



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
Precautionary Review Section E 4/18/90
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:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
<u>Imazalil: 1-(2-(2,4-dichlorophenyl)-2-(2-propenyl)oxy)</u>	<u>13.76%</u>
<u>ethyl)-1H-imidazole</u>	
<u>Inert Ingredient(s):</u>	<u>86.24%</u>
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 (1/24/85). The applicant questioned the FDA/PPS 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. MAIS numbers used are 414 308-01 and 414 308-02.

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 in spite of the fact that valid data was obtained the modified Beuhler protocol was not followed accurately.

3- Current Acute Toxicity Profile:

Category	Category	Category	Category
Acute Oral III	Acute Inhalation III	Acute Dermal III	Primary Dermal Irritation IV
Acute Eye Irritation I	Acute Inhalation Study	Dermal sensitization not a contact sensitizer	Primary Dermal Irritation
	Review Source MLW 11/10/85		

4- No additional Toxicity data is required to support Enilconazole.

LABELING: The hazard indication signal is Danger

1. Since the product is ToxCatagory I due to eye irritation, it hits the triggers for restricted use product and should be so labelled unless the PH team feels that alternative labelling language offsets 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 Practical 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
applications.
Plus lots of Tox I
eye irritation products
currently registered w/it
restricted 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. 131-993

Author(s): C.E. Ulrich

Species: Rat, Sprague Dawley

Sex: 30 male, 30 Female (5/sex/group) Weight: Mean 0^{222-224g}, 162-201g

Source: Charles River, Portage, Michigan

Test Material: Enilconazole (Climafarm 15% EC) Lot 226-22

Quality Assurance (40 CFR \$160.12): included

Summary:

1. LC₅₀ (mg/kg): Males = ; Females = ; Combined = 3.1 mg/L ^{95% Confidence 2.9-2.4 mg}
2. The estimated LC₅₀ is
3. Mean Concentration:
4. Tox. Category: III. Classification: Core minimum

Procedure (~~Deviations From \$81-2~~): 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 thereafter 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 54 L Glass and stainless steel chamber. Aerosol was generated using a positive displacement pump, heated to approximately 50°C, metered to a pneumatic atomizer (spraying systems G 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 dividing 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 (mean)	Geometric Standard Deviation
I	10/10	13.0	4.1	4.1	1.9	1.78
IV	2/10	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 IV showed very dark livers

There were no observable gross pathological 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 II 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 prominently 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 LC₅₀ on combined mortality only. They also cited the fact that the dose-response curve was too steep to calculate LC₅₀ separately for males and females.

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

Product Manager: (21) Reviewer: Lucy D. Markarian
 MRID No.: 414 309-02 Report Date: 4/16/90
 Testing Laboratory: Biosearch Inc. Philadelphia, Pa Report No. 89-6556A
 Author(s): Donna M. Daniels
 Species: Guinea Pig (Hartley)
 Sex: Unspecified Weight: Test 416-560g, Postive Control 391-540g
 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
 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 pad, on clipped skin

	Enilconazole	Naive Control	DNCB Positive control	Vehicle Control for DNCB
INDUCION				
No of Animals	10	10	10	5
Concentration	25% v/v	—	0.15% w/v	—
Solvent	deionized H ₂ O	deionized H ₂ O	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	3/wk	3/wk	3/wk	3/wk
Duration	3 weeks	3 weeks	3 weeks	3 weeks
Reactions	Erythema 10% mild - mod. severe	NR	Erythema mild - mod. severe	NR
CHALLENGE				
	2 week Rest Period	Challenge applied to naive sites		
Concentration	10% v/v	10% + 10% v/v	0.15% w/v	0.15% w/v DNCB
Solvent	deionized H ₂ O	deionized H ₂ O	acetone	acetone
Duration of exposure	24 hrs	24 hrs	24 hrs	24 hrs
Results 24hr	NR	NR NR	Erythema 10% mild - mod. severe	NR
Results 48hr	NR	NR NR	Erythema 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 Imizali

File Last Updated _____

Current Date 7/16/90

Study/Lab/Study #/Date	Material	EPA Accession No.	Results:		TUX. CORE Grade/ Cat. Doc. No.
			LD50, LC50, PIS, NOEL, LEL		
Dermal Sensitization Biosearch Inc. Guinea Pig # 89-6556A 05/08/89	Enilconazole (Clinafarm EC)	414308 - 02	Not a sensitizer	—	Core minimum
Acute Inhalation Toxicity International Research & Development # 131-003 05/12/89	Enilconazole (Clinafarm EC)	414308 - 01	LC50 3.1 mg/L 95% confidence limits 2.9 - 3.4 mg/L	III	Core minimum