107901

(8)

EEE BRANCH REVIEW

DATE: IN 2/2/78 OUT 6/21/78 IN _____ OUT _____ IN _____ OUT _____

FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. 21137-4

PETITION OR EXP. PERMIT NO. 7F1921

DATE DIV. RECEIVED _____

DATE OF SUBMISSION _____

DATE SUBMISSION ACCEPTED _____

TYPE PRODUCTS(S): I, D, H, F, N, R, S Fungicide

DATA ACCESSION NO(S). 232730

PRODUCT MGR. NO. Wilson

PRODUCT NAME(S) Funginex 20% E.C.

COMPANY NAME E.M. Laboratories, Inc.

SUBMISSION PURPOSE Resubmission with data.

CHEMICAL & FORMULATION Triforine - 20% active

100.0 Pesticide Use

Funginex is an aerial or ground applied fungicide to be used on blueberries and peaches.

This submission considers a resubmission of data to support petition #751921 (Blueberries & peaches).

101.0 Chemical and Physical Properties

See review by R.K. Hitch dated August 23, 1977.

102.0 Behavior in the Environment

See review by R.K. Hitch dated August 23, 1977.

103.0 Toxicological Properties

The study under consideration is "The acute toxicity of Triforine technical to the Water flea (Daphnia magna):. The study was validated by D.J. Urban in an Ortho Funginex review dated ~~June 21, 1977~~; 3/14/78 Test I.D. #ES-H-1. This study was found invalid and still is so, for the following reasons:

1. Without solvents, the technical material would not go into solution at the applied or nominal concentrations; thus actual concentrations in the test chambers is suspect.

2. The toxicant concentrations between dose levels were too widely spaced.

3. Test temperature was higher than recommended.

104.0 Hazard Assessment

No hazard assessment will be made at this time. Data submission only.

104.1 Adequacy of Toxicity Data

The study by E.M. Laboratories (Acute toxicity of Triforine technical to the water flea, Daphnia magna) dated December 1977, is inadequate to support

registration. There is sufficient reason to question whether the nominal concentrations approximate the actual concentration available to test organisms. Further, the test did not meet criteria for a definitive basic test. The concentration of toxicant in each treatment should be at least 60% of the next higher level so an LC_{50} with reasonable confidence limits can be calculated. The study must be redone.

107.0 Conclusions

The Daphnia study by E.M. Laboratories dated December 1977 was reviewed and found inadequate to support registration.

The registrant may wish to contact this Section to discuss the problem with the study and possible solutions.

John Tice
June 21, 1978
Environmental Safety Section
EEEB-RD

VALIDATION SHEET CRF # _____ PAGE 1 OF 2

FORMULATION: Ortho Rose Disease Control

% a.i.	SC #	CHEMICAL NAME
Technical		N,N'-[1,4-piperazinediyl-bis(2,2,2-trichloroethylidene)] bis (formamide).

IA	IB	T	(FW)	EC	R		

Validator: D. J. Urban Date: 3/14/78

Test Type: Acute Toxicity of Triforine Technical to the Water Flea (Daphnia magna)

Test ID.# ES-H1

CITATION: Accession No. 232684; Performed by - Gerald A. LeBlanc, EG&G Bionomics, Aquatic Testing Laboratory, 790 Main St, Wareham, Mass, Dated - December, 1977; Submitted by - Chevron Chemical Company, Ortho Division, 940 Hensley St., Richmond, California, 94804; Submitted on - 1/17/78.

VALIDATION CATEGORY: INVALID

RESULTS: 1) 48-hour LC_{50} = 117.13 (51.24 - 261.51) ppm

2) "Mortality data derived from the definative test were used to calculate a median lethal concentration (LC_{50}) and its 95% confidence limits utilizing the moving average angle method (Harris, 1959)[1]."

3) The nominal test concentrations were 0.78, 6.0, 46, 360, and 2800 ppm.

4) The test temperature was 22.± 1°C

5) "At all test concentrations, Triforine technical was visibly present at the test solution surface and bottom. The Triforine also appeared to adhere to daphnids impairing motility although not always killing the organism."

VALIDATION CATEGORY RATIONALE: 1) The solubility of Triforine technical in water is only 28 ppm at room temperatures. Thus, without solvents, it is virtually impossible to get more than this amount into ~~the~~ solution ~~water~~ at any applied or nominal concentration. Further, Triforine was visibly present at the surface

[1] Harris, E.K. 1959. Confidence limits for the LD_{50} using the moving average method. Biometrics Vol. 15, #3, p. 157-161

ULATION: Ortho Rose Disease (6 trial
a.i. SC # CHEMICAL NAME

IA	IB	T	(FW)	EC	R		

Validator: D. J. Urban Date: 3/14/78

Test Type: Acute Toxicity of Triforine Technical to the Water Flea (Daphnia magna)

Test ID.# ES-H1

~~CATEGORY~~:

and bottom of the test chambers, and appeared to adhere to the daphnids; 2.) the concentration of ~~test~~ toxicant in each treatment was only 13% of the next higher one; 3.) the test temperature was higher than the normally recommended test temperature for daphnids — 22±1°C versus 17±1°C.

CATEGORY REPAIRABILITY/RATIONALE: This study may not be reclassified to core or supplemental status. There is sufficient reason to question whether the nominal concentrations approximate the actual concentrations in the test ~~chamber~~ chambers. The observed increase in mortality with the increase in dose could easily be attributed to the increasing rate of entrapment ~~of the test chemical~~ in the Triforine Technical visibly present in the test chambers.

Further, a definitive test must meet ~~the~~ the following criteria: ~~as stated in~~

"Except for the controls, the concentration of toxicant in each treatment must be at least 60% of the next higher one for basic tests." ~~and at least~~

The concentration of the toxicant in each treatment was only 13% of the next higher one.

RECORD OF TELEPHONE CALL OR VISITOR

DATE 4/29/78 2:30 PM

INCOMING CALL ☒ OUTGOING CALL ☐ VISITOR ☐

NAME OF PERSON
Stephen D Poulist, Regulatory Affairs Specialist, Pesticides Div.

NAME & ADDRESS OF COMPANY
EM Laboratories, Inc.
500 Executive Boulevard
Elmsford, NY. 10523

COMPANY TEL. NO. (Include Area Code)

REGISTRATION NO. OR FILE SYMBOL
2137-4

DATE OF LATEST SUBMISSION
8/23/77 FUNGIDEX

BRIEF SUMMARY OF CONVERSATION
Mr. Poulist was seeking a compromise to a four-through bioassay on Daphnids. In the course of our conversation, he mentioned that Acetone was used as a solvent in the reported solubility determination for Trifonine in water (28 PPM).

I told Mr Poulist that I would discuss this with my supervisor.

ACTION TAKEN
I called Mr. Poulist on 5/1/78 (9:15 AM), after discussing the problem with J. Akerman, and See attached sheet for the comments from our comments.

Mr Poulist said he would have the Daphnid study redone using the solvent to prepare the stock solution of the technical grade of Trifonine.

RECORDED BY (Name)
Douglas J Akerman

REFERRED TO (Name)

6

PR FORM 1-5 (OCT. 1968) USDA-ARS

RECORD OF TELEPHONE CALL OR VISITOR

INCOMING CALL ☒ OUTGOING CALL ☐ VISITOR ☐

DATE 4/28/78 11:45 PM

NAME OF PERSON
BEVIER SLEIGHT

NAME & ADDRESS OF COMPANY
BIONOMICS LABS

COMPANY TEL. NO. (Include Area Code)
617-295-2550

REGISTRATION NO. OR FILE SYMBOL
EPA REG. NO. 21137-4

DATE OF LATEST ~~SUBMISSION~~ REVIEW
5/23/77 FUNGINEX

BRIEF SUMMARY OF CONVERSATION

Mr. Sleight inquired about a flow-through test procedure for Daphnia ~~TESTING~~ FUNGINEX. He wanted to get an OK to run a 96-hour flow-through bioassay using DMSO (dimethyl sulfoxide) as a solvent. After consulting with Jim Akerman, I told Mr Sleight that the test procedures were acceptable to me as long as a Solvent Control was run (MAX. Solvent conc. used) Concurrently. He agreed!

ACTION TAKEN

RECORDED BY (Name)
Douglas J. Urban

REFERRED TO (Name)

PR FORM 1-5 (OCT. 1958)

USDA-ARS

We are still concerned about the solubility of this compound in water and carrier solvents. This concern was initially based on the observation that residues were found in test vessels even at 0.78 and 6.0 ppm nominal conc. in the most recent Daphnid bioassay, when the solubility of Trifonine technical in water at room temp was reported to be about 28 ppm.

In our conversation on Friday (April 29th) you reported that acetone was used as a solvent in the reported solubility determination. In light of this

In light of this information, we feel that the following comments are appropriate regarding test procedures for ~~a~~ an aquatic invertebrate bioassay (using Daphnid, preferably):

1.) Because of the testing problems to date, the flow-through technique with measured conc's is still the first choice in testing. However, 96-hour

2.) We could accept a 48-hour static bioassay if the following conditions were met:

a.) the technical product of a.i. (trifonine) is tested.

b.) ~~a solvent is used~~ an acceptable solvent is used (to prepare stock solns) preferably the one in which the test prod. is most soluble. (e.g. acetone, DMF, DMSO)

c.) a solvent control is run concurrently, in addition to the negative control. This solvent

1 control is treated the same as the negative control except that the highest amount of ~~water~~ solvent present in any other test vessel is added to this test vessel.

d.) the conc. of the solvent in any test sol^{n} must not exceed 0.5 ml / liter (or 0.05% of solvent / ~~test~~ test vessel). We suggest that the % solvent in each test vessel be reported.

e) the test be run at recommended ~~test~~ temp's as reported in accepted protocols (eg. Daphnia - 17°C ± 1°C.

f) all other test procedures follow accepted protocols (eg. Stephan or ASTM); * that these protocols be reported; all deviations from said protocols be reported.

SUMMARY OF MEETING WITH REPRESENTATIVES FROM E.M. LABORATORIES, INC.

RECENT DATA SUBMITTED TO SUPPORT THE REGISTRATION OF FUNGINEX 20 % for USE ON PEACHES AND BLUEBERRIES. (EPA REG. NO. 21137-4)

DATE: 4/26/78

ATTENDEES:

E.M. LABS
H. ANDRE KNOLL, Ph.D
STEPHEN D. POULIOT, Regulatories Affairs Specialist. Pesticides Div.

EPA
Robert Panebianco, Assistant to Eugene Wilson, PM-21
Norman Cook, Senior Reviewer, Environmental Safety Section
Douglas Urban, Reviewer, Environmental Safety Section

NOTE: E.M. Laboratories and Chevron Chemical Corp. are cooperating on data requirements for the registration of Funginex

Points of Discussion:

1) Environmental Safety Personnel explained that the Japanese Quail is an unacceptable test species. Even though the reported LD50 was greater than 6,000 mg/kg body weight, we cannot accept the study because of the species tested. The ESS must work under certain regulations and guidelines, and we also must take into account the opinions of our Chief Avian Toxicologist.
The company representatives agreed to have the study redone. The ES personnel suggested that either Bobwhite Quail or Mallard Ducks be tested.

2) ES personnel explained that the recently submitted Daphnia study, performed by Bionomics, and using the technical grade of the active ingredient (Triforine), was unacceptable because: (1) residues in the test vessels was sufficient reason to question whether the nominal concentrations approximated the actual (reported) concentrations in the test chambers; and (2) the test concentrations range (0.78. 6.0, 46, 360, 2800) was unacceptable.
The company reps. pointed out that a water solubility problem exists. Further, they reported that Triforine was insoluble in most common organic solvents. The reported solubility (approx. 28ppm) in water was even suspect. This problem led them to submit the previous Daphnia test on the 6.5% formulated product which was rejected by our section.

The ESS personnel replied that our guidelines call for testing for minimum requirements based on the technical product of the active ingredients. This enables us to set up base line data for hazard assessment for registration and classification actions. Further, all studies that support these actions must be scientifically sound. [redacted] The ESS felt that the recently submitted Daphnia study was not scientifically sound.

The company asked for suggestions xx how to redo the study to the satisfaction of ESS. We suggested a Daphnia bioassay using the flow-xxxx through technique. We referred them to ASTM and Stephen for protocol and procedures, and pointed out that measured concentrations are xx required. Further, we suggested that the testing lab call us regarding any protocol or procedure problems.

The company representatives agreed.

Douglas Urban 4/28/78

107901

(7)

EEB BRANCH REVIEW

DATE: IN 12/6/77 OUT 4/14/78 IN _____ OUT _____ IN _____ OUT _____

FISH & WILDLIFE (ENVIRONMENTAL CHEMISTRY) EFFICACY

FILE OR REG. NO. 21137-4

PETITION OR EXP. PERMIT NO. 7F1921

DATE DIV. RECEIVED 11/28/77

DATE OF SUBMISSION _____

DATE SUBMISSION ACCEPTED _____

TYPE PRODUCT(S): I, D, H, ~~F~~, N, R, S

PRODUCT MGR. NO. 21

PRODUCT NAME(S) Funginex

COMPANY NAME Clarification of Previous Submission

SUBMISSION PURPOSE _____

CHEMICAL & FORMULATION Triforine N.N'-[1,4 piperazinediylbis (2,2,2 Trichloroethylidene)] bis(formamide)

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Resubmission of data for Registration #21137-4

DATE: April 14, 1978

FROM: Environmental Safety Reviewer

Thru: Environmental Safety Section Head

TO: Eugene Wilson, Product Manager 21

The environmental safety section has received the information identifying the species of quail in Test ES-VII C-1 (review by R.K. Hitch, 8/23/77) as Japanese quail, and noting the Daphnia study in progress at time of letter (11/23/77).

The avian acute oral study was re-reviewed by D.J. Urban (3/14/78) and the daphnia study was reviewed at the same time. Neither study was considered adequate to support registration. The quail study tested the Japanese quail, which is not an acceptable test species. The daphnia study was considered unacceptable because of the wide spacing of dosage concentrations and because there was sufficient ~~rea~~ reason to question whether or not the nominal concentrations approximate the actual concentrations in the test chambers.

Larry W. Turner

EPA Form 1320-6 (Rev. 6-72)

REPORT OF TELEPHONE CALL OR VISITOR				NOTE: Complete this form. Write "NA" where not applicable.
X	INCOMING CALL		VISITOR	DATE 10/14/77
	OUTGOING CALL		CONGRESSIONAL	TIME OF CALL 10:00 A.M

NAME AND ADDRESS OF CALLER OR VISITOR

Mr. Steven Poliout
EM Laboratories
Elmsford N.Y

PHONE NO. *(Include Area Code or IDS No.)*

REGISTRATION, ID NO. OR FILE SYMBOL

DATE OF LATEST SUBMISSION

BRIEF SUMMARY OF CONVERSATION

Mr. Poliout called again to discuss the protocol for the aquatic invertebrate acute toxicity study for registration of Fungineb.

ACTION TAKEN OR RECOMMENDED

Informed Mr. Poliout that the study was a 48-hr and not 96-hr, LC_{50} study.

Also informed the registrant that a positive control (w/DDT or other chemical) would not be required.

Ruf

RECORDED BY *(Name)*

REFERRED TO *(Name)*

14

REPORT OF TELEPHONE CALL OR VISITOR				NOTE: Complete this form. Write "NA" where not applicable.
X	INCOMING CALL		VISITOR	DATE 10/13/77
	OUTGOING CALL		CONGRESSIONAL	TIME OF CALL 11:30 A.M

NAME AND ADDRESS OF CALLER OR VISITOR
Steven Pouliot
Em Laboratories
Elmsford N.Y.

PHONE NO. (Include Area Code or IDS No.)
(914) 592-4660

REGISTRATION, ID NO. OR FILE SYMBOL

DATE OF LATEST SUBMISSION

BRIEF SUMMARY OF CONVERSATION

MR. Pouliot wanted to know if A 48HR. LC_{50} Aquatic invertebrate Study conducted with Fungimex 6% active SATISFIED REGISTRATION requirements. Informed MR. Pouliot THAT Regulations require the Study to be run with Technical meterial.

ACTION TAKEN OR RECOMMENDED

In addition, Mr. Pouliot wanted to know if the Study conducted with 6% Fungimex could be used toward Registration of a 20% active ingredient formulation. Informed the REGISTRANT THAT because we did not know how the additional solvents used in the 20% formulation would affect toxicity another Study using the 20% a.i. formulation would be required.

Ruf

RECORDED BY (Name)

REFERRED TO (Name)

107901

EM Laboratories, Inc.

associate of E. Merck, Darmstadt, Germany

500 Executive Boulevard
Elmsford, New York 10523
Phone 914/592-4660
Telex 13-1512

November 23, 1977

Dr. Eugene M. Wilson
Product Manager (21)
Fungicide-Herbicide Branch
Registration Division (WH-567)
Environmental Protection Agency
Washington, D.C. 20460

Dear Dr. Wilson:

This is in response to your letter October 7 concerning the Environmental Hazard evaluation of triforine.

Concerning -

Point 1. The species of quail used in the study, Acute Oral LD_{50} in Birds, Document Number T4, Dr. G. Muacevic, Department for Experimental Pathology and Toxicology, C. H. Boehringer Sohn, Ingelheim/Rhein, West Germany, September 9, 1970, was Japanese quail, coturnix coturnix japonica. The animals were pure-bred and purchased from the breeding station Schloss Schomberg, D-7517 Eppingen, Germany.

Point 2. An Aquatic Invertebrate Acute LC_{50} for Daphnia using technical triforine is in progress. The final report for the study should be available by January 1, 1978.

Sincerely yours,

Stephen Pouliot
Regulatory Affairs Specialist

SP:ri

Enclosures

cc: CELAMERCK F (2)
CELAMERCK M

ACUTE ORAL LD_{50} IN BIRDS

Document Number T4

Dr. G. Muacevic

Department for Experimental Pathology and Toxicology

C. H. Boehringer Sohn

Ingelheim/Rhein, West Germany

Species:

Japanese quail, coturnix coturnix japonica