DATA EVALUATION RECORD

STUDY 2

CHEM 129112 Trifloxystrobin §161-2
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 Unpublished study performed by Pittsburgh Environmental Research Laboratory, Inc., Pittsburgh, PA; and submitted by Novartis Crop Protection, Inc., Greensboro, NC.

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CONCLUSIONS

Degradation - Photodegradation in Water

1. This study is not scientifically valid and does not provide useful information on the photodegradation of trifloxystrobin in sterile pH 5 aqueous buffer solutions. Test solutions were prepared for irradiation in three separate groups (treated and placed in incubation on different days) which may have led to the observed variability in the data. For a valid study, all samples must be treated at the same time and incubated simultaneously.

2. This study does not meet Subdivision N Guidelines for the fulfillment of EPA data requirements on photodegradation in water for the following reasons:

   (i) the experimental method was inadequate;

   (ii) the patterns of formation and decline of the degradates were not adequately defined; and

   (iii) the artificial light source was not adequately compared with sunlight.

3. Uniformly phenyl ring-labeled [^{14}C]trifloxystrobin, at a nominal concentration of 0.3 ppm, degraded with a registrant-calculated half-life of 14.8 days ($r^2 = 0.64$) in sterile pH 5 aqueous buffer solution which was irradiated with a xenon arc lamp (12 hour light/dark cycle) and maintained at 25 ± 1°C for up to 30 days; test solutions were prepared in three separate groups which were treated and placed in incubation on three different days. However, the registrant-calculated half-life is questionable since the data were generated using three different sample sets with three different study initiation dates. The apparent half-life occurred between 1 and 2 days posttreatment based only on the data from the first set of samples incubated. In contrast, the parent compound was stable in the dark control solutions. Based on data from all samples, in the irradiated solutions, the parent compound was initially present at 93.9% of the applied radioactivity, decreased to 30.1% by 2 days, and was 17.5% at 30 days. In the dark control solutions, the parent compound was 89.6% of the applied radioactivity at 30 days posttreatment. In the irradiated solutions, the major degradate CGA-357261 was first detected at 26.1% of the applied radioactivity at 1 day posttreatment, was a maximum of 63.8% at 14 days, and was 48.0% at 30 days. The minor degradate CGA-357262 was a maximum of 9.1% of the applied radioactivity at 2 days posttreatment. The minor degradate CGA-321113 was detected once in the irradiated solutions at 9.1% of the applied (one of two replicates) at 21 days posttreatment. Total [^{14}C]volatiles accounted for a maximum of 7.0% and 0.46% of the applied radioactivity in the irradiated and dark control samples, respectively, at 30 days 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. 13}, dissolved in acetonitrile, was applied at a nominal concentration of 0.3 ppm to filter (0.2 µm) sterilized pH 5 (0.01 M acetate) aqueous buffer solution (p. 14). Test solutions were prepared for irradiation in three separate groups which were treated and placed in incubation on three different days (p. 16; Table IV, p. 34; see Comment #1). Samples prepared for irradiation were treated and placed in incubation on July 25 (0-, 1-, 2- and 21-day samples), August 8 (4-, 7- and 14-day samples), or September 9 (30-day samples); all dark control solutions were prepared and incubated on July 25 (Table V, p. 35). Solutions contained in sterile, silylated borosilicate glass vials equipped with screw tops and Teflon-lined rubber septa were incubated at 25 ± 1 °C in a recirculating refrigerated water bath (Figure 4, p. 52). Dark control solutions were treated with the parent compound and maintained under similar conditions (p. 15; Figure 5, p. 53). Temperature was monitored daily using a temperature probe inserted into a control vial placed in the water bath; temperature data were provided in Figures 9 and 10 (pp. 57, 58). 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. 17). Volatiles traps were collected for analysis and replaced with fresh traps at each sampling interval. For the day 30 irradiated samples, an additional 4 *N* H_2SO_4 volatile trap was added to the trapping system after 7 days of incubation. Samples were irradiated for up to 30 days on a 12-hour light/dark cycle using a xenon arc lamp equipped with a filter to remove wavelengths of <290 nm (p. 15). The mean light intensity of the lamp (measured at 280 nm, 365 nm, and 440 nm) was 2.7×10^{-2} W/cm^2 over the irradiation period (Table II, p. 32). A comparison graph (irradiance *vs.* wavelength) of artificial and natural light (unspecified location and time of year) was presented in Figure 6 (p. 54; see Comment #4). Duplicate samples of irradiated solutions were removed for analysis at 0, 1, 2, 4, 7, 14, 21, and 30 days posttreatment (p. 17); duplicate dark control solutions were removed for analysis at 0, 2, 4, 8, 14, 21, and 30 days posttreatment. Solution pH was measured at each sampling interval (p. 19).

At each sampling interval, duplicate aliquots of each sample were analyzed for total radioactivity by LSC (p. 19); the limit of detection was 0.002 ppm (p. 20). Samples were extracted three times by vortexing with ethyl acetate. The organic fraction was decanted, combined, concentrated, and analyzed for total radioactivity by LSC. The remaining aqueous fraction of selected extracts (days 21 and 30) was also analyzed by LSC. Aliquots of the concentrated extracts were analyzed by reverse-phase HPLC (Alltech Lichrosorb RP-18 column) using a mobile phase gradient of 0.1% aqueous formic acid:acetonitrile (100:0 to 35:65, v:v) with UV (250 nm) and radioactive flow detection (Table III, p. 33); the limit of detection was 0.012 ppm (p. 20). Selected post-extracted samples (day 30) were diluted with acetonitrile, concentrated, and analyzed by HPLC as described above. Samples were co-chromatographed with nonradiolabeled reference

standards. The extracts were further analyzed by two-dimensional TLC on silica gel plates developed sequentially in 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; p. 18); 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 using radiolabeled standards (p. 19). Radioactive areas on selected plates were scraped, mixed with water, and analyzed for total radioactivity by LSC.

Triplicate aliquots of the volatile trapping solutions were analyzed for total radioactivity by LSC (p. 19). At 30 days posttreatment, the additional volatile trap and volatile system tubing was extracted with acetonitrile (p. 17).

To confirm the sterility of the test solutions throughout the incubation, irradiated and dark control samples were analyzed for microbial growth using agar plates of selective media at selected sampling intervals (p. 16); data indicated that the test solutions were sterile (Tables VI-VII, pp. 36, 37). The pH of the irradiated and dark control solutions was 4.9-5.3 and 5.0-5.2, respectively, throughout the incubation period (Tables IV, V, pp. 34, 35).

DATA SUMMARY

Uniformly phenyl ring-labeled [^{14}C]trifloxystrobin (radiochemical purity 99.1%), at a nominal concentration of 0.3 ppm, degraded with a registrant-calculated half-life of 14.8 days ($r^2 = 0.64$) in sterile pH 5 aqueous buffer solution which was irradiated with a xenon arc lamp (12 hour light/dark cycle) and maintained at 25 ± 1 °C for up to 30 days (Figure 11, p. 59). However, the registrant-calculated half-life is questionable since the data were generated using three different sample sets with three different study initiation dates. The apparent half-life occurred between 1 and 2 days posttreatment based only on the data from the first set of samples incubated (July 25 treatment date). In contrast, the parent compound was stable in the dark control solutions (Figure 12, p. 60). Based on data from all samples, in the irradiated solutions, the parent compound was initially present at 93.9% of the applied radioactivity, decreased to 30.1% of the applied by 2 days, and was 17.5% of the applied at 30 days posttreatment (Table X, p. 40; see Comment #1). In the dark control solutions, the parent compound was 89.6% of the applied radioactivity at 30 days posttreatment (Table XII, p. 42). In the irradiated solutions, the major degradate

> methyl (Z,E)-alpha-(methoxyimino)-2-[[[[1-(3-(trifluoromethyl)phenyl] ethylidene]amino]oxy]methyl]benzeneacetate (CGA-357261)

was first detected at 26.1% of the applied radioactivity at 1 day posttreatment, increased with variability to a maximum of 63.8% of the applied by 14 days, and was 48.0% of the applied at 30 days posttreatment (see Comment #3). The minor degradate methyl (Z,Z)-

alpha-(methoxyimino)-2-[[[[1-(3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl] benzeneacetate (CGA-357262) was present at a maximum of 9.1% of the applied radioactivity at 2 days posttreatment and was 1.5% of the applied at 30 days posttreatment. The minor degradate methyl (E,E)-alpha-(methoxyimino)-2-[[[[1-(3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl] benzeneacetate acid (CGA-321113) was detected once in the irradiated solutions at 9.1% of the applied radioactivity (one of two replicates) at 21 days posttreatment. Total [^{14}C]volatiles accounted for 7.0% and 0.46% of the applied radioactivity in the irradiated and dark control samples, respectively, at 30 days posttreatment (Tables VIII, IX, pp. 38, 39; see Comment #5).

Material balances were 90.3%-105.4% and 90.1%-107.8% of the applied radioactivity for the irradiated and dark control samples, respectively (Table VIII, IX, pp. 38, 39).

COMMENTS

1. The experimental method was inadequate; the irradiated samples were not treated at the same time and incubated simultaneously. The samples were treated and placed in incubation on three separate days (July 25, August 8, and September 9). Good laboratory practice dictates that the test samples be treated with the same dosing solution and incubated simultaneously to ensure similar treatment rates and similar testing conditions. The reviewer notes that the data variability observed over time was likely a result of the use of three separate sample sets.

2. The registrant-calculated half-life (14.8 days) does not agree with the apparent half-life. The apparent half-life of the parent occurred between 1 and 2 days posttreatment based only on the data from the first set of samples incubated (July 25 treatment date); the parent compound, initially present at 93.9% of the applied radioactivity, decreased to 78.1% by 1 day and 30.1% by 2 days posttreatment, and was 18.2% of the applied by 21 days (Table X, p. 40). The registrant-calculated half-life is of questionable worth since the data were generated using test systems with three different study initiation dates. The registrant may need to recalculate the half-life of the parent based on the data generated from the July 25 study initiation date (0-, 1-, 2-, and 21-day sampling intervals).

3. The use of data from three different sample sets precluded the accurate determination of the patterns of formation and decline of the degradates, as demonstrated by the variability in the data over time. The reviewer could not determine if the major degradate CGA-357261 remained constant from 2 to 21 days posttreatment; data reported for 4-14 days posttreatment were from a different sample set. The major degradate CGA-357261 was present at 55.4% and 54.2% of the applied radioactivity at 2 and 21 days posttreatment, respectively (Table X, p. 40); CGA-357261 was a range of 47.1% to 63.8% of the applied from 4 to 14 days. In addition, the reviewer could not accurately assess the decline of the minor degradate CGA-357262 since it was sporadically detected from 4 to 14 days

posttreatment; CGA-357262 was a maximum of 9.1% of the applied at 2 days; was 0.0%, 7.5% and 0.0% at 4, 7, and 14 days, respectively; and was 5.0% of the applied at 21 days posttreatment.

4. The artificial light source was not adequately compared to natural sunlight. The of the natural sunlight was not reported. In addition, the date, location and intensity of the natural sunlight depicted in Figure 6 (p. 54) were not reported.

5. In the irradiated test solutions, total [^{14}C]volatiles were ≤2.3% of the applied radioactivity from 0 to 21 days posttreatment, and were then 7.0% of the applied at 30 days (Table VIII, p. 38). The reviewer noted that an additional volatile trap (4 *N* H_2SO_4) was added to trapping system of the day 30 sample and was not used at any other sampling interval (p. 17).

6. The material balance for the dark control samples decreased slightly throughout the incubation period (Table IX, p. 39). The reviewer notes that cumulative volatiles accounted for only 0.46% of the applied radioactivity at 30 days posttreatment. It is unclear whether the material balance losses may have been decreased by the use of additional traps such as that used with the 30-day irradiated sample. The study author did not explain the material balance loss, but did state that the volatile trap tubing for the dark control samples was not extracted for analysis.

7. The aqueous solubility of the parent compound was approximately 0.6 mg/L at 20°C (p. 13).

8. The parent compound contained a second phenyl ring structure which was not radiolabeled. An additional study with the second ring labeled may not be necessary because the total recovery of parent compound and degradates exceeded 90%, suggesting that no new degradates greater than 10% of the dose rate would likely be formed from the unlabeled ring.

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