

US EPA ARCHIVE DOCUMENT

107901

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EEE BRANCH REVIEW

DATE: IN 2/2/78 OUT 6/21/78 IN _____ OUT _____
FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. 21137-4

PERMICHN 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

ACT 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 LC₅₀ 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
EEEE-RD

FORMULATION: Ortho Rose Disease Control
 % a.i. SC # CHEMICAL NAME

IA	IB	T	(FW)	EC	R	
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Validator: D. J. Urban Date: 3/14/78

Technical N,N' -[1,4-piperazinediyl-bis(2,2,2-trichloroethylidene)]bis(formamide).

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

Test ID.# ES-H1

CITATION: Accession NO. 232684; Performed by - Gerald A. LeBlanc, EGG 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:
- 48-hour $LC_{50} = 117.13$ (51.24 - 261.51) ppm
 - "Mortality data derived from the definitive test were used to calculate a median lethal concentration (LC_{50}) and its 95% confidence limits utilizing the moving average angle method (Harris, 1959)"
 - The nominal test concentrations were: 0.78, 6.0, 46, 360, and 2800 ppm.
 - The test temperature was $22 \pm 1^\circ C$
 - "At all test concentrations, Triformine technical was visibly present at the test solution surface and bottom. The Triformine also appeared to adhere to daphniae impairing motility although not always killing the organism."

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

¹ Harris, E.K. 1959. Confidence Limits for the LD_{50} using the moving average angle method. *Biometrics* Vol. 15, #3, pp. 157-164

REGISTRATION:	Ortho Rose Disease Control	IA	IB	T	(FW)	EC	R			
a.i.	SC #	CHEMICAL NAME					Validator:		Date:	
							D. J. Urban		3/14/78	
						Test Type:				
						Acute Toxicity of Triporine Technical to the Water Flea (<i>Daphnia magna</i>)				
						Test ID. # ES-H1				

~~Observation:~~
 and bottom of the test chambers, and appeared to adhere to the daphnids;
 2.) the concentration of ~~the~~ 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 - $22 \pm 1^\circ\text{C}$ versus
 $17 \pm 1^\circ\text{C}$.

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

Further, a definitive test must meet ~~the~~ the following
 criteria: ~~that the~~

"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

INCOMING CALL

OUTGOING CALL

VISITOR

4/29/78 2:30 PM

NAME OF PERSON

Stephen J Pauliot, Regulatory Affairs Specialist, Pesticide Div.

NAME & ADDRESS OF COMPANY

E.M. Laboratories, Inc.
500 Executive Boulevard
Elmsford, N.Y. 10523

COMPANY TELEPHONE NO. (Include Area Code)

REGISTRATION NO. OR FILE SYMBOL

21137-4

DATE OF LATEST SUBMISSION

8/23/77 FUNGIDEX

BRIEF SUMMARY OF CONVERSATION

Mr. Pauliot was seeking a compromise to a flow-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 Triphenyl in water (28 ppm).

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

ACTION TAKEN

I called Mr. Pauliot on 5/1/78 (9:15 AM), after discussing the problem with J. Sherman, and see attached sheet for ~~the comments from~~ our comments.

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

RECORDED BY (Name)

Stephen J. Sherman

REFERRED TO (Name)

RECORD OF TELEPHONE CALL OR VISITOR

DATE

INCOMING CALL

OUTGOING CALL

VISITOR

4/28/78

11:45 AM

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 INSPECTION REVIEW

8/23/77 FUNGINEX

BRIEF SUMMARY OF CONVERSATION

Mr. Sleight inquired about a flow-through test procedure for ~~for~~ ^{TESTING} ~~the~~ 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 us 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)

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 2 most recent Saphid bioassay, when the solubility of Trifluoromethyl in water at room temp was reported to be ~~3~~ 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 felt that the following comments are appropriate regarding test procedures for ~~our~~ ^{our} aquatic invertebrate bioassays (using bottom, preference):

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

However,

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

- The technical product of a.i. (trifluoromethyl) is ^{tested} ~~to~~.
- ~~to~~ ~~what~~ ~~is~~ ~~used~~ ~~as~~ ~~an~~ ~~acceptable~~ ~~solvent~~ ~~is~~ ^{to prepare stock solns} ~~used~~ ~~is~~ ~~preferable~~ ~~to~~ the one in which the test prod. is most soluble. (eg. acetone, DMF, DMSO)
- a solvent control is run concurrently, in addition to the negative controls. This solvent

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

d.) The conc. of the solvent in any test solⁿ must not exceed 0.5 ml/liter, (or 0.05% of solvent ~~per~~ 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 - $17^{\circ} \pm 1^{\circ} \text{C}$).

f.) all other test procedures follow acceptable 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, Regulatory 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 required * for the registration of Funginex
ments

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 W 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 concentration 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 ESx 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. ~~_____~~
~~_____~~ The ESS felt that the recently submitted Daphnia study was not scientifically sound.

The company asked for suggestions ~~on~~ how to redo the study to the satisfaction of ESS. We suggested a Daphnia bioassay using the flow-~~thru~~ through technique. We referred them to ASTM and Stephen for protocol and procedures, and pointed out that measured concentrations are ~~in~~ 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

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EEE BRANCH REVIEW

DATE:	IN <u>12/26/77</u> OUT <u>4/14/78</u>	IN _____ OUT _____	IN _____ OUT _____
	FISH & WILDLIFE	<u>ENVIRONMENTAL CHEMISTRY</u>	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, ~~XX~~ 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)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

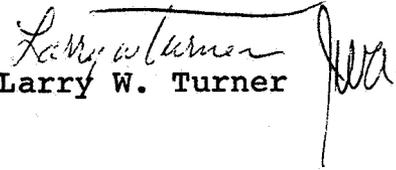
SUBJECT: Resubmission of data for Registration
#21137-4

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 reason to question whether or not the nominal concentrations approximate the actual concentrations in the test chambers.


Larry W. Turner

REPORT OF TELEPHONE CALL OR VISITOR			NOTE: Complete this form. Write "NA" where not applicable.
<input checked="" type="checkbox"/> INCOMING CALL		VISITOR	DATE 10/14/77
<input type="checkbox"/> OUTGOING CALL		CONGRESSIONAL	TIME OF CALL 10:00 A.M.
NAME AND ADDRESS OF CALLER OR VISITOR Mr. Steven Poliouit 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. Poliouit called again to discuss the protocol for the aquatic invertebrate acute toxicity study for registration of Funginep.			
ACTION TAKEN OR RECOMMENDED			
<p>Informed Mr. Poliouit that the study was a 48-hr and not 96-hr, LC₅₀ study.</p> <p>Also informed the registrant that a positive control (w/DDT or other chemical) would not be required.</p> <p style="text-align: right;">Ruf</p>			
RECORDED BY (Name)		REFERRED TO (Name)	

REPORT OF TELEPHONE CALL OR VISITOR			NOTE: Complete this form. Write "NA" where not applicable.
<input checked="" type="checkbox"/> INCOMING CALL		VISITOR	DATE 10/13/77
<input type="checkbox"/> OUTGOING CALL		CONGRESSIONAL	TIME OF CALL 11:30 A.M.
NAME AND ADDRESS OF CALLER OR VISITOR Steven Pouliot E M 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			
<p>MR. Pouliot wanted to know if A 48hr. L₅₀ Aquatic in VERTEBRATE Study conducted with Funginex 6% active satisfied REGISTRATION REQUIREMENTS. Informed MR. Pouliot THAT REGULATIONS REQUIRE THE Study to be run with <u>Technical material</u>.</p>			
ACTION TAKEN OR RECOMMENDED			
<p>In addition, Mr. Pouliot wanted to know if The Study conducted with 6% Funginex 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.</p> <p style="text-align: right;">Ruf</p>			
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 LD₅₀ 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 LC₅₀ 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

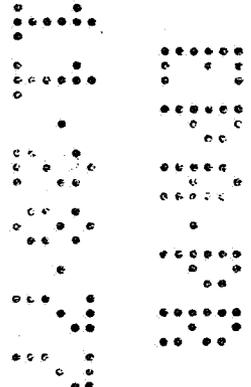
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Enclosures

cc: CELAMERCK F (2)
CELAMERCK M

representing **CELAMERCK GMBH & Co. KG, Ingelheim, Germany**

affiliate of Cella GmbH, Ingelheim and E. Merck, Darmstadt, Germany



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ACUTE ORAL LD₅₀ 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*

