DATA EVALUATION RECORD

STUDY 1

CHEM 129112 Trifloxystrobin §161-1
CAS No. 141517-21-7
FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 44496727
Cohen, S. P. 1997. Photodegradation of [phenyl(A)-U-^{14}C]-CGA-279202 in an aqueous buffered solution under artificial sunlight and hydrolysis in pH 5, 7 and 9 buffered solutions. PERL Study No.: ME 9600199. Novartis Study No.: 273-96. Unpublished study performed by Pittsburgh Environmental Research Laboratory, Inc., Pittsburgh, PA; and submitted by Novartis Crop Protection, Inc., Greensboro, NC.

DIRECT REVIEW TIME = 27 Hours

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CONCLUSIONS

Degradation - Hydrolysis

1. This study is scientifically valid and provides useful information on the hydrolysis of trifloxystrobin.

2. This study meets Subdivision N Guidelines for the fulfillment of EPA data requirements on hydrolysis.

3. Uniformly phenyl ring-labeled [^{14}C]trifloxystrobin, at a nominal concentration of 0.3 μg/mL, was hydrolytically stable in pH 5 sterile aqueous buffer solution and hydrolyzed with registrant-calculated half-lives of 55.2 days ($r^2 = 0.98$) and 19.8 hours ($r^2 = 0.96$) in pH 7 and pH 9 sterile aqueous buffer solutions incubated in darkness at 25 ± 1 °C for up to 30 days. Data reported are the means of two replicates. In the pH 5 buffer solution, the parent was present at 89.6% of the applied radioactivity at 30 days posttreatment; no degradates were detected. In the pH 7 buffer solution, the parent was initially present at 97.2% of the applied radioactivity and decreased to 66.9% by 30 days posttreatment. The major degradate CGA-321113 was initially (7 days) present at 8.9% of the applied and was a maximum of 29.2% at 30 days posttreatment. In the pH 9 buffer solution, the parent was initially present at 100.0% of the applied radioactivity, decreased to 44.6% by 15 hours, and was last detected at 18.2% at 48 hours posttreatment. The major degradate CGA-321113 was initially (8 hours) present at 19.7% of the applied and was a maximum of 103.6% at 720 hours posttreatment.

METHODOLOGY

Uniformly phenyl ring-labeled [^{14}C]trifloxystrobin {CGA-279202; methyl (E,E)-alpha-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl] benzeneacetate; radiochemical purity 99.1%, specific activity 37.7 μCi/mg; p. 208}, dissolved in acetonitrile, was added to filter-sterilized (0.20 μm) 0.01 M pH 5 (acetate), pH 7 (phosphate), and pH 9 (borate) aqueous buffer solutions at a nominal concentration of 0.3 μg/mL (pp. 209-211). Aliquots of the treated buffer solutions were added to sterile, siliconized borosilicate glass vials equipped with screw tops and Teflon-lined rubber septa; solutions were incubated in darkness at 25 ± 1 °C. To trap volatiles, sterile, humidified air was drawn through the system and into an ethylene glycol and two 2 *N* KOH traps in series (p. 212; Figure 4, p. 250). The volatile trap solutions were collected for analysis and replaced with fresh trap solutions at each sampling interval. Duplicate samples were removed for analysis from the pH 5 test system at 0, 1, 2, 4, 8, 14, 21 and 30 days posttreatment; from the pH 7 test system at 0, 7, 14, 21 and 30 days posttreatment; and from the pH 9 test system at 0, 8, 15, 48, 360 and 720 hours posttreatment.

At each sampling interval, duplicate aliquots of each sample were analyzed for total radioactivity by LSC (p. 212); the limit of detection was approximately 0.002 ppm (p. 214). Samples were extracted by vortexing with ethyl acetate; the organic fraction was removed and the procedure was repeated twice. The extracts were combined, concentrated by rotary evaporation, and analyzed for total radioactivity by LSC. Aliquots of the concentrated extracts were analyzed by HPLC (Alltech Lichrosorb RP-18 column) using a mobile phase gradient of 0.1% aqueous formic acid:acetonitrile (100:0 to 35:65 to 0:100, v:v) with radioactive flow detection (Table II, p. 225); the limit of detection was approximately 0.012 ppm (p. 214). Eluent fractions were collected at one-minute intervals and analyzed by LSC (p. 213). Samples were co-chromatographed with nonradiolabeled reference standards which were visualized with UV (250 nm) light. To confirm compound identities, samples were analyzed by two-dimensional TLC on silica gel plates developed perpendicularly with toluene:chloroform:ethyl ether:formic acid (60:34:5:1, v:v:v:v) and toluene:ethyl acetate:acetic acid (70:30:1.5, v:v:v); areas of radioactivity on the plates were quantitated using radioimage scanning. Samples were co-chromatographed with nonradiolabeled reference standards which were visualized by UV (254 nm) detection. Selected concentrated extracts were also analyzed by TLC as described previously (p. 214). Radioactive areas were scrapped from the plate and analyzed for total radioactivity by LSC.

Triplicate aliquots of the volatile trapping solutions were analyzed for total radioactivity by LSC (p. 214).

To confirm the sterility of the test solutions throughout the incubation, test samples were analyzed for microbial growth using agar plates at selected sampling intervals (p. 210); plate counts were reported in Tables VII-IX (pp. 230-232).

DATA SUMMARY

Uniformly phenyl ring-labeled [^{14}C]trifloxystrobin (radiochemical purity 99.1%), at a nominal concentration of 0.3 μg/mL, was hydrolytically stable in pH 5 sterile aqueous buffer solution and hydrolyzed with registrant-calculated half-lives of 55.2 days (r^2 = 0.98) and 19.8 hours (r^2 = 0.96) in pH 7 and pH 9 sterile aqueous buffer solutions incubated in darkness at 25 ± 1 °C for up to 30 days (Figures 7-9; pp. 253-255; see Comment #1). Data reported are the means of two replicates. In the pH 5 buffer solution, the parent was present at 89.6% of the applied radioactivity at 30 days posttreatment; no degradates were detected (Table XIII, p. 236).

In the pH 7 aqueous buffer solution, the parent was initially present at 97.2% of the applied radioactivity and decreased to 66.9% of the applied by 30 days posttreatment (Table XV, p. 238; see Comment #9). The major degradate

(E, E)-alpha-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl] ethylidene]amino]oxy]methyl]benzeneacetic acid (CGA-321113)

was initially present at 8.9% of the applied radioactivity at 7 days posttreatment and increased to a maximum of 29.2% by 30 days posttreatment.

In the pH 9 aqueous buffer solution, the parent was initially present at 100.0% of the applied radioactivity, decreased to 44.6% of the applied by 15 hours, and was last detected at 18.2% at 48 hours posttreatment (Table XVII, p. 240). The major degradate

CGA-321113

was initially present at 19.7% of the applied radioactivity at 8 hours posttreatment, increased to 66.8% of the applied by 15 hours, and was 103.6% at 720 hours posttreatment.

Mean material balances for the pH 5 test systems were 99.7-107.8% of the applied radioactivity from 0 to 14 days posttreatment, decreased to 93.6% by 21 days, and were 90.1% at 30 days posttreatment (Table X, p. 233). Mean material balances for the pH 7 and pH 9 test systems were 96.7-100.0% and 96.4-112.9% of the applied radioactivity, respectively, with no clear pattern of loss throughout the incubation period (Tables XI-XII, pp. 234-235).

COMMENTS

1. The reported registrant-calculated half-life of uniformly phenyl ring-labeled [^{14}C]trifloxystrobin in pH 7 aqueous buffer solution was 55.2 days (p. 221). The half-life was estimated assuming the continuation of the apparent degradation pattern beyond the scope of the observed data. However, data which appear linear may become curvilinear with time and half-life estimates based on such data may be inaccurate.

2. A phosphate buffer system was utilized to study the test compound at pH 7 in water (p. 209); Subdivision N Guidelines recommend that borate or acetate buffers be utilized to minimize catalysis effects of the buffer.

3. Limits of detection were reported for LSC and HPLC analyses (p. 214); however, limits of quantitation were not. Both limits of detection and quantitation should be reported to allow the reviewer to evaluate the adequacy of the test method for the determination of the test compound and its degradate.

4. The study was conducted using uniformly phenyl ring-labeled [A-^{14}C]trifloxystrobin (Figure 1, p. 243). The compound contained a second phenyl ring structure which was

not radiolabeled. Data for an additional study utilizing the second ring may not be required.

5. The study author stated that due to poor extraction efficiency observed in the 48-hour sample (pH 9), 48-, 360- and 720-hour samples were diluted with acetonitrile and concentrated by rotary evaporation prior to HPLC analysis (p. 214).

6. The study author stated that no significant volatile formation occurred (p. 220). Total [^{14}C]volatiles accounted for 0.46%, 0.70% and 0.60% of the applied radioactivity in the pH 5, 7 and 9 buffer solutions, respectively.

7. The study author stated that variability in the levels of soluble radioactivity was observed in the test solutions and that this variability was partially due to the poor solubility of the test substance in aqueous solutions and its tendency to adsorb to the test vessels (p. 219). The aqueous solubility of the parent compound was approximately 0.6 mg/L at 20 °C (pH not reported; p. 13); solubility of the parent in the buffer solutions was not reported.

8. Mean material balances for the pH 5 test systems were 99.7-107.8% of the applied radioactivity from 0 to 14 days posttreatment, decreased to 93.6% by 21 days, and were 90.1% at 30 days posttreatment. The study author did not provide an explanation for the material loss.

9. The reviewer noted that the percentage of the applied data for the pH 7 test system were not based on the initial (day 0) mean recovery (0.260 ppm; Table XVI, p. 239). The study author erroneously stated in a footnote that the application rate for the pH 7 test system was 0.268 ppm (Table XV, p. 238). As a result, the initial (day 0) mean recovery was only 97.2% of the applied radioactivity. Percentage of the applied data should be based on an initial mean recovery of 100%. Because the data were not calculated based on the correct value for the initial concentration, the "percentage of the applied" data for each interval need to be recalculated using an initial concentration of 0.260 ppm.

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