

107901

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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

PERMITION 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

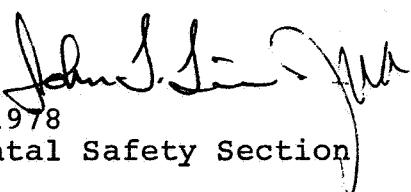
The study by E.M. Laboratories (Acute toxicity of Triforine technical to the water flea, Daphnia magna) dated December 1977, is inadequate to support

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 LC<sub>50</sub> 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

FORMULATION:

% a.i.

SC #

CHEMICAL NAME

Technical

*Ortho Rose Disease Control*  
 $N,N'$ -[1,4-piperazinediyl-  
 bis(2,2,2-trichloroethylidene)]  
 bis(formamide).

IA

IB

T

(FW)

EC

R

Validator:

Date:

Test Type:

*D. J. Urban* 3/14/78  
 Acute Toxicity of  
 Triofrine Technical to the  
 Water Flea (*Daphnia magna*)

Test ID. # ES-H 1

CITATION:

Accession NO. 232684; Performed by - Gerald A. Le Blanc,  
 EGG Bionomics, Aquatic Testing Laboratory, 790 Main St.,  
 Waltham, 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 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)"

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

4) The test temperature was  $22 \pm 1^\circ C$

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

VALIDATION CATEGORY RATIONALE: 1) The solubility of Triofrine technical<sup>in wa</sup>  
 only 28 ppm at room temperatures. Thus, without solvents, it is virtually  
 impossible to get more than this amount into ~~the water~~<sup>solution</sup> at any applied  
 or nominal concentration. Further, Triofrine 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 Co. test  
a.i. SC # CHEMICAL NAME

IA	IB	T	(FW)	EC	R		
Validator: D. J. Urban					Date: 3/14/78		
Test Type: Acute Toxicity of Trifluralin 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 ~~toxicant~~ 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~~ <sup>chambers</sup>. 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 Trifluralin 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 <input checked="" type="checkbox"/>	OUTGOING CALL <input type="checkbox"/>	VISITOR <input type="checkbox"/>	4/29/78 2:30 PM

NAME OF PERSON

Stephen J Pouliot, Regulatory Affairs Specialist, Pesticide Div.

NAME &amp; ADDRESS OF COMPANY

EM Laboratories, Inc.  
500 Executive Boulevard  
Elmsford, NY 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. Pouliot 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 Trifluralin in water (28 ppm).

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

ACTION TAKEN

I called Mr. Pouliot 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. Pouliot said he would have the Daphnid study redone using the solvent to prepare the stock solution of the technical grade of Trifluralin.

RECORDED BY (Name)

Stephen J. Pouliot

REFERRED TO (Name)

RECORD OF TELEPHONE CALL OR VISITOR			DATE
INCOMING CALL <input checked="" type="checkbox"/>	OUTGOING CALL <input type="checkbox"/>	VISITOR <input type="checkbox"/>	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 ~~REVISION~~ REVIEW

8/23/77 FUNGINEX

BRIEF SUMMARY OF CONVERSATION

Mr. Sleight inquired about a flow-through test procedure for ~~Daphnia~~ <sup>TESTING</sup> 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 <sup>were</sup> 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. Elshan

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 most recent Saphid bioassay, when the solubility of Trifluoromethane in water at room temp was reported to be about 28 ppm.

In our conversation on Friday (April 29<sup>th</sup>) you reported that acetone was used <sup>as a solvent</sup> 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~~ <sup>our</sup> aquatic invertebrate bioassays (using bottom, preference):

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

However,

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

- a.) The technical product of a.i. (Trifluoromethane) is <sup>tested</sup> ~~to~~.
- b.) ~~the solvent used~~ <sup>to prepare stock solutions</sup> an acceptable solvent is used ~~it~~ - preferably ~~the~~ 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 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 sol<sup>n</sup> 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 -  $17^{\circ}\text{C} \pm 1^{\circ}\text{C}$ ).

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 ~~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

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EEE BRANCH REVIEW

DATE: IN 12/6/77 OUT 4/14/78 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, ~~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

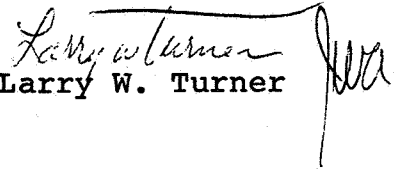
SUBJECT: Resubmission of data for Registration  
#21137-4

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		<input type="checkbox"/>	VISITOR	
<input type="checkbox"/>	OUTGOING CALL		<input type="checkbox"/>	CONGRESSIONAL	
				DATE	10/14/77
				TIME OF CALL	10:00 A.M.
NAME AND ADDRESS OF CALLER OR VISITOR Mr. Steven Poliou 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. Poliou called again to discuss the protocol for the aquatic invertebrate acute toxicity study for registration of Funginep.					
ACTION TAKEN OR RECOMMENDED Informed Mr. Poliou that the study was a 48-hr and not 96-hr, LC <sub>50</sub> 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)	

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
	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 MR. Pouliot wanted to know if A 48hr. LC50 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> .					
ACTION TAKEN OR RECOMMENDED 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.  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<sub>50</sub> in  
Birds, Document Number T4, Dr. G. Muacevic, Department for Experi-  
mental 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<sub>50</sub> for Daphnia using  
technical triforine is in progress. The final report for the study  
should be available by January 1, 1978.

Sincerely yours,



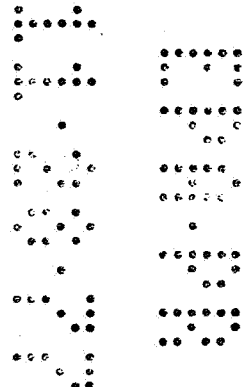
Stephen Pouliot  
Regulatory Affairs Specialist

SP:ri

Enclosures

cc: CELAMERCK F (2)  
CELAMERCK M

representing **CELAMERCK GMBH & Co. KG, Ingelheim, Germany**  
affiliate of Cella GmbH, Ingelheim and E. Merck, Darmstadt, Germany



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ACUTE ORAL LD<sub>50</sub> 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*

