DATA EVALUATION RECORD

STUDY 1

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CONCLUSIONS

Degradation - Photodegradation in Water

1. This study is scientifically valid and provides useful information on the photodegradation of difenoconazole in pH 7 aqueous buffer solutions. However, the registrant-calculated half-life is of questionable accuracy because >50% of the parent compound degraded during the interval in which the half live occurred. Additionally, although the analytical method appeared to be adequate for the analysis of samples collected up to the half-life (and, thus, for a determination of photodegradation of the parent), the method was inadequate for the characterization of residues at later sampling intervals. Also, replicate samples were not utilized at each sampling interval. Typically, a study is considered valid only if duplicate samples, at a minimum, are prepared and incubated at each sampling interval.

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 analytical method was inadequate for the separation and identification of all radioactivity;

   (ii) radioactivity comprising >10% of the applied radioactivity was isolated but not identified; and

   (iii) total light intensity was not reported.

3. Triazole ring-labeled [3,5-^{14}C]difenoconazole, at a nominal concentration of 1 ppm (actual concentration of 0.86 ppm), degraded with a registrant-calculated half-life of 6 days ($r^2 = 0.97$) in sterilized pH 7 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. However, the registrant-calculated half-life is of questionable accuracy because >50% of the parent compound degraded during the interval in which the half-life occurred. In contrast, the parent compound was relatively stable in the pH 7 dark control solutions. Reported data are reviewer-calculated means of duplicate aliquots. In the irradiated solutions, the parent compound was initially 98.3% of the applied radioactivity, decreased to 55.4% by 5 days, was 15.8-16.4% from 9 to 15 days posttreatment, and was 2.3% at 30 days. The major degradate CGA-71019 was initially (day 5) 9.2% of the applied radioactivity, was a maximum of 12.9% at 9 days posttreatment, and was 8.6-11.2% from 15 to 30 days. An unidentified major degradate (Unknown 2) was 4.0-5.6% of the applied radioactivity from 1 to 3 days posttreatment, was a maximum of 19.1% at 9 days, and was 3.9-6.1% from 22 to 30 days. An unidentified major degradate (Unknown 1) was initially (day 2) 6.6% of the applied radioactivity, was a maximum of 14.0% at 5 days posttreatment, and was 0.3% at 30 days. The minor degradates CGA-205375 and

CGA-205374 were present at ≤2.9% and ≤1.5% of the applied radioactivity, respectively, throughout the incubation period. Uncharacterized polar radioactivity was initially (day 2) 0.5% (one sample) of the applied radioactivity, increased to 13.5% by 5 days posttreatment, was 48.3% at 9 days, and was a maximum of 84.6% at 30 days. In the dark control solutions, the parent compound was present at 99.7-104.8% of the applied radioactivity from 0 to 22 days posttreatment, and decreased to 88.4% by 30 days. The minor degradate CGA-205374 was detected once, at 1.4% of the applied radioactivity at 5 days posttreatment.

METHODOLOGY

Triazole ring-labeled [3,5-^{14}C]difenoconazole {CGA-169374; 1((2-(2-chloro-4-(4-chlorophenoxy)phenyl)-4-methyl-1,3-dioxolan-2-yl)-1H-1,2,4-triazole; radiochemical purity 97.2%, specific activity 27.4 μCi/mg, pp. 13, 34; and radiochemical chemical purity 98.8%, specific activity 28.2 μCi/mg, p. 14; see Comment #9), dissolved in acetonitrile, was added at a nominal concentration of 1 ppm (actual concentration 0.86 ppm) to filter-sterilized (0.2 μm) pH 7 (NaH_2PO_4 mixed with K_2HPO_4; final molarity not specified) aqueous buffer solution (p. 14). The test solutions were placed in individual quartz test tubes, and the tubes were stoppered, placed in a photolysis unit, and maintained at 25 ± 1 °C using a ethylene glycol/water bath (p. 17; Figure 2, p. 68); temperature was monitored continuously using a computer monitoring system (p. 15). Dark control samples were prepared in auto-injector vials, wrapped in foil, and maintained under similar conditions. Volatiles were not trapped. 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; Tables II, IV, pp. 24, 26). The spectral distribution and light intensity were measured continuously throughout the incubation period. The light intensity reaching the samples was 3.3-4.6 x 10^5 W/cm^2 (p. 17); total light intensity for the duration of the study was not reported. Light intensity measured on a clear, sunny, summer day at Agrisearch Incorporated, Frederick, MD was approximately 3.0-3.6 x 10^{-5} W/cm^2 (p. 17); a graph of the data was not provided. A comparison graph of artificial light *vs.* global radiation was provided in Figure 5 (p. 38). Single samples of the irradiated solutions and dark controls were removed for analysis at 0, 1, 2, 5, 9, 15, 22, and 30 days posttreatment (p. 18; see Comment #2). Five additional bulk samples were prepared for degradate identification (p. 16). Bulk samples I and II were prepared at a nominal concentration of 1 ppm (actual concentrations of 0.94 ppm and 0.96 ppm, respectively) and irradiated on a 12-hour light/dark cycle for 9 days as previously described for the kinetic study (pp. 16, 17). Bulk samples III, IV, and V were prepared at a nominal concentration of 20 ppm (actual concentration of 19.82 ppm, 20.41 ppm, and 21.21 ppm, respectively). Bulk sample III was irradiated continuously for 108 hours (equivalent to nine 12-hour exposure days); Bulk sample IV was irradiated continuously for 360 hours (equivalent to 30 12-hour days); and Bulk sample V was irradiated continuously for 108 hours (equivalent to nine 12-hour exposure days).

At each sampling interval, duplicate aliquots of the irradiated and dark control solutions were analyzed for total radioactivity by LSC (p. 17); the limit of detection was 0.005 ppm (p. 20). Aliquots of the test solutions were analyzed by two-dimensional TLC using silica gel plates developed twice with acetonitrile followed by toluene:acetone (75:25, v:v; p. 19). Samples were co-chromatographed with nonradiolabeled reference standards of the parent and the following potential degradates: CGA-205374, CGA-205375, CGA-142856, CGA-71019, CGA-107069, CGA-160199, and GB-XLIII-42-1 (p. 14; Table VIII, p. 30; Figure 1, p. 34). Nonradiolabeled standards were visualized with UV light (254 nm) or iodine vapors. Areas of radioactivity on the TLC plates were located using radioimage scanning.

To separate the polar origin material, the TLC plates were developed again in the second dimension using acetonitrile:ammonium hydroxide:water (90:15:15, v:v:v). To confirm compound identities, selected samples (0, 5, 9, and 30 days) were analyzed by reverse-phase HPLC (Zorbax ODS column) using a mobile phase gradient of acetonitrile:water (50:50 to 75:25, v:v) with UV (254 nm) and radioactive flow detection (p. 27); the limit of detection was 0.005 ppm. Eluent fractions were collected at one-minute intervals and analyzed for total radioactivity by LSC. Samples were co-chromatographed with nonradiolabeled reference standards. To further confirm compound identities, bulk samples (with the exception of bulk II) were analyzed by two-dimensional TLC, as previously described.

The bulk samples were further analyzed in order to identify the degradate compounds (p. 19; see Comment #6). Bulk samples I-III were used to develop the experimental methods, while bulk samples IV and V were analyzed (Appendix D, p. 127). The bulk samples were extracted with chloroform; both the aqueous and organic phase extracts were analyzed by reverse-phase HPLC (Appendix D, p. 129; Figure 3, Appendix D, p. 143). The aqueous phase was further analyzed by TLC, HPLC, and HPLC/MS; the organic phase was further analyzed by HPLC/MS and NMR. Both polar and nonpolar compounds were isolated from bulk sample IV (Appendix D, p. 127). The parent compound was not detected. Four organic-soluble degradates, two aqueous soluble degradates, and the parent compound were identified in bulk sample IV (p. 22; see Comment #3); aqueous-soluble degradates (each <10% of the applied radioactivity) were isolated but not identified. The structures of the identified degradates are presented in Figure 1 (Appendix D, pp. 140, 141).

To monitor the sterility of the test solutions, irradiated and dark control samples were analyzed for bacterial growth using agar plates at each sampling interval (p. 16). The samples were reported to be sterile (p. 21); tabular data were not reported.

DATA SUMMARY

Triazole ring-labeled [3,5-^{14}C]difenoconazole (radiochemical purity 98.8%), at a nominal concentration of 1 ppm (actual concentration of 0.86 ppm), degraded with a registrant-calculated half-life of 6 days ($r^2 = 0.97$) in sterilized pH 7 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 (Table 10, p. 32; Figure 7, p. 40). However, the registrant-calculated half-life is of questionable accuracy because >50% of the parent compound degraded during the interval in which the half-life occurred (see Comment #1). In contrast, the parent compound was relatively stable in the pH 7 dark control solutions. Reported data are reviewer-calculated means of duplicate aliquots. In the irradiated solutions, the parent compound was initially present at 98.3% of the applied radioactivity, decreased to 55.4% of the applied by 5 days, was 15.8-16.4% of the applied from 9 to 15 days posttreatment, and was 2.3% of the applied at 30 days posttreatment (Table IX, p. 31). The major degradate

CGA-71019 (see Comment #8)

was initially (day 5) 9.2% of the applied radioactivity, was a maximum of 12.9% of the applied at 9 days posttreatment, and was 8.6-11.2% of the applied from 15 to 30 days posttreatment (Table IX, p. 31). The unidentified major degradate designated as

Unknown 2

was 4.0-5.6% of the applied radioactivity from 1 to 3 days posttreatment, was 9.9% of the applied at 5 days posttreatment, increased to a maximum of 19.1% of the applied by 9 days posttreatment, and was 3.9-6.1% of the applied from 22 to 30 days posttreatment. The unidentified major degradate designated as

Unknown 1

was initially (day 2) 6.6% of the applied radioactivity, increased to a maximum of 14.0% of the applied by 5 days posttreatment, was 2.5-2.6% of the applied from 9 to 15 days posttreatment, and was 0.3% of the applied at 30 days posttreatment. The minor degradates CGA-205375 and CGA-205374 were present at ≤2.9% and ≤1.5% of the applied radioactivity, respectively, throughout the incubation period. Uncharacterized polar radioactivity was initially (day 2) 0.5% (one sample) of the applied radioactivity, increased to 13.5% of the applied by 5 days posttreatment, was 48.3% of the applied at 9 days posttreatment, was 59.5% of the applied at 15 days posttreatment, and was a maximum of 84.6% of the applied at 30 days posttreatment (see Comment #3). In the dark control solutions, the parent compound was present at 99.7-104.8% of the applied radioactivity from 0 to 22 days posttreatment, and decreased to 88.4% of the applied by 30 days posttreatment. The minor degradate CGA-205374 was detected once, at 1.4% of

the applied radioactivity at 5 days posttreatment. Uncharacterized polar radioactivity was detected once, at 4.2% of the applied radioactivity at 30 days posttreatment.

Material balances (based on LSC analysis of individual replicates) were 96.4-105.9% and 92.6-104.8% of the applied radioactivity for the irradiated and dark control solutions, respectively (Table VI, p. 28; see Comment #7).

COMMENTS

1. The registrant-calculated half-life is of questionable accuracy because greater than 50% of the parent compound degraded during the interval in which the half-life occurred. The parent compound was 55.4% of the applied radioactivity at 5 days and decreased to 15.8% of the applied radioactivity by 9 days (reviewer-calculated means; Table IX, p. 31); however, the parent compound was 16.4% of the applied radioactivity at 15 days posttreatment, thus the reviewer was only able to conclude that the apparent half-life occurred between 5 and 15 days posttreatment. The use of replicate samples may have decreased the variability over time and allowed for a more accurate calculation of the half-life (also see Comment #2).

2. Duplicate samples were not utilized for each sampling interval. Instead, duplicate aliquots were removed from an individual sample at each sampling interval. The reviewer noted that ten samples were prepared for incubation and there were seven sampling intervals at which incubated samples were removed for analysis (p. 16, Table VI, p. 28). The reviewer could not determine if duplicate samples were removed at any of the seven intervals, or if the additional three samples were not used. Scientifically sound laboratory practice dictates that, at a minimum, duplicate samples should be prepared for each sampling interval and treatment.

3. The analytical method was inadequate for the separation and identification of all radioactivity. Uncharacterized polar radioactivity was 13.5-84.6% from 5 to 30 days posttreatment (Table IX, p. 31). However, based on the example TLC chromatographs provided, the majority of the uncharacterized polar radioactivity reported in the table is uncharacterized origin material (Figures 10-12, pp. 43-45). In an additional analysis to characterize [^{14}C]residues, bulk samples IV and V were further extracted, purified, and analyzed (Appendix D, pp. 127-132; also see Comment #6). Multiple organic and aqueous components were isolated; five organic-soluble components (parent and four new structures) and two aqueous-soluble components (CGA-145286 and CGA-107069) were identified (Appendix D, pp. 136-138; Figure 4, p. 144). Additional unidentified degradates, each accounting for <10% of the applied radioactivity, were isolated and described as aqueous-soluble compounds (Appendix D, p. 127). An attempt was made to correlate the results of the additional analysis with the results of the main study

(Appendix D, p. 138); however, it is not clear to the reviewer that the results of the two analyses actually correspond. Thus, the reviewer was unable to confirm that the uncharacterized polar radioactivity or the unidentified degradates (also see Comment #4) reported in the main study were characterized by the additional analyzes reported in Appendix D. Clarification by the registrant is necessary.

4. Two major degradates (designated as Unknowns 1 and 2) present in the irradiated samples at respective maximums of 14.0% (day 5) and 19.1% (day 9; reviewer-calculated means of duplicate aliquots; Table IX, p. 31) were not identified. Samples were further analyzed (Appendix D, pp. 119-169); however, due to the method of reporting, the reviewer was unable to determine if Unknowns 1 and 2 were the same compound as any of the degradates identified in the analysis reported in Appendix D. Subdivision N Guidelines require that all degradates present at ≥ 10% of the applied radioactivity be identified. Identification of major degradates is a critical element of the aqueous photolysis study. Failure to identify one (or more) significant degradates limits the understanding of the aqueous photolysis under actual use situations; hence, the environmental fate of the pesticide is unclear (US EPA *Pesticide Reregistration Rejection Rate Analysis*, EPA 738-R-93-010, 1993, p. 31).

5. The total intensity of the artificial light source was not reported. Subdivision N Guidelines require the determination of the total intensity of the artificial light source over the course of the study.

6. The further analysis of the bulk samples was performed by the study sponsor (CIBA-GEIGY, p. 19). The methods and results of these analyses were presented only in Appendix D (pp. 119-169), and were not included in the results section of the main text.

7. An unexplained material loss was observed in the dark control samples after 22 days posttreatment. Material balances (based on LSC analysis, prior to residue characterization) were 100.0-104.8% of the applied radioactivity from 0 to 22 days posttreatment, without a pattern of loss, but decreased to 92.6% of the applied by 30 days posttreatment. A similar decrease was observed in the parent compound over the same interval (Table IX, p. 31). The study author did not discuss this loss.

8. The study author did not provide the chemical name for the reference standards of the potential degradates. The chemical structures were reported in Figure 1 (p. 34). In future studies submitted to EPA, it is necessary that the complete chemical names and structures of the degradates be provided.

9. Two batches of radiolabeled parent compound were used in the study (pp. 13, 14). The initial batch (radiochemical purity 97.2%, specific activity 27.4 μCi/mg) was utilized in the test solutions used in the kinetic study samples and bulk samples I-IV (p. 16); the

second batch (radiochemical chemical purity 98.8, specific activity 28.2 μCi/mg) was utilized in the test solution used in bulk sample V.

10. The study author reported the temperature as 25 ± 1 °C; however, the reviewer noted that the temperature was variable over time at 23.9-26.9 °C throughout the study (Table I, p. 23).

11. The aqueous solubility of [^{14}C]difenoconazole at pH 7 was reported to be 3 ppm at 25 ± 1 °C (p. 13).

12. The parent compound contained other ring structures which were not radiolabeled.

13. The absorption spectrum of the pesticide was not reported.

14. The molarity of the pH 7 buffer solution used in the experiment was not reported.

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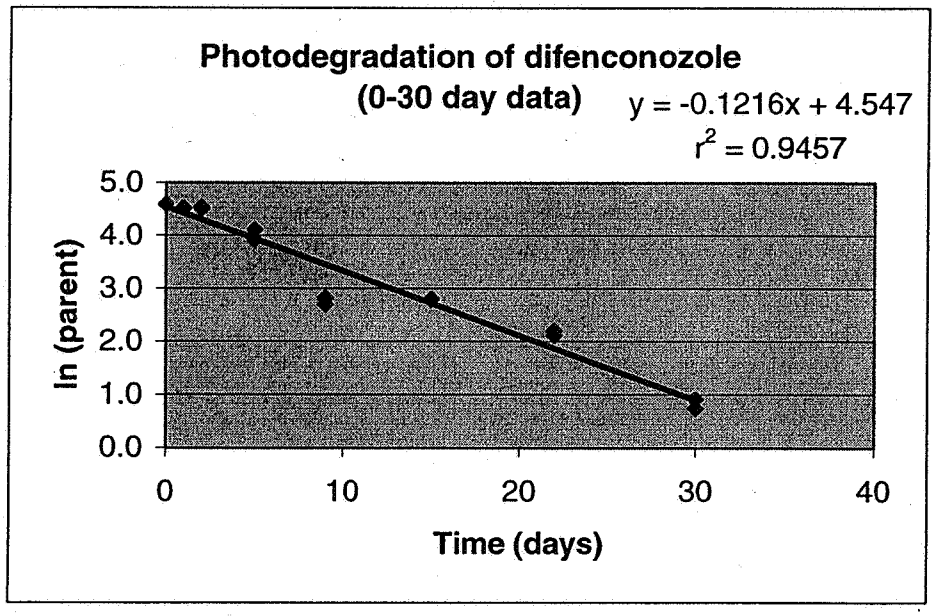
Difenoconazole #1 MRID 42245128 161-2

Time (days)	parent (%)	Ave. parent (ug/g)	Time (days)	ln parent
0	98.3	98.3	0	4.6
1	91.1		1	4.5
1	91.6	91.3	1	4.5
2	90.9		2	4.5
2	93.8	72.0	2	4.5
5	50.1		5	3.9
5	60.6	37.8	5	4.1
9	14.9		9	2.7
9	16.7	16.6	9	2.8
15	16.5		15	2.8
15	16.3	12.3	15	2.8
22	8.3		22	2.1
22	9.1	5.6	22	2.2
30	2.1		30	0.7
30	2.5	1.3	30	0.9



half-life= 5.7 days

RIN 0509-04

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Pages 10 through 19 are not included.

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