EEB's file
9-16-92

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

MEMORANDUM

SUBJECT: EEB's Answer to Elanco Products' Company Response to Our Review of the Benefin Daphnia magna Acute Toxicity Study MRID 145757 (a 48-hour study). - D171483.

FROM: Douglas Urban, Acting Chief
Ecological Effects Branch
Environmental Fate and Effects Division (H7507C) 9/16/92

TO: Tom Myers, Chemical Reviewer,
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7508W)

We agree in general with the registrant's response (11/20/91) to EEB's evaluation of their aquatic study entitled: "The Acute Toxicity of Benefin (EL-110, Compound 54521) to Daphnia magna in a Static-Renewal Test System (March, 1985), Accession No. 145757.

At the end of Attachment 1 (page 2) the registrant states: "If this study were repeated as requested by the Agency, we do not expect the results to be significantly different from the study being discussed. We are aware of the toxic difficulties encountered due to the low aqueous solubility of Benefin; however, we find no evidence that the registrant has made reasonable additional efforts in trying to enhance the solubility/accommodation of Benefin in the aqueous phase.

In agreement with the registrant we are not, at present, requesting that the Daphnia study be repeated until the registrant develops and submits a solubility profile of Benefin so as to establish if there is/are any other acceptable solvents or methods that may enhance the solubility/accommodation of Benefin under actual test conditions. The test organisms and the corresponding toxicological end points may be omitted from the pretesting evaluation of the solvents and other solubility/accommodation enhancing methods.

Some solvents, other than acetone, accepted by EPA at concentrations not to exceed 0.55 ml/l are:

dimethylformamide
triethylene glycol
methanol
ethanol

Other EEB-suggested approaches for chemicals with water solubilities under 100 ppm (mg/l) are:

- sonication
- saturation (solubility) columns
- minor changes in environmental conditions (i.e., temperature, Ph) which are within reasonable testing limits.
- Use of a more soluble formulation (i.e., emulsifiable concentrate) if available
- Use of formulated product rather than the active ingredient

The study would only have to be repeated using a method or solvent to enhance solubility/accommodation of the chemical in the water phase if the method or solvent used increases substantially said solubility/accommodation under testing conditions. Substantial is defined for our purposes as at least twice the solubility obtained in the submitted study (MRID No.145757).

Regardless of the variable that is introduced in order to improve the solubility of the chemical, testing, if necessary, would otherwise proceed according to guidelines instructions.

EEB will make a final decision on Benefin testing once the results from the above-suggested efforts have been received and evaluated.

Should you require further assistance on this issue, please contact Alvaro Yamhure of the EEB staff at (703) 305-6179.

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Some solvents, other than acetone, accepted by EPA at concentrations not to exceed 0.55 ml/l are:

CONCURRENCES								
SYMBOL	EEB	H7507C	H7507C					
SURNAME	YAMHURE	Rea	D Urban					
DATE	9/16/92	9-16-92	9/16/92					

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

DATE: 11/14/90

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reregistration Phase 3 - Initial Submission of **Benfluralin** - Chemical No. **084301** - N-butyl-N-ethyl-a-trifluoro -2,6-dinitro-p-toluidine ID#: 084301001471; Company: 001471 Elanco Products Co.
PM Team Reviewer: Thomas Jr Luminello

FROM: Alvaro A. Yamhure, Biologist (H7507-C)
Ecological Effects Branch
Environmental Fate and Effects Division

THRU: James W. Akerman, Chief (H7507-C)
Ecological Effects Branch
Environmental Fate and Effects Division

TO: Jay S. Ellenberger, Chief (H7508)
Generic Chemical Support Branch
Special Review and Reregistration Division

The registrant - Elanco Products Co. (subsidiary of Eli Lilly & Co.) has presented to EPA most of the studies needed to attain eventual reregistration of its herbicide Benfluraline or Benefin. As shown in the attached Ecological Effects Branch (EEB) data requirements check list for pesticide registration, the registrant has submitted ten (10) new studies and summaries of older studies which have been evaluated by EPA and which are still considered valid by the registrant to fulfil present reregistration requirements.

The March, 1985 study titled: "The Acute Toxicity of Benefin (EL-110, Compound 54521) to Daphnia magna in a Static Renewal System", also identified by EPA's MRID No. 145757 was reevaluated on 11/30/88 by one of our scientist for registration standard purposes and (see page No.4 of the attached copy of the reregistration standard document) it was concluded that:

"Data from a [aquatic invertebrate] life cycle test are required to support the registration of the EP [end product] if an aquatic invertebrate LC50 value is less than 1.0 mg/L."

Said study indicated the LC50 value of the technical material to be >0.1 ppm. Further, at the time, the experimenter that conducted this study had serious solubility problems with the test material,

with precipitate forming and filtration being used to remove the precipitate. The solubility problem produced analytical dose values too close to each other to be considered different. All that could be said about the results obtained was that the LC50 had a value >0.1 ppm. For these reasons, the validity of this study is highly questionable. Further, from the toxicological point of view, the result obtained is unacceptable because the LC50 can not be placed within a fairly narrow range of values and this starting value for Daphnia is under 1.0 ppm making Benfluralin highly toxic to the test organism.

Given an LC50 under 1.0 mg/L, the requirements imposed by EPA guideline 72-4(b)

> " The Daphnia magna life-cycle study is required to support registration of an end-use pesticide product that is applied directly to water or expected to be transported to water from the intended use site, and when any of the following conditions apply: ...
>
> ... If any LC50 or EC50 value determined in testing required by 40 CFR 158.145 [72-1, -2, or -3] is less than 1 mg/l;"

are very clear and require that the registrant complete and present to EPA a scientifically valid Guideline 72-4(b) Daphnia magna life-cycle (21-day) renewal chronic toxicity test.

The registrant has presented a new 7/31/90 study to fulfill the requirements of Guideline 72-4 which, if found valid after review and evaluation, should close this data gap. The study is presently under review and is identified as follows:

> Mohr, R.R. et al., 1990. "The Chronic Toxicity of Benefin to Daphnia magna in a Flow-Through Life-Cycle Test." Performed by the Toxicology Division, Eli Lilly Research Laboratories of Greensfield, IN 46140. --- MRID No. 416138-06

The above mentioned Benefin data gap has been pointed to in the corresponding "List B" forms. This memorandum is for clarification purposes and for the record.

Attachments

2/14/90

ENVIRONMENTAL FATE AND EFFECTS DIVISION
ECOLOGICAL EFFECTS BRANCH

List B Phase 4 - Response on Existing Studies Reviewed

Chemical a.i.Name: BENFLURALIN Case No.: 814851
Chemical No.: 084301

Reviewers Name: ALVARO A. YAHKURE
Phone No.: 557-3179
Date: 12/11/90

Use Pattern(s): COMMERCIAL/INDUSTRIAL/LAWNS; TURF; ORNAMENTAL/SHADE TREES; HERBACEOUS PLANTS; ALFALFA; BIRDSFOOT TREFOIL; CLOVER; LETTUCE; PEANUTS.

Guideline No.: 72-2*
Title: THE ACUTE TOXICITY OF BENEFIN (EL-110, COMPOUND 54521) TO DAPHNIA MAGNA IN A STATIC RENEWAL TEST SYSTEM - MRID 145757
MRIDs and Dates of Studies Reviewed: SUMMARY MRID No.: 92004-006
STUDY DATED: MARCH, 1985

MRIDs and Dates of Fully Acceptable Studies:

Comments:

Given an LC50 under 1.0 mg/L, the requirements imposed by EPA guideline 72-4(b)

> " The Daphnia magna life-cycle study is required to support registration of an end-use pesticide product that is applied directly to water or expected to be transported to water from the intended use site, and when any of the following conditions apply: ...
>
> ... If any LC50 or EC50 value determined in testing required by 40 CFR 158.145 [72-1, -2, or -3] is less than 1 mg/l;"

are very clear and require that the registrant complete and present to EPA a scientifically valid Guideline 72-4(b) Daphnia magna life-cycle (21-day) renewal chronic toxicity test.

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> Mohr, R.R. et al., 1990. "The Chronic Toxicity of Benefin to Daphnia magna in a Flow-Through Life-Cycle Test." Performed by the Toxicology Division, Eli Lilly Research Laboratories of Greensfield, IN 46140. --- MRID No. 416138-06

TO AAY on 12/9/91

D171483
DPBARCODE (RECORD)
084301
SHAUGHNESSY NO

REVIEW NO.

EEB REVIEW

DATE IN: 12-3-91 OUT:
ASSIGNED: 12-10-91
CASE # :814851 REREG CASE #: 2030
SUB. # :S407222 LIST B
ID # :084301-1471

DATE OF SUBMISSION 11-20-91

DATE RECEIVED BY EFED 12-3-91

SRRD/RD REQUESTED COMPLETION DATE 1-19-92

EEB ESTIMATED COMPLETION DATE 1-19-92

SRRD/RD **ACTION** CODE/TYPE OF REVIEW 620 3C2B 90-DAY RSP

MRID #(S)

DP TYPE 999

PRODUCT MANAGER, NO. CHRISTINE RICE 52 TOM MYERS

PRODUCT NAME(S) BENEFIN

TYPE PRODUCT

COMPANY NAME ELANCO PRODUCTS CO

SUBMISSION PURPOSE REVIEW SUBMISSION TO SEE IF IT UPGRADES PREVIOUSLY REVIEWED STUDY (MRID # 145757, INVERT ACUTE TOX TEST), UPDATE DATA TABLE IF STATUS OF STUDY CHANGES

COMMON CHEMICAL NAME BEENEFIN

REVIEWER: ALVARO YAMHURE

DP BARCODE: D171483 REREG CASE # 2030

CASE: 814851 DATA PACKAGE RECORD DATE: 11/21/91
SUBMISSION: S407222 BEAN SHEET Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REREGISTRATION ACTION: 620 3(C)2(B) 90 DAY RESPONSE
CHEMICALS: 084301 N-Butyl-N-ethyl-a,a,a-trifluoro-2,6-dinitro-p-tolu 100.00 %
ethafin

ID#: 084301-001471
COMPANY: 001471 ELANCO PRODUCTS CO.
PRODUCT MANAGER: 52 CHRISTINE RICE 260-5986 703-~~308-8177~~ ROOM: CS1 3F3
PM TEAM REVIEWER: TOM MYERS 703-308-8074 ROOM: CS1 4N1
RECEIVED DATE: 11/20/91 DUE OUT DATE: 02/03/92

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 171483 EXPEDITE: N DATE SENT: 11/20/91 DATE RET.: / /
CHEMICAL: 084301 N-Butyl-N-ethyl-a,a,a-trifluoro-2,6-dinitro-p-toluidine (No
DP TYPE: 999 Miscellaneous Data Package
ADMIN DUE DATE: 01/19/92 CSF: N LABEL: N

ASSIGNED TO	DATE IN	DATE OUT
DIV : EFED	12/03/91	/ /
BRAN: EEB	12/03/91	/ /
SECT:	/ /	/ /
REVR :	/ /	/ /
CONTR:	/ /	/ /

* * * DATA REVIEW INSTRUCTIONS * * *

Please review the attached correspondence for upgrading the invertebrate toxicity study. Does the registrants response adequately address our concerns to upgrade the study or is a new study required.

- Guideline 72-2(a) MRID 145757 Invertebrate Tox.

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL

RESPONSE TO U.S.EPA REVIEW OF A PHASE 3 BENEFIN INVERTEBRATE TOXICITY STUDY/FIFRA GUIDELINE REQUIREMENT NUMBER 72-2(a) (MRID 00145757).

This is a response to the U.S. EPA's Special Review and Registration Division (phase 4 data call-in) regarding benefin. The agency concluded after reviewing the environmental studies that the invertebrate toxicity study (MRID 00145757) was unacceptable. A response to the reviewer's interpretation of the invertebrate study results follows.

RESPONSE TO AGENCY'S INTERPRETATION OF STUDY RESULTS FOR INVERTEBRATE TOXICITY STUDY

ACUTE TOXICITY OF BENEFIN TO DAPHNIA MAGNA (MRID 00145757)

Reviewer's Comments: "As indicated in our response to your Phase II submission, this study is inadequate. There were serious solubility problems with the test material, with precipitate forming and filtration being used to remove the precipitate. The solubility problem produced analytical dose values too close to each other to be considered different. The LC50 was inconclusive. A new study is required."

DowElanco's Response: "We feel that the results of this study adequately reflect the toxicity of benefin to the invertebrate, *Daphnia magna*. This study was specifically designed to address solubility and stability issues associated with the presence of benefin in water. For example, since benefin degrades rapidly in water, test solutions were renewed daily to provide more consistent exposure concentrations. Exposure concentrations selected for this study were 25, 50 and 100 mg/L. These concentrations were selected based on the results of a pilot study which showed 63% immobilization of daphnids at 100 mg/L. No mortality or signs of toxicity was observed at concentrations <100 mg/L. Although the solubility of benefin was known to be 0.1 mg/L, test levels were selected to meet U.S. EPA requirements (i.e., highest exposure level = 100 mg/L). Since these concentrations were 250 to 1000 times above the water solubility, a considerable amount of undissolved benefin was expected to remain in solution. To determine if this undissolved benefin contributed to toxicity, daphnids were exposed to both filtered and unfiltered test solutions at all treatment levels.

Results from this study indicated that over each 24-hour renewal period concentrations in unfiltered solutions declined substantially, primarily due to the settling of undissolved benefin. However, concentrations of benefin in filtered solutions remained relatively stable during each 24-hour renewal period. The analyzed concentrations in all filtered solutions were at or near the water solubility of 0.1 mg/L.

Daphnia exposed to nominal benefin concentrations of 25 and 50 mg/L in both unfiltered and filtered test solutions appeared normal throughout the study. At the 100 mg/L treatments immobilization frequencies after 48 hours of exposure were 63% in unfiltered solutions and 5-7% in filtered solutions. Since the mean concentrations of benefin in all filtered solutions were at or near the water solubility of test compound, it is unlikely that organisms in any test solutions were exposed to dissolved benefin concentrations above 0.1 mg/L. Because there was no apparent relationship between the concentration of benefin and the immobilization of *Daphnia*, it is doubtful that the observed toxicity was caused by benefin. Since exposure levels were 1000 time the water solubility of benefin, it is possible that one or several of the impurities in the technical material may have contributed to the mortality observed at the 100 mg/L exposure level.

Based on results from the study with *Daphnia magna*, the acute no-observed-effect concentration (NOEC) of benefin was reported to be 0.1 mg/L, which is the water solubility of the test compound. The 48-hour EC50 of benefin was >0.1 mg/L. Using nominal concentrations, the NOEC and 48-hour EC50 of benefin were 50 mg/L and > 50 < 100 mg/L, respectively.

If this study were repeated as requested by the Agency, we do not expect the results to be significantly different from the study being discussed.