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

AUG 21 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#6F3316 (RCB Nos. 1018, 1019) - Fenoxaprop-ethyl (HOE 33171) on Soybeans and Rice - Amendment Dated May 22, 1986 (Accession No. 263029)

FROM: Nancy Dodd, Chemist
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and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
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The petitioner, American Hoechst Corporation, submits an amendment dated May 22, 1986 to PP#6F3316 for tolerances for residues of the herbicide fenoxaprop-ethyl [(±)-ethyl 2-[4-[(6-chloro-2-benzoxazolyl)oxy]phenoxy]propanoate] and its metabolites 2-[4-[(6-chloro-2-benzoxazolyl)oxy]phenoxy] propanoic acid and 6-chloro-2,3-dihydrobenzoxazol-2-one on soybeans, rice, and rice straw at 0.05 ppm. The amendment is submitted in response to RCB's review of February 4, 1986 (N. Dodd) and a meeting on April 10, 1986. The amendment consists of a revised label and additional residue data.

The deficiencies listed in the February 4, 1986 review and discussed in the April 10, 1986 meeting are outlined below followed by the petitioner's responses and RCB's discussions/conclusions.

1

RCB's Deficiency #1

One inert is not cleared for the proposed use on rice. The petitioner must formally ask for an exemption from the requirement of a tolerance for one of the inerts when used on rice. Refer to the Confidential Appendix of this review.

Petitioner's Response to Deficiency #1

The petitioner has revised the label so that this use on rice complies with 40 CFR 180.1001(d), [redacted] when applied "prior to formation of edible parts of food plants . . . ." The revised label states "Do not apply Whip 1EC Herbicide after the late tillering stage of the rice development (but prior to panicle initiation)." (The previous label stated "Do not apply Whip after the panicle initiation stage of rice development.")

RCB's Discussion Concerning Deficiency #1

Application [redacted] prior to formation of rice grain.

RCB's Conclusion #1

Deficiency #1 is resolved.

RCB's Deficiency #2

The proposed tank mixing of fenoxaprop-ethyl with Blazer® 2L and Basagran® 4SL are prohibited by restrictions which Rohm and Haas Company and BASF Wyandotte Corporation have placed on their labels. The inclusion of Whip 1EC on the Rohm and Haas and Wyandotte labels and/or the permission for American Hoechst Corporation to tank mix Whip 1EC with Blazer 2L and Basagran 4SL needs to be resolved by these companies (the petitioner, Rohm and Haas, and BASF Wyandotte) (see the Proposed Use section of this review for further details).

Petitioner's Response to Deficiency #2

The petitioner has deleted Basagran and Blazer tank mix directions pending reconciliation with BASF and Rohm and Haas, respectively.

RCB's Conclusion #2

Deficiency #2 is resolved.

RCB's Deficiency #3

Since Whip 1EC contains [redacted] the inclusion of Whip 1EC on the Rohm and Haas Propanil label and/or the permission for American Hoechst Corporation to tank mix Whip 1EC with Propanil needs to be resolved by the petitioner and Rohm and Haas (see the Proposed Use section of this review for further details).

Petitioner's Response to Deficiency #3

The petitioner indicates that Propanil is specifically prohibited as a tank mix or sequential treatment within 6 days of a Whip application.

RCB's Conclusion #3

Deficiency #3 is resolved.

RCB's Deficiency #4a

In a soybean metabolism study, the petitioner has claimed that total radioactive fenoxaprop-ethyl residue in seeds was less than 0.005 ppm (PHI's 51 to 126 days); however, although the proposed analytical method has the capability to analyze about one-third of the terminal residue (after loss), the field studies (discussed later in this review) indicated that more total terminal residue could be present in seeds.

Petitioner's Response to Deficiency #4a

The petitioner indicates that residues were found when soybeans were sprayed at full bloom when small pods had formed and at high application rates in order to create residues for processing studies. The petitioner submits documents which indicate the stage of growth of the soybeans at the second spraying (Tab D-3) and a residue protocol (Tab D-4) which indicates that the second application was to be made at bloom.

The petitioner supplies the following information on stage of growth at the time of the second application (Tab D-3) for the three processing studies:

Study #	Stage of Growth
09-IN-82-999	full bloom or R2 stage*
16-MS-84-22	at bloom (i.e., flowers with some pods)

* "The R2 stage of growth is reached when open flower(s) are found on one of the two uppermost nodes. At this stage on an indeterminate variety, lower nodes could have already flowered with pods formed."

Study #	Stage of Growth
IN-NE-82-01	no information**

RCB's Conclusion #4a

Deficiency #4a has been resolved for the proposed use on soybeans.

RCB's Deficiency #4b

Considering the structure, systemic properties, etc. for fenoxaprop-ethyl, RCB defers to Toxicology Branch (TB) as to whether the identification of 55 percent and 28 percent of the residue in soybeans and rice, respectively, is adequate for TB considerations. Although the petitioner has made an effort towards understanding the metabolism of fenoxaprop-ethyl in soybeans, rice, and the lactating cow, RCB reserves any ~~final conclusion~~ until TB has had a chance to comment on this issue. If TB feels that further identification of residues is needed for toxicological considerations, then the petitioner should do further metabolic work. In order to further identify the nature of the ^{14}C activity, the petitioner may want to consider, among various possibilities, the following: exhaustive reflux extraction with HBr or HI instead of HCl; exhaustive extractions with other solvents such as ether, acetone, etc.; enzymatic hydrolysis; column chromatography of polar residues in the water phase by gel permeation chromatography and/or ion-exchange chromatography; and electrophoresis of polar residues in the water phase. The preceding are only some suggestions. The petitioner, of course, will want to use the best available technology in order to provide the necessary metabolism understanding.

Petitioner's Response to Deficiency #4b

1. The petitioner indicated that Toxicology Branch has concluded that no further metabolic work is needed (in EPA letter dated March 19, 1986).

2. In response to RCB's suggestion that exhaustive extraction with other solvents could decrease the amount of bound residue, the petitioner submits

** In IN-NE-82-01, no detectable residues (< 0.05 ppm) were found in seed, meal, crude oil, refined oil, and soapstock; residues in hulls were not detectable (< 0.02 ppm) except for residues of 0.02 ppm for two treatments at 0.2 lb ai/A and a 73-day PHI.

preliminary studies (A32816, Tab D-5) to show that "exhaustive extraction with other solvents does not decrease the amount of bound residues." The report compares the following extraction solvents for extracting ^{14}C-HOE 33171 from soybean plants: methanol, acetone, acetonitrile/water, dichloromethane/water, and water. Dichloromethane/water and acetonitrile/water were comparable in extraction efficiency. Acetonitrile/water was selected as the best extraction system since it is easier to handle.

RCB's Discussion Concerning Deficiency #4b

1. TB's response to RCB's deference is contained in the TB memorandum of March 7, 1985 (Clint Skinner):

> "The identified metabolites in rice and soybeans were all located in the rat metabolism study except for HOE 40356 which is only a deacetylated more polar cleavage product of HOE 53022 which is found in the rat. Since these metabolites are largely tested in the animal studies, since they are produced by the animal, these are of no concern.
>
> Since a number of bacterial and mammalian genotoxicity tests have been performed with mammalian metabolism, and were negative, we have no evidence that the known metabolites are of toxicological concern.
>
> Because the total residue in rice and soybean is of the order of 0.05 ppm, even if the unidentified plant metabolites are more toxic than the parent, no serious concern is expressed in toxicology."

2. Since TB feels that further identification of residues is not needed, further metabolic work is not needed at this time.

RCB's Conclusion #4b

RCB will consider Deficiency #4b to be resolved for the proposed use on soybeans and rice only. At the April 10, 1986 meeting, the petitioner was told that for any future higher tolerances of 0.1 ppm or more on any raw agricultural commodity, more metabolic work would probably be needed. Accordingly, the petitioner has agreed to do more metabolic work (see RCB's April 22, 1986 Memorandum of Conference).

RCB's Deficiency #5a

The petitioner uses hydrochloric acid as a cleaving agent for plant residues with the intent of converting the parent compound and the metabolite HOE 53022 to HOE 54014 (6-chloro-2,3-dihydrobenzoxazol-2-one) which is also one of the metabolites that was defined. But, is HCl the right choice of acid for cleaving the preceding compounds? One notice that ethereal bonds (-O-) are located at two positions in HOE 33171 and HOE 53022. According to March (Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, p. 344, McGraw-Hill, New York, 1968) the following is stated:

> "Ethers may be cleaved by heating with concentrated HI or HBr. HCl is seldom successful. HBr reacts more slowly than HI, but it is often a superior reagent since it causes fewer side reactions."

Petitioner's Response to Deficiency #5a

The petitioner indicates that the preferred cleavage site is not an ether but an imidocarbonate ester structure. An hydrolysis study with HBr is submitted (Report A32818, Tab D-6). The petitioner indicates that HCl is the best cleaving agent since other cleaving agents produce artifacts.

RCB's Conclusion #5a

Deficiency #5a is resolved.

RCB's Deficiency #5b

At this time, RCB will reserve its conclusion on the acceptance of the proposed analytical methodology for regulatory purposes until RCB has received an answer to its deference to TB concerning the adequacy of the characterization of residues for toxicological consideration and/or the nature of the residue in plants and animals is finalized. More work may need to be done on the proposed analytical methodology.

Petitioner's Response to Deficiency #5b

TB has determined that no further metabolic work is needed.

RCB's Conclusion #5b

Resolution of Deficiency #5b is pending on the receipt of a satisfactory method trial.

A method trial is to be conducted by EPA (PP#6F3316, review of N. Dodd dated February 4, 1986).

RCB's Deficiency #5c

RCB has requested (January 8, 1986 telephone conversation between N. Dodd, EPA, and William Horton, American Hoechst Corp.) the petitioner to submit the metabolic standards HOE 53022 and HOE 54014 to its North Carolina depository in preparation for an EPA method trial. Although the analytical procedure is questionable, RCB will submit it for a method trial. After TB has answered RCB's deference concerning the toxicological significance of the residue and work has been finalized on the proposed regulatory procedure, a final determination will be made as to what residues need to be regulated.

Petitioner's Response to Deficiency #5c

The petitioner indicates that the requested standards were delivered on February 20, 1986.

RCB's Conclusion #5c

The residues to be regulated are fenoxaprop-ethyl [(±)-ethyl 2-[4-[(6-chloro-2-benzoxazolyl)oxy]phenoxy]propanoate] (HOE 33171) and its metabolites 2-[4-[(6-chloro-2-benzoxazolyl) oxy]phenoxy]propanoic acid (HOE 53022) and 6-chloro-2,3-dihydrobenzoxazol-2-one (HOE 54014). These are determined by the plant and animal analytical methods.

Deficiency #5c is resolved, pending a satisfactory method trial.

RCB's Deficiency #6a

Adequate storage stability data are available for the parent compound fenoxaprop-ethyl only.

Petitioner's Response to Deficiency #6a

The petitioner submits the report "Storage Stability of Pesticide Residues," Hans Eglis (Ciba-Geigy) J. Agric Food Chem, 1982, 30, 861-866 (Tab D-7). The abstract is below:

> "The stability of residues of 19 plant protection agents or plant regulators in different substrates at -20 °C were determined as were the hydrolysis half-life times in neutral solutions at +50 and +70 °C. The following correlations between these two properties were found: (1) residues are

stable for at least 1 year if half-life times are above 10 days at 70 °C; (2) residues are unstable if half-life times are below 1 day at 50 °C, especially in crops with a high water content; (3) residue stabilities need examination if half-life times lie in between. On the basis of this, it is proposed that residue stabilities can be derived from hydrolysis data and a residue stability study should be run only in doubtful cases. It is shown that such studies can be performed with fortified samples."

The petitioner has previously informed EAB that "hydrolysis of fenoxaprop-ethyl at 50 °C in pH 7 water was 5.3×10^3 min. or 3.7 days. At 20 °C and pH 7, the half-life of fenoxaprop-ethyl was estimated to be 100 days. In this study the hydrolytic product, fenoxaprop, was stable to further hydrolysis even at 50 °C."

The petitioner indicates that fenoxaprop is more stable to hydrolysis than fenoxaprop-ethyl at 20 °C and 50 °C. The petitioner believes that this indicates that fenoxaprop is more stable under frozen conditions than fenoxaprop-ethyl.

Since the residue method involves refluxing of HOE 54014 at approximately 100 °C in acidic ethanol-water for 8 to 24 hours, the petitioner believes that HOE 54014 would be stable under frozen conditions.

RCB's Conclusion #6a

Fenoxaprop and HOE 54014 appear to be at least as stable as fenoxaprop-ethyl.

RCB concludes that adequate storage stability data are available for supporting the proposed use on soybeans and rice. Deficiency #6a is resolved.

RCB's Deficiency #6b

Since it appears that fenoxaprop-ethyl is highly systemic and much more of the metabolites are present in the terminal residues of weathered crops than the parent compound, the petitioner should also submit storage stability data for those major metabolites that will be regulated. At this time, we do not know what these regulated metabolites will be since more metabolic work may need to be done.

Petitioner's Response to Deficiency #6b

The petitioner indicates that little or no residue is translocated into the edible parts of plants. The petitioner submits a translocation study (Doc. No. A31868, Tab D-8).

The petitioner indicates that TB has concluded that no further metabolic work is needed.

RCB's Discussion Concerning Deficiency #6b

Little translocation occurs in sorghum and soybeans in 7 days.

RCB's Conclusion #6b

Since TB has concluded that it could tolerate the findings of the metabolic studies ~~on hand in~~ order to support the "proposed use" on soybeans and rice, the proposed tolerance expression that regulates fenoxaprop-ethyl (parent compound) and the metabolites fenoxaprop and HOE 54014 is adequate at this time. It may need to be changed after more metabolic work has been done.

Deficiency #6b is resolved for the proposed use on soybeans and rice.

RCB's Deficiency #7a

At this time, RCB must reserve its conclusion on the adequacy of the proposed 0.05 ppm fenoxaprop-ethyl tolerance on soybeans and possibly soybean fractions; more work may have to be done on plant metabolism and the analytical procedure that is proposed for regulatory purposes. The petitioner should be informed that it may be necessary for him to reanalyze some of his reserve field soybean samples as a result of the preceding work. Also, if the storage stability data for the parent and major metabolites are not adequate, then new field residue data may need to be generated.

Petitioner's Response to Deficiency #7a

The petitioner indicates that the 0.05 ppm tolerance on soybeans and soybean fractions is supported. The petitioner reports that TB has decided that additional metabolic work is not necessary.

RCB's Discussion Concerning Deficiency #7a

Dr. J.R. Wilcox, Purdue University, 8-317-494-8074, indicates that the time interval from before bloom to maturity can be as short as 60 days for early maturing varieties such as McCall and Clay. The flowering to maturity interval is shorter for early maturing varieties than for other varieties.

RCB's Conclusion #7a

Pending a successful method trial, RCB's questions concerning metabolism, analytical methods, and storage stability are resolved for the proposed use on soybeans and rice only. (Refer to Conclusions #4b, 5a, 5b, 5c, 6a, and 6b.) However, additional residue data reflecting the proposed use and shorter PHI's are needed. Since the time from before bloom to maturity can be as short as 60 days, RCB requires some residue data for PHI's of approximately 60 days for the proposed use (i.e. soybeans treated before bloom). The data base upon which to establish a 0.05 ppm tolerance on soybean and soybean fractions, especially for early maturing varieties, is too scant.

RCB's Deficiency #7b

The recovery/validation data for fenoxaprop-ethyl in soybeans/soybean fractions could be misleading even though at face value most of them would seem to be acceptable. Generally, RCB will approve of validation data where the concerned residues necessary for regulation are added to the samples before analyses, but there must be a good correlation between the accountable residues in the metabolism study and the accountable residues recovered by the proposed analytical procedure.

Petitioner's Response to Deficiency #7b

The petitioner states that "there is a good correlation between the accountable residues in the kinetic study and the residues recovered by the proposed analytical procedure."

RCB's Conclusion #7b

Deficiency #7b is resolved. The residues of concern (parent, fenoxaprop, and HOE 54014) are determined by the analytical methods.

RCB's Deficiency #8

In view of the above, RCB reserves its final conclusion concerning the adequacy of the proposed 0.05 ppm fenoxaprop-ethyl tolerance on rice grain and straw; more work may have to be done on the plant metabolism and the proposed analytical procedure for regulatory purposes. The petitioner should be informed that it may be necessary to reanalyze some of his reserve field rice samples as a result of the preceding work; the storage stability study on both the parent compound and the major metabolites must be adequate in order to accept these data from reanalyses. Otherwise, it may be necessary to generate some new field residue data.

Petitioner's Response to Deficiency #8

The petitioner indicates that the 0.05 ppm tolerance on rice grain and straw is supported. The petitioner repeats that TB has decided that additional metabolic work is not necessary.

RCB's Discussion Concerning Deficiency #8

"Six Decades of Rice Research in Texas" published by the Texas Agricultural Experiment Station and the United States Department of Agriculture in June 1975, p. 10, Figure 2-1, indicates that the PHI for rice could be as short as 52 days. The residue data reflect PHI's of 78 to 131 days. The data base upon which to establish a 0.05 ppm tolerance on rice, especially early maturing varieties, is too scant.

RCB's Conclusion #8

Pending a successful method trial, RCB's questions concerning metabolism, analytical methods, and storage stability are tentatively resolved. (Refer to Conclusions #4b, 5a, 5b, 5c, 6a, and 6b.) However, additional residue data reflecting the proposed use and shorter PHI's (i.e. approximately 52 days) are needed.

RCB's Deficiency #9a

No cattle or poultry feeding studies have been submitted. Soybeans, soybean hulls, rice straw, and hulls may be fed to livestock.

Petitioner's Response to Deficiency #9a

The petitioner indicates that feeding studies are not required since measurable residues are not found in the raw agricultural commodities or fractions.

11

RCB's Conclusion #9a

For the proposed use on soybeans and rice, RCB tentatively concludes that cattle and poultry feeding studies will not be required. However, if the proposed use on soybeans and rice is replaced or finite tolerances are proposed in the future, then the petitioner will need to submit these studies for review.

RCB must review the results from the method trial and additional residue data that are requested before making a final conclusion on the need for cattle and poultry feeding studies.

RCB's Deficiency #9b

RCB must reserve its conclusion on the immediate need for cattle and poultry feeding studies until the plant metabolism, proposed analytical methodology, and field residue studies have been considered adequate.

Petitioner's Response to Deficiency #9b

Same as #9a.

RCB's Conclusion #9b

Same as #9a.

RCB's Deficiency #11

The identity of HOE S1728 (ATA TH-T of the Hoechst Company), which is an emulsifier solution used in the analytical method, is needed.

Petitioner's Response to Deficiency #11

The petitioner submits the identity of HOE S1728 (Tab D-9). HOE S1728 contains approximately 35 percent active material [redacted] HOE S1728 is commercially available.

RCB's Conclusion #11

Deficiency #11 is resolved.

Other Considerations

An International Residue Limits (IRL) Status sheet was attached to RCB's review of February 4, 1986. There are no Codex, Canadian, and Mexican tolerances for fenoxaprop-ethyl on soybeans and rice. Therefore, no compatibility questions exist with respect to Codex.

Recommendations

RCB recommends against the establishment of the proposed tolerance of 0.05 ppm fenoxaprop-ethyl on soybeans, rice, and rice straw for reasons given in Conclusions 5b, 7a, 8, 9a, and 9b above.

cc: RF, Circu, Reviewer-N.Dodd, EAB, EEB, FDA, D. Marlow, TOX, PM #23, PP#6F3316, PMSD/ISB-Eldredge
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