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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

FEB 2 1990

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MEMORANDUM

SUBJECT: PP#9F3714. EPA Reg. No. 8340-GI. Fenoxaprop-ethyl in or on Wheat. Amendment of August 21,1989. Amended Sections B and F and Responses to Deficiencies. MRID Nos 412233-01, 412085-02 and 412086-01. DEB Nos 5828 and 5829.

FROM: Joel Garbus, Ph.D., Chemist
Tolerance Petition Section III
Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Richard D. Schmitt, Ph.D, Chief
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Health Effects Division (H7509C)

TO: JoAnne Miller, PM-23
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Registration Division (H7505C)

In response to our August 8,1989 memo (J. Garbus, PP#9F3714), the petitioner has submitted revised Sections B and F, a goat metabolism study, and a wheat processing study. The deficiencies from our memo will be stated, followed by the petitioner's response and our comments.

Conclusions and Recommendations

1. Deficiencies 2, 3, and 6f are resolved. Deficiency 4b is partially resolved. Deficiencies 6e and 7a remain unresolved.

2 The nature of the residue in plants and animals is adequately understood for this proposed use on wheat. The residues of concern are fenoxaprop-ethyl, its free acid, fenoxaprop, and 6-chloro-2,3-dihydrobenzoxazol-2-one.

3a. The presence of residues in milk and tissues at all feeding rates in the feeding study demonstrates the potential for residues to transfer. We conclude that this is a Section 180.6(a)(2)

situation with respect to secondary residues in meat, milk, poultry, and eggs.

3b. The petitioner should propose tolerances at the limit of detection (0.01 ppm) for meat, meat by-products, and milk resulting from the use proposed in this petition.

3c. A method validation for a proposed enforcement method (HRAV-4) is needed for wheat grain and straw. The method validation has been requested of the Agency's Analytical Chemistry Branch.

3d. A method validation of the proposed enforcement method AL 06/84 for residues in meat and milk is required. However, before an Agency validation can be conducted the petitioner will need to submit a complete description of the methodology which includes representative chromatograms and validation data of fortified samples. A study of an independent validation and of the accountability study titled "HOE 033171-14-C: Nature of Residues in Milk and Tissues of Cows after Dosing 50 mg/Cow/Day at Three Consecutive Days." K. Krenzler, E. Dorn and H. M. Kellner. Hoechst Internal Report Fo 337/85, A30492 should also be submitted for our review.

4a. The site of the ^{14}C label used in the goat metabolism study submitted in this amendment was not identified. Presumably it is located in the benzoxazol ring. Acceptance of this study for the proposed use on wheat is predicated on the petitioner verifying that the labeled site is in the benzoxazol ring. Provided that this is the case the residues of concern in ruminants and hogs are fenoxaprop-ethyl, its free acid, fenoxaprop, and 6-chloro-2,3-dihydrobenzoxazol-2-one.

4b. For any future tolerance requests on potential livestock feed items which can lead to higher livestock exposure to regulated residues of fenoxaprop-ethyl, the unidentified residues in tissues and milk, except kidney, from the goat metabolism study must be characterized/identified. Both rings of fenoxaprop-ethyl should be labeled.

5a. In regard to deficiency 6e, we conclude that the 0.05 ppm proposed for wheat <u>grain</u> most likely would be accommodated by the proposed revised label instructions and that the revised label giving application timing in terms of growth stages rather than fixed PHI's is acceptable.

5b. However, until additional data are submitted we cannot be certain that the proposed tolerance of 0.5 ppm for wheat <u>straw</u> will be sufficient to encompass the minimum interval from application to harvest. The maximum residue value (0.36 ppm) upon which the proposed tolerance of 0.5 ppm was based was obtained with a 70 days PHI. At present it remains only an assumption that the proposed tolerance would not be exceeded at a 60 day PHI.

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5c. Therefore, the petitioner can submit growth-stage information for all varieties of wheat grown under all US cultural conditions so as to indicate the range of time that could elapse between application as per the label instructions and harvest.

The petitioner will need to relate the residue data previously submitted in terms of PHI's to wheat growth stages. When we are in possession of this additional information we can determine if the proposed tolerance of 0.5 ppm on wheat straw is adequate.

As an alternative to supplying he above information, the petitioner can submit a revised Section B that includes a 70 day PHI.

Recommendation

DEB continues to recommend against the establishment of tolerances for fenoxaprop-ethyl on wheat for the reasons stated above in conclusions 3b, 3c, 3d, 4a, 5b, and 5c. The petitioner needs to do the following:

- Propose tolerances for meat, meat byproducts, and milk (See Conclusion 3b).
- Submit validation data and chromatograms plus an independent laboratory validation for method Al 06/84; submit the accountability study noted in Conclusion 3d.
- Indicate the site of the radiolabel in the goat metabolism study (Conclusion 4a)
- Submit a revised Section B or additional information on wheat as requested in Conclusion 5c.

With regard to Conclusion 3c, DEB is requesting a method validation for method HRAV-4

Detailed Considerations:

Deficiency No 2:

The registrant states that the active ingredient is always used in combination with a chemical safener in wheat. However, there are no warnings or directions for use with a chemical safener on the proposed labeling for use with wheat.

The petitioner should have a warning on the label against the use of fenoxaprop-ethyl alone on wheat and should provide tank-mixing directions for use with the herbicides MCPA and 2,4-D.

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Response

"Fenoxaprop-ethyl will not be used on wheat in a tank-mix combination with safeners." It will be used in a formulated pre-mix. The Tiller label and the CSF list the proposed safeners which are other herbicides registered for use on wheat as active ingredients. "In view of the above no warnings or directions for use in tank mixes are required."

Comment

We agree that the inclusion of herbicides registered for use on wheat as safeners in the formulation of Tiller and their listing on the label as active ingredients precludes the need on the label for the special warnings or directions requested in our previous memos.

We conclude that the deficiency is resolved.

Deficiency 3:

> The petitioner should remove wheat straw from the feeding restriction because RCB regards the restriction as impractical.

Response

The grazing restriction has been removed from the label.

Comment

This deficiency is resolved.

Deficiency 4b:

> The nature of the residue in ruminants is not adequately defined for the proposed uses since wheat straw cannot be restricted for feed use. Additional characterization of the tissue and milk residue is needed.
>
> The petitioner states that the dose used in the metabolism study was 100 times the concentration of residue expected in cattle feed. The petitioner should submit the feeding level in terms of ppm herbicide in the diet of the animal.

Response

The petitioner has submitted a study entitled "HOE-033171-^{14}C Metabolism in the Lactating Goat Following Repeated Oral Administration." The study is dated August 4, 1989, and was conducted in response to DEB's review of May 20, 1988.

^{14C}-HOE 03371 (fenoxaprop-ethyl) mixed with unlabelled material was administered to a lactating goat for three consecutive days. The daily dose of 250 mg was equivalent to 134 ppm based on the animals feed consumption per day. The site of the label is not specified although it can be presumed to be in the benzoxazol ring. The petitioner should verify that the site of the label was in the benzoxazol ring.

Samples of milk, urine, and feces were collected from the animal at various times. Twenty four hours after the last dose the animal was killed and tissue and blood samples taken for examination. The total radioactivity in the samples of fluids and tissues was determined. Milk and urine samples were added directly to scintillation fluid and radioactivity was determined by LSC.. Feces and tissues were homogenized with acetonitrile/water and radioactivity was determined in homogenates, extracts, and residues by LSC.

For the determination of individual metabolites, samples of urine were directly subjected to TLC and HPLC. Milk, feces, and tissues were extracted with organic solvents. After cleanup, the extracted material was subjected to TLC and HPLC. Additionally the extracts were subjected to enzymatic and chemical hydrolysis to cleave possible conjugates and the treated material was subjected to TLC and HPLC. The results were expressed in terms of parent equivalents.

At sacrifice, 87.7% of the total cumulative dose had been excreted via urine or feces while a total of 0.54% of the dose had been excreted in milk. Radioactive levels in fat and muscle were 0.12% (0.31 ppm) and 0.42% (0.15 ppm) of the administered radioactivity, respectively. Kidney tissue at 7.7 ppm and liver tissue at 1.96 ppm represented 0.15 and 0.25% of the administered dose.

HPLC analysis of the final urine sample revealed the presence of approximately 21 major and minor radioactive components. A peak corresponding to the free acid of fenoxaprop-ethyl accounted for 51% of the radioactivity, while two other major unidentified components accounted for an additional 14.4%. The remaining 18 peaks were less than 5% each.

In fecal extracts, 3 radioactive components were detected and characterized as parent (66%), the free acid (16%), and an unidentified component.

Milk, containing 1.35 ppm equivalents of fenoxaprop-ethyl, could not be analyzed directly by TLC or HPLC. It was necessary to extract milk exhaustively with organic solvents and to subject the resultant aqueous phase to prolonged acid hydrolysis to release radioactivity amenable to chromatography. After these procedures, it was determined that 34% of the recoverable radioactivity was parent (0.46 ppm), 8.6% was the free acid of fenoxaprop-ethyl (0.12

ppm), 7.4% was 6-chloro-2,3-dihydro-benzoxazol-2-one ((0.1 ppm), and 19% was 5-hydroxy-6-chloro-2,3-dihydro-benzoxazol-2-one (substituted benzoxazolone) (0.25 ppm). Of the 31% unidentified radioactivity, 11% was reported as workup losses.

In kidney extracts the free acid of fenoxaprop-ethyl accounted for 75% of the total recoverable radioactivity with 7.7% as the substituted benzoxazolone. Thirteen percent of the radioactivity in kidney tissue was not identified and 4% was reported as workup loss.

In liver a total of 34.2% of the TRR could be identified. All of this radioactivity was associated with the intact benzoxazolone moiety after acid hydrolysis and was reported as 18% free acid and 16% substituted benzoxazolone. Workup losses were reported as 11% and 55% of the TRR was unidentifiable.

In muscle a total of 34.52% of the TRR could be identified, all of which was associated with the intact benzoxazolone moiety. The free acid and the substituted benzoxazolone were reported as 26% and 9% of the identified radioactivity, respectively. Workup losses were 10% and 55% of the TRR was not identified.

In fat a total of 27% of the TRR was identified; 15% was reported as the free acid of fenoxaprop-ethyl and 12% as the substituted benzoxazolone.

The petitioner concludes that the majority (52%) of administered fenoxaprop-ethyl was excreted as unchanged parent. Parent did not accumulate in muscle, fat, kidney, or liver and was not excreted in urine. The free acid of fenoxaprop-ethyl was a major component in all tissue extracts while 6-chloro-2,3-dihydrobenzoxazol-2-one was a minor constituent.

Comment

The petitioner's study of the animal metabolism of fenoxaprop-ethyl indicates the major metabolites expected in milk and tissues are the parent, the free acid of fenoxaprop-ethyl, and 6-chloro-2,3-dihydrobenzoxazol-2-one. The parent and these metabolites are included in the proposed tolerance for wheat and are determined by the proposed analytical method.

While there are significant unidentified residues in all tissues and milk, except kidney, the expected low livestock exposure from the residues in wheat grain and straw (see discussion of meat and milk residues under deficiency 7a below) permits our accepting the ruminant metabolism study for the proposed use only. This acceptance is predicated on the petitioner identifying the site of the radiolabel used in the goat metabolism study.

Therefore, we can conclude that the nature of the residue in ruminants and hogs is adequately understood for this proposed use on wheat only. The residues of concern are the parent compound, its metabolite, fenoxaprop, [2-(4-(6-chloro-2-benzoxazolyloxy)-phenoxy)-propionic acid], and 6-chloro-2,3-dihydrobenzoxazol-2-one. The unidentified residues must be characterized for any future tolerance request for uses on potential livestock feeds which could lead to higher livestock exposure. In any future metabolic studies, both rings should be labeled.

We reiterated the conclusion made by M. Bradely in her memo of 5/20/88 in regard to PP#8F3599 that a metabolism study in poultry is not needed at this time as no detectable residues are expected in the poultry feed item, wheat grain.

We conclude that this deficiency has been resolved.

Deficiency 6e.

> The residue data are inadequate to determine the residue levels on wheat grain and straw at 60 days PHI. At 70 days PHI, residues in wheat grain are not expected to exceed the proposed 0.05 ppm tolerance while residues in wheat straw would probably not exceed 1 ppm.
>
> The petitioner should propose a 1 ppm tolerance on wheat straw and a 70 day PHI for use on wheat or submit additional residue data for wheat grain and straw for the crop sampled at 60 days PHI.

Response

In response the petitioner has proposed a 0.5 ppm tolerance on wheat straw and has deleted reference to a fixed PHI from its revised label.

In the field trials on wheat supporting this petition, the highest residue level found on straw at the proposed label rate was 0.36 ppm at 70 days PHI. The petitioner has rounded up this value to 0.5 ppm and has proposed this value as the tolerance.

Instead of a specific PHI, the revised label carries instructions for application at a specific growth stage (after wheat begins to tiller, at the 4-5 leaf stage equivalent to 1-2 tillers but prior to the beginning of jointing). Harvest would be at normal maturity, identified as the growth stage when kernels cannot be dented by pressure exerted by a fingernail. According to the literature regarding the growth stages of wheat, the interval between the end of tillering and maturity is the order of 60-70 days. The petition cites as precedent for this type of label instruction recent labels for wheat herbicides (Assert, Finesse, etc.) that do not have numerical PHI's but rely upon the growth

stage of the cereal grain for the timing of application and harvest.

Comment

In principle, DEB has no objection to label instructions for cereal grain herbicides that have application times related to plant growth stages. However, the residue field trials should be conducted under this timing and reported as such.

The residue data supplied to support this petition gives the time of application as days prior to harvest. These PHI's are in the range of 62 to 73 days. This is generally the accepted time for the interval of time between the end of tillering and the beginning of jointing. To validate this assumption the petitioner should review the data for its wheat residue field trials so as to determine the growth stage of the wheat when the herbicide was applied. The petitioner can resubmit the data in terms of growth stages rather than PHI's. Such a submission would support the label instructions of the revised label.

Alternatively, the petitioner can submit a revised Section B that includes both a 70 day PHI and growth-stage information for all varieties of wheat grown under all US cultural conditions so as to indicate the range of time that could elapse between application as per the label instructions and harvest.

Until such data is submitted we cannot be certain that the proposed tolerance of 0.5 ppm for straw will be sufficient to encompass the minimum interval from application to harvest. The maximum residue value (0.36 ppm) upon which the proposed tolerance of 0.5 ppm was based was obtained with a 70 days PHI. At present it remains only an assumption that the proposed tolerance would not be exceeded at a 60 day PHI.

We have no objection to a revised label that includes application times in terms of growth stages. However, the petitioner will need to relate the residue data previously submitted in terms of PHI's to wheat growth stages. When we are in possession of this additional information we can determine if the proposed tolerance of 0.5 ppm on wheat straw is adequate. Alternatively the petitioner can submit a revised Section B that includes a 70 day PHI.

Deficiency 6f.

Wheat should be treated at the highest practical exaggeration not to exceed 5X, and processed. If 2X is the highest practical exaggeration rate, less than the theoretical factor of 7x (14% bran and 14% shorts), no additional processing studies are needed and no food additive tolerance is needed.

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Response

The petitioner has submitted a study entitled " Determination of Fenoxaprop-ethyl and its Metabolites in Wheat Grain and Milled Products."

Fenoxaprop-ethyl formulated as Tiller herbicide was applied to wheat at the 50% late flag leaf stage. The application rate was 0.9 lbs AI/A which is 5 times the maximum proposed rate. Grain was harvested at maturity, 62 days after application. The frozen, stored grain was transported to Texas A and M 's research annex where, within 2 weeks of harvest, the grain was milled into fractions. Reserved, unprocessed grain and the milled fractions were frozen and transported to HRAV's analytical laboratories in Sommerville, NJ, for analyses of residues of toxicological concern, (parent and metabolites), using method HRAV-4.

No residues at or above the limit of detection (0.05 ppm) were found in the grain or any of the milled fractions, bran, shorts and germ, middlings, low grade flour, patent flour.

Comment

This processing study satisfies the deficiency.

The absence of detectable residues of fenoxaprop-ethyl in wheat milling fraction derived from grain treated at the 5X exaggerated rate precludes the need for food and feed additive tolerances.

Deficiency 7a.

> It is apparent that tolerances will be needed for meat and meat byproducts of cattle, horses, and sheep. The tolerance needed depends on the results of the requested characterization of residue in the large ruminant metabolism study and on the wheat straw tolerance level.

Response

The petitioner concludes that no tolerances for milk, meat, and MBYP will be needed, based on the following observations.

The dose used in the metabolism study cited above (response to deficiency 4b) was 268 times the tolerance residue proposed for wheat straw and 2680 times the level expected at a feeding rate of 10% straw in cattle diets. Extrapolating linearly from the exaggerated rates of the metabolism study to the expected residue in wheat straw results in calculated residues in all tissues and milk considerably below the limit of detection of the enforcement methodology.

The results of a cattle feeding study conducted at 4, 12, and 40 X the expected residue in diets derived from wheat at proposed tolerance levels indicate that no measurable residues of fenoxaprop-ethyl or its metabolites would occur in milk, meat, or MBYP.

Comment

To determine the need for tolerances for secondary residues in animal tissues, DEB relies upon long-term feeding studies and not upon short-term metabolic studies. In this instance, the petitioner has submitted a ruminant feeding study as a part of PP#8F3599.

In this study, lactating cattle were feed a 1:1 mixture of parent and 6-chloro-2,3-dihydrobenzoxazol-2-one. Calculations based upon theoretical livestock diets consisting of feedstuffs containing tolerance level amounts of fenoxaprop-ethyl showed that the maximum amount for lactating cattle would be 3 mg per animal per day based on a 600 kg bodyweight. Consequently animals were fed, as part of a normal ration, 3 mg of the parent and 3 mg of the substituted benzoxazolone for 28 days. Other groups of animals received 9 and 30 mg respectively. Milk was collected through out the feeding study; animal tissues were obtained at sacrifice 28 days after the study was initiated. Milk and tissues were analyzed by method AL 06/84 that converts residues to the common moiety of the substituted benzoxazolone. The limit of detection of this method is reported as 0.01 ppm.

The daily dose of 3 mg parent plus 3 mg 6-chloro-2,3-dihydrobenzoxazol-2-one did not result in any detectable residues in milk, kidney, or fat. In 1 of 3 liver samples 0.02 ppm was detected; in 1 of 9 muscle samples 0.02 ppm was detected.

At the 10X rate of feeding 22 of 72 milk samples had residues of from 0.01 to 0.03 ppm. At this feeding level, residues in kidney were 0.04 to 0.09 ppm (n=3), in liver 0.10 to 0.20 ppm (n=3), below the limit of detection in fat (n=9), and 0.01 ppm in 1 of 9 fat samples.

The 3 mg per animal rate is equivalent to 0.2 ppm based upon a daily consumption of 15 kg of feed on a dry weight basis. If wheat straw were the only component in the diet, the daily consumption would be 0.05 ppm (the tolerance level of 0.5 ppm at 10% of the diet). Thus the 1X feeding study was conducted at a rate 4 times that expected from the tolerance proposed for this RAC. Assuming a linear relationship between the amount fed and tissue residue levels, the results of the feeding study indicate that feeding 0.05 ppm would result in residues below the limit of detection.

DEB agrees that it is reasonable to conclude that no detectable residues of fenoxaprop-ethyl or its metabolites would occur in milk or tissues of animals fed fenoxaprop-ethyl treated wheat straw.

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However, the presence of residues in milk or tissues at all feeding rates in the feeding study demonstrates the potential for residues to transfer. Section 180.6(a)(2) regarding secondary residues applies in this situation.

The petitioner should propose tolerances at the limit of detection (0.01 ppm) for meat, meat by-products, and milk resulting from the use proposed in this petition. The petitioner will need to submit complete details including representative chromatograms of method Al 06/84 together with an independent validation. The Agency will need to conduct its own validation when the proposed enforcement methodology is received.

Note: We will also need a copy of the accountability study titled: "HOE 033171-14-C: Nature of Residues in Milk and Tissues of Cows after Dosing 50 mg/Cow/Day at Three Consecutive Days." Authored by K. Krenzler, E. Dorn and H. M. Kellner. Hoechst Internal Report Fo 337/85, A30492.

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