Shaughnessy No.: _____

Out [redacted] date: [redacted] 17 FEB 1984

To: R. Mountfort
Product Manager #23
Registration Division (TS-767)

From: Samuel M. Creeger, Chief
Environmental Chemistry Review Section 1
Exposure Assessment Branch
Hazard Evaluation Division (TS-769c)

COPY

Attached, please find the EAB review of:

Reg./File No.: 8340-EUP-T

Chemical: Ethyl 2-[4-((6-chloro-2-benzorazolyl)oxy)phenoxy) propanoate

Type Product: Herbicide

Product Name: WHIP

Company Name: American Hoechst

Submission Purpose: response to review

ZBB Code: other

Action Code: 711

Date In: 2/3/84

EFB No.: 4184

Date Completed: 2/14/84

TAIS (Level II)	Days
52	3.0

Deferrals To:

_____ Ecological Effects Branch

_____ Residue Chemistry Branch

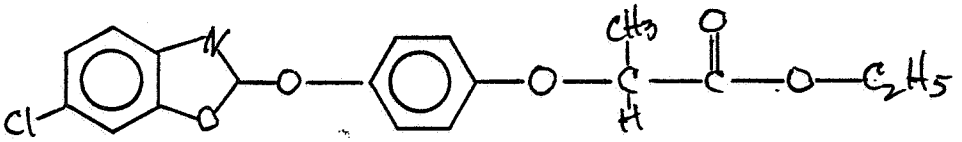
_____ Toxicology Branch

1.0 INTRODUCTION

Chemical Name and Type of Pesticide: fenoxaprop-ethyl (proposed common name), ethyl 2-[4-[(6-chloro-2-benzoaxazolyl)oxy]phenoxy] propanoate, 12.5% ai, herbicide.

Trade Name: Whip 1 EC Herbicide
HOE-33171

Chemical Structure:



American Hoechst is responding to a previous review (3 Nov. 1983) that dealt with an application for an EUP to use WHIP 1 EC Herbicide for grass control in soybeans.

2.0 DISCUSSION

The registrant listed the comments from our review and responded to each point by point (see attachment #1).

In response to our comment on additional radiolabeling in the phenyl ring of the molecule, they cited data pertaining to this and enclosed a pre-publication draft of a paper (attachment #2).

Attachment #3 gives the actual calculations (using Arrhenius equation) used to determine the half-life during hydrolysis at ambient temperature.

3.0 RECOMMENDATION

3.1 EAB finds all the responses submitted American Hoechst to be satisfactory in answering the comments made in a previous review (3 Nov. 1983).

3.2 Specifically, we can state the following concerning the studies submitted to date:

1. Hydrolysis - Accepted in the initial EUP review and information on half-life calcualtions was provided.

2. Aerobic soil metabolism - Presently acceptable. Responses to comments were satisfactory.

3. Rotational crop - Not included in the EUP application, but was subsequently sent in, reviewed, and found satisfactory. The study was found to support a 120-day or one-year rotated crop interval.

4. Fish accumulation - Not included in the EUP application. A non-radiolabeled study using pumpkin seed sunfish in a flow-through system was summarized in the registrant's responses and indicated a maximum bioaccumulation factor of 384. This study will only support the EUP. A new, radiolabeled study using bluegill sunfish will be started in February, 1984.

5. Leaching - Accepted in review of EUP application.

3.3 The data requirements to support an EUP program to use WHIP 1EC Herbicide on soybeans are satisfied.

Herbert L. Manning

Herbert L. Manning, Ph.D.
Review Section #1
EAB/HED

Attachment #1 (pages 1-5)

WHIP™ 1EC HERBICIDE

EPA EUP File Symbol 8340-EUP-T
Pesticide Petition No. 3G2940

Below is a reply to the November 22, 1983 letter from Mr. J. Stone of the EPA, addressing the Exposure Assessment Branch review of the above petition.

1. The EAB review states the absence of a rotational crop study. The rotational crop study was, in fact, included as part of the original submission. The Agency was directed to its location in an earlier response from American Hoechst. This study has subsequently been reviewed by the Exposure Assessment Branch and found to be satisfactory as noted in the EPA letter dated January 13, 1984. A requested statement regarding crop failure has been added to the label.

2. The EAB reviewer states:

"For the aerobic soil metabolism study, the following must be addressed:

(a) It was noted that only the chlorophenyl part of the Hoe 33171 molecule was radiolabeled. Since the M_2 degradate resulted from a splitting off of the phenylethyl propionate moiety, it would have been useful to have had the phenyl ring labeled so its fate would be known. One of two options is available:
   (i) The study could be repeated with labeling in the phenyl ring of the phenol ethyl propionate moiety.
   (ii) The fate of this moiety could be discussed and supported from other chemical or environmental studies.

(b) How do you account for the metabolites M1, M2, and M3 being present at zero time?

(c) What exactly is meant by zero time sampling?

(d) The half-life of HOE-33171 (less than 1 day) and its conversion to the free acid is very rapid. Had these soils been treated in the past with an ester?"

In an address to (a), above, please find under Tab 2 (attached) a review of the literature addressing the fate of the so-called "phenyl ring" in compounds with structures similar to HOE-33171. The fate of this ring in soybean cell suspension cultures is also addressed, using HOE-33171 radiolabeled in the dioxyphenyl ring with ^{14}C at the number one carbon position.

The metabolite found was 4-hydroxyphenoxy propionic acid, conjugated with glucose, either with the phenolic hydroxyl group or the carboxyl group of the acid.

This metabolite was similar to those found in the metabolism of compounds with similar structures.

In an address to (b) and (c), above, Hoechst AG personnel (who conducted the study) state that zero time sampling means up to about 4 hours after application, due to logistical considerations and the fact that extraction of soil via the approach employed takes finite time. As HOE-33171 is a very rapidly degrading substance, small amounts of the metabolites can be present in the samples.

Addressing (d), above, the soils used in this study had not been treated in the past with an ester. The very rapid conversion of the active ingredient to the free acid is a property of the compound well known from many trials. Probably this is due to catalytic effects of the soil particles.

3. The EAB reviewer states that:

"While the anaerobic study is not an EUP requirement, it is needed for registration and certain concerns we have with it have to be addressed:

(a) Foreign soils used in lab studies must have the same characteristics as U.S. soils for proposed use. Features to be matched are:

- o soil class
- o % organic matter
- O pH soil
- o ratio of soil bacteria to soil fungi to soil actinomycetes

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(b) EPA environmental chemistry guidelines require aerobic aging of treated soil. The study submitted aged untreated soil.

(c) How do you account for the high levels of metabolites at zero time sampling?

(d) Soil contains far fewer microbes capable of growing under anaerobic conditions than aerobic conditions, a fact strongly supported by environmental studies. In this study, the half-life of the parent compound was about equal to the value under aerobic conditions, a most unlikely observation. The half-life for the major degradate was several times that under aerobic conditions, an expected and reasonable finding. How do you account for the half-life of the parent being the same under aerobic and anaerobic conditions?"

The anaerobic study will be repeated exactly according to EPA guidelines. To confirm this, the protocol for such a study will be submitted in advance to the EPA for evaluation prior to initiation of the study. However, the EAB reviewer is correct that an anaerobic soil study is not a requirement for an EUP, therefore, this should not be a problem.

4. The EAB reviewer states:

"A rotational crop study, or 18-month restriction placed on the label, and fish accumulation (bluegill sunfish, flow-through) study are required for the EUP."

As stated previously, a rotational crop study was submitted in the original submission. This has been discussed above in point number 1 of this response.

A pumpkinseed sunfish, flow-through study is submitted herein under Tab 3. The study was conducted at Hoechst AG in Frankfurt, West Germany, and utilized non-radiolabeled compound HOE-33171. The analytical method employed in the study involves the hydrolysis of the parent compound to 6-chloro-2,3-dihydrobenzoxazol-2-one, which is derivatized and analyzed. Thus, the analytical method encompasses all the metabolites of the HOE-33171 and quantifies the total residue present in both fish and water.

The fish were established in aquaria and compound HOE-33171 was metered into the flowing water at a concentration of 0.031 mg/L. The concentration of the compound in the tank water was 0.033 mg/L. Within 3 days, the test substance was accumulated to a maximum of 11.9 mg/kg in the fish and a maximum bioaccumulation factor of 384. A plateau (concentration in the fish) was achieved at 6 mg/kg and continued through day 28 of the study, at which time the depuration phase was initiated. On day 29, the fish had eliminated most of the test substance. Only 0.4 mg/kg could be detected at this sample day. As the analytical baseline of detection for this test substance was 0.3 mg/kg, the test was terminated after day 21 of the elimination phase (test day 50), when depuration had reached this level for a sequence of days.

The degradation pathway rapidly follows an anticipated sequence of hydrolysis to the free carboxylic acid and, subsequently, to the 6-chloro-2,3-dihydrobenzoxazol-2-one. The method of analysis was developed to encompass detection of the parent compound and all the above metabolites. Thus the fragment 6-chloro-2,3-dihydrobenzoxazol-2-one represents the sum of all the residual compounds. It is a similar situation as with the "fragment" carbon - 14, which would represent the sum of the total residues in a study with radiolabeled HOE-33171.

A study of bioaccumulation of radiolabeled HOE-33171 in bluegill sunfish will be initiated in February, 1984 at ABC Laboratories in Missouri. The HOE-33171 will be radiocarbon-labeled in 2 separate positions: 1) the phenyl portion of the 6-chlorobenzoxazole moiety, and 2) the dioxyphenyl ring. The 2 labeled compounds will be studied separately to determine bioaccumulation and metabolism in the sunfish.

5. The EAB reviewer states:

"Please submit the actual calculations that used Arrhenius equations." Attached, under Tab 4, are the calculations of half-life periods at ambient temperature with the Arrhenius equation. The calculations are from Dr. S. Gorbach of the Hoechst AG Analytical Laboratory, whose group performed the hydrolysis studies. The calculation and the results are explained.

The attached reports, data, and explanations constitute an address to the Exposure Assessment Branch review of the HOE-33171 Herbicide (Whip Herbicide™) petition for an EUP.

Dr. J. O'Grodnick
Dr. H. H. North
January 26, 1984

Fenoxaprop-ethyl scientific reviews

Page _____ is not included in this copy.

Pages 9 through 14 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

_X_ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
