R.F.

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

APR 21 1989

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP7F3540. DPX-L5300 on Grain and Straw of Wheat and Barley. Letter and Submission Dated 12/5/88. DEB No. 4850, 4852, 4851. Mrs 40927201, 40927203

FROM: R. W. Cook, Chemist
Tolerance Petition Section I
DEB/HED (H7509C)

TO: L. Schnaubelt, Acting PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Toxicology Branch/Fungicide/Herbicide Support
Health Effects Division (H7509C)

THRU: Richard D. Schmitt, Acting Chief
DEB/HED (H7509C) Richard Schmitt

Summary of Deficiencies:

Deficiencies Outstanding

Magnitude of the Residue

The submitted residue data do not adequately reflect the proposed use, in that there are no residue data at the previously proposed 40-day preharvest interval (PHI). The petitioner's proposal to satisfy this deficiency by eliminating all expressions of PHI in terms of days after last application and substituting a growth stage is not practical.

The petitioner should either submit residue data reflecting the previously proposed 40-day PHI or propose a PHI in terms of days after last application which is adequately supported by submitted residue data. We suggest the petitioner consider a PHI of 45 days for both barley and wheat.

A revised Section B expressing PHI in terms of days is needed. The petitioner could leave the Zadoks codes on the label in parentheses after the numerical PHI expressed in days.

Nature of the Residue in Animals

Ruminant animal metabolism and feeding studies are required.

Conclusions:

1. The previous deficiencies regarding the method validation, multiresidue method protocols, and storage stability data are resolved or in abeyance at this time. It must be recognized that if other information comes to light, additional data in these areas may be required.

2. The Magnitude of the Residue in Processed Commodities deficiency is resolved by use of exaggerated field residue trials in lieu of actual residue data on grain fractions.

3. The deficiency regarding the proposed use and magnitude of the residues in barley and wheat is not resolved. The petitioner should consider the alternative as described above.

4. We can draw no conclusions regarding the nature and magnitude of the residue in animals until animal feeding and metabolism studies are submitted and reviewed.

5. Our DEB deferral to TOX Branch on whether plant metabolites need to be included in the tolerance for barley and wheat has been resolved. For the presently proposed uses, the tolerances on barley and wheat can be expressed in terms of parent compound only.

Recommendation

We recommend against the proposed tolerances based upon the unresolved deficiencies discussed above.

BACKGROUND

The petitioner's amendment is in response to the DEB review of 4/26/88.

DETAILED CONSIDERATIONS

Directions for Use

The petitioner has submitted revised labeling and use directions. Two changes in use directions are of interest. The PHI expressed in terms of days has been removed and the timing of the application related to crop stage and Zadoks scale. We have considered this change under Magnitude of the Residue and have concluded that it is not practical; the label should bear

specific instructions in terms of last application to harvest, expressed in days.

Secondly, the use directions now include instruction for "sequential treatment" whereby the application is split into two or more treatments, provided the total amount applied does not exceed the label-permitted maximum. The timing of the last application is not changed. We have no objection to this change.

Deficiency: Residue Analytical Methods

We withhold judgment on the adequacy of these analytical methods for residue data gathering and/or enforcement purposes pending completion of method validations by COB/BUD chemists, and receipt/review by DEB of the report from COB on the results of these validations.

Recovery data by the modified analytical method are needed.

Petitioner's Response: (Mrid40927203)

No response necessary regarding the method trials in EPA laboratories.

Comments and Conclusions

We note that the petitioner's Comment Summary (page 105) states that "The unrevised version is amply supported by recovery data." We note the term "amply supported" does not appear in our review.

In any case, the petitioner submits Section 6: Residue Analytical Method MRID No. 40927203 which provides additional information. Firstly, we stipulate the petitioner's references to AMR-481-87 are intended to be references to AMR-841-87 as contained in MRID No. 40245529 (see pages 105, 106, and 107). The petitioner reports that the main difference between unmodified method (AMR-337-85) and the revised method (AMR-337-85, Revision A) is the use of Zorbax®-Sil LC column in the first method and the "μ-Porasil" column in the second method. The petitioner points out that analysis information pages showed this information. We note that the analysis information sheets specify the name of the method without the "Revision A" designation, for both "Zorbax" and "μ-Porasil" methods. Thus, the analysis information sheets contain ambiguous information.

The petitioner presents a letter from one of the contractor laboratories indicating that the method used was, in fact, the revised method. Finally, the petitioner summarizes recovery data by crop and method; this recovery data table is attached.

It is concluded that adequate recovery data are now available for method AMR-337-85, Revision A.

Comparison of DPX-L5300 Recovery Data by Two Methods

Crop	Method	Range
Wheat grain	AMR-337-85, Rev. A	55-112%
Wheat grain	AMR-337-85	70-108%
Wheat straw	AMR-337-85, Rev. A	74-120%
Wheat Straw	AMR-337-85	70-110%
Barley grain	AMR-337-85, Rev. A	86-117%
Barley grain	AMR-337-85	76-110%
Barley straw	AMR-337-85, Rev. A	71-115%
Barley straw	AMR-337-85	70-118%

Deficiency: FDA Multiresidue Protocols

FDA multiresidue information via protocols I through IV must be submitted for DPX-L5300. Testing through these four protocols may be required for any additional metabolites of toxicological concern.

Petitioner's Response: (Mr.440927203)

The petitioner has submitted a report "Testing of DPX-L5300 through FDA Multi-Residue Protocols I - IV," DuPont Study AMR 875-87, Biospherics Study No. 87-003, Revision 1, by John Fomenko and Christine L. Olinger. The study indicates that DPX-L5300 will not be detected by Multiresidue Protocols I, II, III, or IV.

Comments and Conclusions

This deficiency is resolved. The study will be forwarded to FDA for their information. If FDA considers the report deficient in any aspect, they will inform EPA so that the petitioner can be notified of these additional requirements.

Deficiency: Proposed Tolerances

"We withhold judgment on the adequacy of the proposed tolerances pending completion of method validations by COB/BUD chemists and receipt/review by RCB of the report from COB on the results of these validations, and further, pending submission of adequate residue data for DPX-5300 in wheat and barley grain and straw (See Magnitude of the Residue below)."

Petitioner's Response

The petitioner does not respond to the first part of the deficiency regarding method trials in EPA labs. The method trial has been completed (see memoranda of 6/15/88 and 6/27/88). The method trial of Method AMR-337-85 Revision A: Determination of Residue of DPX-L5300 in Crops by Liquid Chromatography was considered successful and that the method is satisfactory for gathering of residue data and for enforcement purposes for DPX-L5300 in grain and straw of wheat and barley.

The petitioner responds to the second part of the deficiency by submitting a discussion of the Magnitude of the Residue (DuPont Report No. AMR-841-87 Supplement 1. 11/23/88). This supplement, with several subsections, will be discussed below. The resolution of this deficiency will be determined below.

Deficiency: Nature of the Residue in Plants

The petitioner should verify the accuracy of the reported value, 0.90 ppm of unknown phenyl-^{14}C in straw (Table 8, MRID No. 40245503). If this value is correct, additional plant metabolism studies will be required to identify these unknowns.

We defer to Toxicology Branch (TB) the question whether plant metabolites are of toxicological concern and whether they should be included in the tolerance expression. Further, we believe that metsulfuron methyl, a herbicide in its own right and a metabolite of Londax® should be included in the tolerance expression.

Petitioner's Response: (Mrid40927201)

The petitioner replies that the reported value of 0.90 ppm of unidentified ^{14}C residue is a typographical error and should read 0.09 ppm. Further, this 0.09 ppm consists of at least nine minor unidentified metabolites.

This response is adequate and additional plant metabolism studies are not being required at this time on the basis of this study. Pending TB concurrence that additional plant metabolites need not be regulated, we consider this portion of the deficiency resolved.

The petitioner argues that it is not necessary to include metsulfuron methyl in the tolerance expressions for the following reasons:

1. Residues of metsulfuron methyl were 0.01 ppm in wheat forage, not straw or grain for which tolerances are still being sought.

2. The residue of 0.01 ppm resulted from application rates of 4X normal application.

Comments and Conclusions

We have met with representatives of TOX Br. (Meeting 4/18/89, Roger Gardner and Ed Budd [TOX Br.] and R. Quick [DEB] to discuss whether metabolites should be included in the plant tolerance expression for DPX-L5300. Saccharin and sulfonamide metabolites need not be included in the tolerance. At this time, we will not include metsulfuron methyl in the tolerance expression. However, if detectable residues of metsulfuron methyl are found in raw agricultural commodities or food/feed items considered in future petitions, we would include those residues in the DPX-L5300 tolerance expression.

We further note the petitioner's correction to the table on page 13 of the review.

Deficiency: Nature of the Residue in Animals

In order to determine the need for a tolerance and the appropriate tolerance levels in animal tissues, animal metabolism and animal feeding studies are required. Apparent real detectable residues of DPX-L5300 are found in the animal feed item straw (from exaggerated application rates and at intervals greater than the proposed 40 day PHI). If TB concludes that there are additional compounds of toxicological concern, additional animal metabolism and animal feeding studies of such additional metabolites may be required.

Petitioner's Response (MRID 40927203)

The petitioner submits a response (Section 5: Animal Metabolism and Feeding Studies). There are two major points to the petitioner's views.

1. 40 CFR 180.6(a)(3) applies; that is, there is no reasonable expectation of finite residues in meat, milk, poultry, and eggs; and

2. No animal metabolism and animal feeding studies have been required for the DuPont product Harmony.

Comments and Conclusions

The second argument is not persuasive. The subject of the current petition is DPX-L5300, not Harmony Herbicide.

Additional material proposed by the petitioner in support of the first conclusion is the information that samples showing

detectable residues in straw came from exaggerated surfactant rates and from exaggerated application rates. As previously noted, straw samples with detectable residues were from wheat straw sampled at 56 to 74 days or barley straw at 69 days after last application, rather than the 40-day PHI as originally proposed. We also note that the ^{14}C metabolism studies showed ^{14}C residues in wheat straw at 63 days.

The petitioner, assuming 10 percent straw at 0.1 ppm in the cow's diet, estimates 150 µg/day dietary intake. Then, based upon excretory rates in rats (reported to be > 90%), the petitioner contends only a very small portion of the intake is available for concentration in milk. This assumption is not correct, since lactation is also considered excretion. Therefore, rather than considering only that residue remaining after urinary and fecal excretion, the entire dietary intake should be considered available for concentration in milk, and yielding about 0.01 ppm (equivalent to DPX-L5300) in milk, at the assumed 10 percent dietary intake level for straw. At a higher dietary intake of straw, the possible residue level in milk is correspondingly higher.

Based upon the several detectable residues from exaggerated rates, the ^{14}C study, and estimates of possible residues in milk, ruminant animal metabolism and feeding studies are required.

Deficiency: Magnitude of the Residue

We conclude that the submitted residue data for DPX-L5300 in wheat germ and straw and barley grain and straw are not sufficient to conclude that residues of DPX-L5300 will not exceed the proposed tolerances at the proposed 40 day PHI. Additional residue data reflecting the use as proposed, i.e., 40 day PHI, and adequate geographic representation are needed. Data should be from the same States as the existing data.

Petitioner's Response: (Mrd40927203)

The petitioner submits "Section 4: Growth Stages: Preharvest Interval." Included in this section are a number of arguments against submitting additional residue data.

1. Revised raw data tables which now include Zadoks growth stages for each field trial and summarized tables of Zadoks codes versus PHI.

2. A PHI of 40 days would probably result from rapid maturation caused by elevated temperatures. Studies conducted on other chemicals (not DPX-L5300) are reported to show increased metabolism due to increased temperature.

3. Weed pest growth stages, as described in the proposed use directions, are reported in other studies to correlate well with certain Zadoks growth stage codes.

Based upon these arguments, the petitioner is now proposing to eliminate any reference of application timing to PHI and substitute application timing based upon Zadoks growth stage codes. Thus, the petitioner contends the field residue data adequately reflect the use directions.

Comments and Conclusions

We have reexamined the previously submitted forms titled "Data on Residue Samples" (AMR-841-87) which apparently contain the pertinent field information such as location, crop, application dates, harvest dates, application rates, rainfall, etc., for all the submitted residue studies. We note that the line titled "Growth Stage at Application" does not mention any Zadoks codes in any of 59 studies, unless the expression CER is related to the Zadoks codes. Only 14 of 59 studies contain the expression "CER," while the remainder are blank (5) or contain numerous descriptive terms including "4-5 leaf," "begin tillering," "3-tillers," "2 node," "late jointing," and "2nd node elongated," among other expressions. Thus it appears that the reported Zadoks codes were not made in the field at the timing of application, but are in fact estimates or interpretations of the above-listed expressions. Such estimates or interpretations merely illustrate the difficulty of determining application timing as related to Zadoks growth stages, and to the PHI thereafter. We conclude that the petitioner's proposal to eliminate the expression of PHI in terms of days is not practical. As a practical matter, a wheat grower will keep field records in terms of application dates and harvest dates. Therefore, the use directions will include the prescribed PHI expressed in terms of days after last application, and if desired by the petitioner, an expression relating to Zadoks growth stage codes.

After considering the petitioner's arguments, we again conclude that the submitted residue data do not reflect the proposed use in regard to the proposed 40-day PHI. The petitioner should be advised to either submit, as previously requested, residue data reflecting the proposed use including the 40 day PHI, or alternatively, propose use directions including a PHI in terms of specific days between last application and harvest which are adequately supported by the previously submitted residue data.

This alternate entails submission of an appropriate Section B. We note the "Revised Express Labeling" in the "administrative / response document" does not specify an adequate PHI interval in terms of calendar days, and hence is not adequate. The

petitioner must resubmit labeling defining a specific PHI expressed in terms of days.

We suggest the petitioner consider a 45-day PHI for both wheat and barley. The Zadoks code could be parenthetically included after the numerical PHI.

Deficiency: Magnitude of the Residue in Processed Commodities

A processing study using samples treated with the "highest practical exaggeration rate" should be conducted and the results submitted for review. Residue data should be submitted for wheat bran, flour, middlings, and shorts, and for barley hulls, bran, flour, and pearl barley. Appropriate food/feed additive tolerances should be proposed for wheat milling fractions and barley milling fractions, if needed.

Petitioner's Response: (Mrid40927203)

The petitioner argues that several factors indicate that the studies are not required:

The wheat metabolism study showed no grain residues at 63 days from 4X application;

Field residue data showed no grain residues at PHIs of 42 to 90 days;

Exaggerated rates greater than 4X in spring wheat and 7X in winter barley and winter wheat cause significant crop damage; and

Grain milling fractions are not likely to contain DPX-L5300.

The petitioner has tabulated information about grain fractions:

Fraction	Weight % of Original Grain
Wheat flour	71
Wheat bran	13
Wheat shorts	16
Wheat (durum) middlings or semolina	69
Barley flour	47
Barley hulls	12
Barley bran	5
Pearl barley	58

Grain fractions in terms of concentration factors (CF):

Fraction	CF
Wheat flour	1.4
Wheat bran	7.7
Wheat shorts	6.3
Middlings	1.4
Barley flour	2.1
Barley hulls	8.3
Barley bran	20
Pearl barley	1.7

Thus, assuming wheat or barley grain residues at the proposed tolerance levels of 0.05 ppm, theoretical concentrations of DPX-L5300 could reach:

Fraction	CF		Tolerance		Total ppm
Wheat flour	1.4	x	0.05	=	0.07
Wheat bran	7.7	x	0.05	=	0.38
Wheat shorts	6.3	x	0.05	=	0.31
Middlings	1.4	x	0.05	=	0.07
Barley flour	2.1	x	0.05	=	0.10
Barley hulls	8.3	x	0.05	=	0.41
Barley bran	20	x	0.05	=	1.0
Pearl barley	1.7	x	0.05	=	0.08

The petitioner remarks about the draft guidance from carbendazim; he should be aware that portions of the draft guidance were quoted on page 27 of the subject review.

Comments and Conclusions

Based upon the current Branch guidance, the exaggerated rate field studies appear to suffice in lieu of an actual grain fraction residue study. This deficiency is resolved pursuant to current guidance.

Deficiency: Meat, Milk, Poultry, and Eggs

Since apparent real residues of DPX-L5300 have been found in straw (albeit from exaggerated application rates and longer PHIs than currently proposed), residue data for meat, milk, poultry, and eggs could be required.

Petitioner's Response: (M.1409273.03)

The petitioner's response is discussed above, under "Nature of the Residue in Animals."

Comments and Conclusions

Since detectable residues have occurred in the livestock feed item straw, we have determined that ruminant animal metabolism and animal feeding studies are required. In a similar manner, since grain samples have not shown detectable residues, we are placing poultry metabolism and poultry feeding study requirements in abeyance at this time. The detection of finite residues in poultry feed items will reimpose the need for poultry metabolism and poultry feeding studies.

Deficiency: Storage Stability Data

If additional metabolites of toxicological concern are regulated, storage stability data will be required.

Petitioner's Response: (M#440927203)

The petitioner responds that no storage studies will be conducted unless additional metabolites of toxicological significance are regulated.

Comments and Conclusions

The response is adequate at the current time. The petitioner should be aware that future changes in the nature of the residue may necessitate the need for additional storage stability data.

cc: RF,Circ,RCook,PP7F3540,DPX-L3500 Registration Standard File, TOX(RGardner),ISB/PMSD(EEldredge)
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KENCO Typing corrected 3/22/89:RWCook
Draft Corrections April 20, 1989.RWCook
Final Corrections April 21, 1989.RWCook