on the same site, applied on gauze patch on clipped skin

		Enilconazole	Naive control	DNCB Positive control	Vehicle Control for DNCB
INDUCTION	No OF Animals	10	10	10	5
	Concentration Solvent	25% V/V deionized H_2O	— deionized H_2O	0.15% W/V 25% EtOH in saline	— 25% EtOH in saline
	Volume of Application	0.4 ml	0.4 ml	0.4 ml	0.4 ml
	duration of Application	6 hrs	6 hrs	6 hrs	6 hrs
	number of Applications	9	9	9	9
	Frequency Duration	3/wk 3 weeks	3/wk 3 weeks	3/wk 3 weeks	3/wk 3 weeks
	Reactions	Erythema 10/10 mild - mod. Severe	NR	Erythema mild - mod. severe	NR
	2 week Rest Period - Challenge applied to naive sites				
CHALLENGE	Concentration Solvent	10% V/V deionized H_2O	10% + 10% V/V deionized H_2O	0.15% W/V acetone	0.15% W/V DNCB acetone
	Duration of exposure	24 hrs	24 hrs	24 hrs	24 hrs
	Results 24 hr	NR	NR NR	Erythema 10/10 mild - mod Severe	NR
	48 hr	NR	NR NR	Erythema 10/10 mild - moderate	NR

Based on the results of this test with 10/10 animals showing no reaction at challenge - Enilconazole cannot be considered a sensitizer.

The Dermal Sensitization study is classified as core-minimum for the following reasons:

1. The sex and age of the Guinea Pigs are not specified
2. Some of the animals used were not within the required weight range namely they were heavier. It is not known if they were heavier, because they were older
3. The protocol was not followed accurately. Less than required volume was applied per induction and challenge application. The induction applications were not washed following exposure
4. It is not specified how the skin was prepared (clipped or clipped & depilated) prior to the challenge. DNCB, a strong sensitizer can induce sensitization on clipped skin, however a weak sensitizer would need depilated skin to induce sensitization reaction at the challenge

Tox Chem No. 497AB Imizalil File Last Updated _____ Current Date 4/18/90

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
Dermal Sensitization Biosearch Inc. Guinea Pig # 89-6556A 05/08/89	Enilconazole (Clinafarm Ec)	414308 -02	Not a sensitizer	—	Core minimu
Acute Inhalation Toxicity International Research & Development # 131-003 05/12/89	Enilconazole (Clinafarm Ec)	414308 -01	LC_{50} 3.1 mg/L 95% confidence Limits 2.9 - 3.4 mg/L	III	Core minim