Shaughnessy No.: new chemical

Date Out of EAB: 15 MAY 1984

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Attached, please find the EAB review of...

Reg./File # : 352-EUP-RRI

Chemical Name: DPX H6573

Type Product : Fungicide

Product Name : DuPont DPX H6573 FUNGICIDE

Company Name : DuPont

Purpose : New Chemical: EUP use on Peanuts

ZBB Code : other

Action Code(s): 700

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Deferrals to:

x Ecological Effects Branch

x Residue Chemistry Branch

____ Toxicology Branch

1.0 INTRODUCTION

This is the first action from DuPont for its new fungicide DPX-H6573 (hereinafter DPX). The registrant has submitted data in Accession 252481, to support a proposed EUP use on peanuts.

2.0 STRUCTURE

A copy of the technical data sheets is appended to this review.

3.0 DIRECTIONS FOR USE

A copy of the proposed EUP labelling is appended to this review. In brief, the product is to be applied as an emulsifiable concentrate containing 40% ai, at a rate of 1.75 to 4.8 fluid ounces (0.73 to 2.0 oz. ai) per acre, by either air or ground equipment.

Reapplications may be made at 14 to 21 day intervals, as needed.

The label prohibits application within 14 days of harvest, rotating any crop other than peanuts for 12 months following the last application, harvesting of treated crops and the grazing or feeding of forage or hay to livestock.

4.0 EXPERIMENTAL PROGRAM

A copy of the experimental program is appended to this review. In brief, the registrant proposes to apply a total of 7.2 kg ai to about 50 acres in three states (AL,FL and GA), to begin in late June-early July with 3 to 4 replicate applications at 2-3 week intervals. Applications will be at a rate pf 9.6 fl oz./A, twice the maximum rate.

The experimental program is to run for one year only.

5.0 REVIEW OF SUBMITTED DATA

Five studies have been submitted with Accession 252481, in support of the proposed terrestrial field crop use.

5.1 Neal, L.W. 1984. Octanol/Water Partition Coefficient of DPX H6573. Document AMR-157-83. (Company Confidential). Experimental Station. Agricultural Chemicals Department. E.I. DuPont de Nemours and Company. 6 pages, 1 table, 2 figures, 1 reference.

Introduction

In order to assess the potential for DPX to bioaccumulate, the K_{ow} was determined.

Experimental

Fully phenyl-ring-labeled ^{14}C DPX was synthesized, and found to have a specific activity of 21.2 uCi/mg with a radiochemical purity >99%. The N-octanol used was thoroughly extracted and distilled prior to use. Distilled deinized water was buffered to pH 7.

In six consecutive triplicate experiments, a 40 ppm solution of DPX was partitioned against an equal volume of buffered distilled water with vigorous hand and mechanical shaking, followed by centrifugation. Aliquots of N-octanol and buffer solution were taken for analysis by LSC counting.

Results and Discussion

Results from the six partitioning experiments are appended to this review (report table 1). Extracts were subjected to TLC separation, confirming that parent DPX was the only labeled component present. Average K_{ow} values were $5.55(\pm 0.45) \times 10^3$.

Conclusion

DPX-H6573 is in the intermediate range of bioaccumulation potential (K_{ow}'s of 10^2 to 10^6).

This study is acceptable.

5.2 Cadwgan, G.E., 1984. Hydrolysis of ^{14}C-Phenyl-Labeled and ^{14}C-Triazole-Labeled DPX-H6573. Document No. AMR-159-83. Experimental Station. Agricultural Chemicals Department. E.I. DuPont de Nemours & Co. 4 pages, 2 tables, 5 figures.

Introduction

The rate of hydrolysis of DPX was studied in sterile buffered solutions of pH 5, 7 and 9 at 25°C.

Experimental

Stock solutions of uniformly ^{14}C-Phenyl-Labeled DPX-H6573 (99% radiopure, 43.9 uCi/mg, 1.09 mg/ml acetone) and of Triazole-3-^{14}C-Labeled DPX-H6573 (99% radiopure, 36.5 uCi/mg, 1.34 mg/ml acetone) were prepared.

Duplicate 200 ml aliquots of pH 5, 7 and 9 buffers (specifications reviewed and found acceptable) were placed into 250 ml stoppered Erlenmeyer flasks and autoclaved 3 x 1 hrs. Aliquots of each standard were added to each respective set of 3 flasks, to a final concentration of approximately 1 ppm, followed by thorough mixing. All flasks were maintained at 25°C in the dark throughout the experimental period.

Samples were withdrawn at day 0, 6, 8, 12, 16, 23 and 34 from each flask after suitable mixing, mixed with an equal volume of unlabeled DPX-H6573 and subjected to LSC quantification. A duplicate aliquot was analyzed by reversed-phase HPLC to determine purity.

Results and Discussion

Both labeled compounds were found to be stable to hydrolysis at all pH values tested over the entire 34 day period. Recoveries approached 100% in all tests. HPLC peak was clean and well resolved.

Conclusion

DPX-H6573 does not appear to hydrolyze over the pH range 5-9.

This study was well done, and is acceptable in support of the Hydrolysis data requirement.

5.3 Chrzanowski, Robert L. 1984. Aerobic Soil Metabolism of ^{14}C-DPX-H6573. Document No. AMR-140-83. (Interim Report) Experimental Station. Agricultural Chemicals Department. E.I. DuPont de Nemours & Co. 6 pages, 10 tables, 7 figures, 2 references.

Introduction

The rates of metabolism of ^{14}C-Phenyl-Labeled and ^{14}C-Triazole-Labeled DPX-H6573 were determined under aerobic conditions using Woodstown sandy loam (Delaware) and Flanagan silt loam (Illinois) soils. The current submission is a 6 month interim report.

Experimental

Soils used in this study (characteristics summarized in report tables I and II, appended to this review) were seived to pass 2 mm, and 50 gm aliquotted into 80-250 ml biometer flasks. Of these, 24 flasks were subjected to 1 hour of autoclaving on each

of 3 successive days, and tightly capped to assure sterility. Analytical grade DPX was prepared identically to that used in the hydrolysis study reviewed in section 4.2. Stock solutions were prepared by dissolving 22.5 mg of both radiolabeled and unlabeled compounds respectively, in 12 ml methanol, then making them q.s. to 25 ml with distilled water.

Soils were treated as follows: For each compound, 28 ul of each radiolabeled stock solution were added to 14 unsterilized and 6 sterilized flasks (total of 80 flasks treated), which corresponds to an actual application rate of 2.14 oz ai/acre. All soils were immediately adjusted to 70% of normal moisture-holding capacity with sterile distilled deionized water. Sidearm traps consisted of 10 ml 0.1 N NaOH and phenolphthalein indicator. Each flask was then purged with O_2, stoppered, and placed in an incubator at 26°C, in the dark.

Side-arm trapping solution was taken for analysis (LSC) and replaced weekly. At that time, flasks were again purged with O_2 to assure aerobicity.

Soils were sampled in duplicate at weeks 0, 2, 4, 8, 16 and 24 (unsterilized flasks), and at weeks 0, 8 and 20 (sterilized flasks).

Soils were thoroughly extracted (3x) with ethyl acetate, centrifuged, then extracted (3x) with acetonitrile/water (50:50 v/v). Combined extracts were concentrated (rotevap) to 5 ml and analyzed by TLC with ethyl acetate/acetonitrile (80:20 v/v). Spots were counted on a Berthold automatic TLC analyzer. The R_f value of DPX was found to be 0.50 in this system, with polar compounds remaining origin-bound. Trace non-polar metabolites were found at R_f 0.75 to 0.85.

Results and Discussion

The distribution of metabolites in each of the soils tested is summarized in report tables VII-X, appended to this review. The first halflife was estimated by the authors to be 8 to 12 months, based on "extrapolation" from existing data. Origin-bound polar metabolites accounted for 2-7% of the total radioactivity at 8 weeks. Less than 1% of the parent compound was recovered as radio CO_2 after 24 weeks.

Conclusion

Apparently, DPX-H6573 is very resistent to degradation by microbes under aerobic conditions, having an "extrapolated" soil halflife in two soil types exceeding 8 months. Overall, material balance seemed very good.

Since no LSC was performed on individual spots, EAB is unsure of the accuracy of the Berthold automatic TLC analyzer quantification. In addition, the one-dimensional TLC chromatography did not appear to have adequately resolved the various components which may have been present. Finally, none of the possible degradates have yet been identified (although the author reports that this task is under way.)

Recommendation

Since this is only an interim report, EAB will assume that the deficiencies noted above will be resolved by subsequent submissions. It cannot be overemphasised that the identification of degradates and reasonable estimation of soil halflife must be done before this study can be accepted in support of the aerobic soil metabolism data requirement.

For purposes of this EUP, EAB will assume that DPX-H6573 is persistent in the soil with a half-life in excess of one year, and that major degradates become tightly bound to the soil where they are further degraded (rate unknown).

5.4 Harvey, John 1984. Crop Rotation Study with ^{14}C-DPX-H6573 in the Greenhouse Document No. AMR-165-83. (Interim Report) Experimental Station. Agricultural Chemicals Department. E.I. DuPont de Nemours & Co. 10 pages, 6 tables, 1 figures, 2 references.

Introduction

A confined (greenhouse) accumulation study in rotated crops was conducted, to estimate the potential accumulation of DPX-H6573 in a representative small grain (barley), leafy vegetable (cabbage) and root crop (beets).

Experimental

Uniformly phenyl-ring-labeled ^{14}C DPX-H6573 was synthesized and found to be >99% percent radiopure with a specific activity of 21.2 uCi/mg.

Soil used in the study (a Sassafras Sandy Loam - characteristics summarized in report table I, appended to this review) was added to 16" diameter red clay flower pots (calculated volume 0.021 M^3) and evenly treated with 60 ml of a stock solution (3.57 mg, 40.3 uCi) consisting of 41.7 mg of ^{14}C DPX-H6573 (490 uCi) in 60 ml acetone made q.s. to 700 ml with distilled water. This treatment rate was said to be equivalent to an actual application of 4.1 oz ai/A. Four pots were aged for 30 days and 4 others were aged for 120 days, prior to planting crops.

Four additional pots were treated at a rate of 3.5 oz ai/A (50 ml containing 3.0 mg, 33.6 uCi), then aged for 2 weeks and retreated at a rate of 4.2 oz ai/A (50 ml containing 3.71 mg, 44.7 uCi). These twice-treated pots were then aged 30 days prior to planting.

After the aging periods, a single pot in each group was seeded with barley (Custer), soybeans (Amsoy), beets (Early Wonder), and Cabbage (Market Pride - transplant not seed), respectively.

Soil samples were taken at intervals to crop maturity. Plant materials were sampled at 15 day intervals until maturity, from the 30th day.

Total soil radiolevels were determined by combustion to CO_2 followed by LSC quantification. Plant tissue samples with freeze-dried, then similarly combusted and LSC quantified.

Residues were characterized by multiple extraction in a blender with acetone:water (80:20 v/v), followed by concentration to 1/10 volume and reextraction with hexane. Aqueous and hexane fractions were LSC-counted separately. Radioactivity in insolubles was determined by air drying followed by combustion and LSC quantification.

Hexane and ethyl acetate extracts were analyzed by HPLC using Zorbax SIL stationary phase and hexane/propanol-2/methanol/acetic acid/water (750:125:125:2:1, v/v/v/v/v) mobil phase at 1 ml/min. and 30°C column temperature. Parent retention time was 5.8 min. Effluent was collected in on minute intervals prior to parent elution, then at 3 minute intervals following parent elution. Each subsample was counted by LSC.

Results and Discussion

The 3 treatment protocols evaluated were:

- single treatment + aging for 30 days
- single treatment + aging for 120 days
- 2 treatments @ 14 day interval + aging for 30 days

Treatments were approximately equivalent to application rates of 1/4 lb ai/A. Analysis of soil residues (estimated day 0 values of 0.1 ppm and 0.2 ppm for the single and double applications, respectively) exhibited some variability. However, based on the results of the aerobic metabolism study reviewed in §5.3 above, it is likely the variability resulted from inadequate sampling rather than degradation over the period of the study.

Total ^{14}C in each of the 4 crops tested the three intervals is summarized in report tables II and III, appended to this review. At maturity, residues were definitely present in all samples

analyzed, and ranged from <0.01 ppm (reported on a dry weight basis as parent DPX-H6573) in whole cabbage 45 days after planting, to 2.16 ppm in barley straw.

Extracts were fractionated, but no further attempt was made at identification.

Conclusion

Under all three conditions studied, DPX-H6573 appears to be taken up by all 4 both rotated crops tested. Significant radioresidues were found in barley straw.

This study cannot be accepted in support of the confined accumulation data requirement, due to numerous significant deficiencies. Since only a single experiment was conducted under each application condition, the reported data cannot be considered statistically significant. In addition, the no proof was provided for the sensitivity of the method of analysis used to quantify radioresidues. No attempt was made to identify metabolites. It is also not clear why whole samples were analyzed instead of edible vs. inedible portions (e.g. aerial vs. root components).

Additional deficiencies include failure to provide sample chromatograms, material balances and recovery efficiencies.

EAB will assume, for purposes of this EUP, that additional data is to be provided in subsequent reports, and that deficiencies noted above will be addressed by the registrant. Additionally, EAB assumes, due to the absence of tolerances for the various groups, and the likely presence of residues in edible portions of each commodity, that all crops grown under this EUP will be destroyed, and that the label will bear a suitable statement to that effect.

5.5 Hutton, D.G. and D.J. Kasprzak. 1984. Residue Study with ^{14}C-Phenyl-labeled DPX-H6573 in Bluegill Sunfish. Document No. AMR-171-83. Haskell Laboratory of Toxicology and Industrial Medicine E.I. DuPont de Nemours & Co. 7 pages, 7 tables, 16 figures. November 23, 1983.

Introduction

The degree and distribution of bioaccumulation of DPX-H6573 was measured in Bluegill Sunfish over a 28 day period.

Experimental

The experiment was conducted in 4 standard 57 liter rectangular glass aquaria. Well water was added to each tank and a recirculating system established to effect six volume turnovers per day.

Water temperature was maintained at 22.1±0.1 °C. A total of 176 bluegill (68 for each tank) were acclimated for >3 months prior to initiation of the study.

Fully phenyl-ring-labeled ^{14}C DPX-H6573 was added to two of the tanks, at final concentrations of 0.009 and 0.09 mg/L. The technical grade DPX used had a specific activity of 16.55 uCi/mg and a radiopurity of 95.8%. Throughout the uptake phase of the experiment, DPX-H6573 averaged 0.00919±0.00049 mg/L (338±18 DPM/mL) and 0.0920±0.0076 mg/L (336±28 DPM/mL) for the low and high concentrations, respectively. The third tank served as a dimethylformamide (solvent) control. The fourth tank served as a blank control.

Fish and water samples were taken on days 0, 1, 3, 7, 14, 21 and 28, with 10 additional fish being taken on day 28 for metabolite identification. Remaining fish were then transferred to two clean aquaria for the 14 day depuration, during which time samples were taken on days 1, 3, 7, 10 and 14. Throughout the study, only one fish died.

Water samples were analyzed by LSC counting. Fish were carefully dissected into muscle, liver and viscera and subjected to combustion and LSC quantification. Whole carcasses were homogenized, digested and counted by LSC.

Specific residues were isolated by dissection, lyophylization and multiple solvent extraction. Aliquots of extracts were LSC counted, and TLC chromatographed against known standards. Some of the origin-bound residues were scraped from the plate and subjected to enzymatic cleavage with beta-glucuronidase, concentrated via a Bond-Elut® C-18 adsorbent column, then quantified by TLC. Remaining unextractables were quantified by LSC counting.

Resulting data were further processed to eliminate those (few) points which were found to exceed the mean by more than 3 standard deviations. A total of 13 values (of 768) were thus eliminated from the data set.

Results and Discussion

Bioconcentration factors for all components analyzed are summarized in report table I, appended to this review. Average whole body levels peaked on day 14, at 250x and 160x for the low and high doses, respectively. Maximum accumulation was seen in liver (8500x, low dose) and viscera (2700x, low dose). Depuration was fairly rapid, with day 14 values low but not nil. Residue identification is summarized in report tables VI and VII, appended. Some identification was possible, and hydroxycompounds "A" and "B" were noted (see structures in report figure 3, appended). Overall material balance (recoveries) were about 90%.

Conclusion

This study was very well done. DPX H6573 has a moderate tendency to bioaccumulate in bluegill sunfish, but depuration occurs rapidly to low but measurable levels upon removal of the fish to uncontaminated environments.

This study is acceptable in support of the accumulation in fish data requirement.

6.0 EXECUTIVE SUMMARY

Proposed Label: Appears to be reasonably complete, although the crop destruct clause might be more strongly worded.

Experimental Program: Adequately delineates the proposed course of the study.

Octanol/Water Partition Coefficient: The K_{ow} was found to be 55000. This study was well done, and is acceptable.

Hydrolysis: DPX H6573 was found to be refractory to hydrolysis over the pH range of 5-9. The study was well done, and is acceptable.

Aerobic Soil Metabolism: DPX H6573 was found to be refractory to degradation in the soil, with a projected half-life in excess of one year. As submitted, this interim report contains numerous deficiencies, and is incomplete. Possible degradates have not been identified. EAB anticipates the submission of additional data from this registrant to clarify outstanding questions.

Accumulation in Rotated Crops (Confined Study): Evaluation of representatives of the leafy vegetable, small grain and root crops suggests that residues may be expected at all planting intervals. As submitted, this interim report contains numerous deficiencies, and is incomplete. EAB anticipates the submission of additional data from this registrant to clarify outstanding questions.

Accumulation in Fish: DPX H6573 tends to accumulate in bluegill sunfish, with maximum bioconcentration found in viscera and liver. Depuration appears to return body levels to low but measurable amounts. This study is acceptable in support of the accumulation in fish data requirement.

7.0 CONCLUSIONS and RECOMMENDATIONS

Due to the apparently limited amount of active ingredient to be used in this EUP, EAB will concur with a one-year program only. We anticipate that the issues raised in this review, as well as additional data requirements, will be satisfactorily addressed over the next 12 months, or at least prior to any additional EUP requests for this product.

In addition to those issues raised in this review, EAB has the following specific concerns:

- The apparent long halflife of DPX H6573 in soil may result in increasing soil levels from season to season, thereby increasing the environmental burdon. This factor should be monitored closely by the registrant.

- DPX H6573 tends to accumulate in fish. Extreme care must be taken in preventing movement of this product from the treated field to nearby ponds and waterways.

- The presence of significant residues in the major food groups necessitates that all crop materials be destroyed at the conclusion of the study. In addition, treated areas may not be planted to any other crops.

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May 15, 1984