

DATA EVALUATION REPORT

AC 303,630 (PIRATE): Photodegradation in Water (161-2)
MRID 434928-46

CITATION: Mangels, G. 2 Dec 1994. AC 303,630: Photodegradation in water. Laboratory Project ID: E-92-14. American Cyanamid Report No. ENV 94-042. Unpublished study performed and submitted by American Cyanamid Company; P.O. Box 400; Princeton, NJ 08543-0400.

REVIEWER: Alex T. Clem, Environmental Scientist, CRS 3
EFGWB/EFED/OPP/OPPTS/USEPA

Alex Clem
9/30/96

CONCLUSIONS. *This study is acceptable and satisfies the data requirement. No additional information on the photodegradation of AC-303630 in water is required at this time. However, the registrant is advised to regard carefully the comment section of this report before submitting future studies.*

Phenyl ring- and pyrrole-labeled [^{14}C]AC-303630 [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile] photodegraded with calculated half-lives of 5.1-5.4, 6.9-8.1, and 4.8-4.9 days in sterile, aqueous pH 5, 7, and 9 buffer solutions, respectively, that were continuously irradiated for 30 days at 25°C using a filtered xenon arc lamp. The lamp had an emission spectrum comparable to natural sunlight and an initial intensity of 0.25 watts/m² at 340 nm; 24 hours of artificial irradiation appeared to be approximately equivalent to 1 day of sunlight in June. One degradate, 2-bromo-4-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-4-carbonitrile (CL-357806), was identified in the irradiated solutions; it was reported that "several" minor photodegradates were isolated, each < 10% of the applied. In the dark control solutions for both radiolabels, [^{14}C]AC-303630 did not degrade under similar incubation conditions.

METHODOLOGY

Phenyl ring-labeled [$\text{U-}^{14}\text{C}$]AC-303630 or pyrrole-labeled [$2\text{-}^{14}\text{C}$]AC-303630 [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile; radiochemical purities $\geq 97\%$; specific activities 53.39 and 56.53 uCi/mg, respectively; Moravek Biochemicals], dissolved in acetonitrile, was added at 0.065 ppm to 200 mL aliquots of filter-sterilized (0.22 μm) pH 5 (acetate; "0.6 mL of concentrated acetic acid to one liter of Millipore grade water"), 7 (0.007 M phosphate), or 9 (0.01 M borate) buffer solutions contained within sterile 250-mL Erlenmeyer flasks; the concentration of acetonitrile in the treated solutions was 0.5% by volume. The samples in the Erlenmeyer flasks were placed in a Ci-65 Weather-ometer photolysis chamber and irradiated continuously for 30 days using a borosilicate glass-filtered xenon arc lamp (Atlas Electric Devices Co.), which had an emission spectrum comparable to natural sunlight and an initial intensity of 0.25 watts/m² at 340 nm; 24 hours of artificial irradiation appeared to be approximately equivalent to 1 day of sunlight in June (Figure 1). The temperature of the photolysis chamber was maintained

at 25 ± 1 C. To serve as dark controls, additional buffer solutions contained in 16-ounce bottles were treated with phenyl ring- or pyrrole-labeled [^{14}C]AC-303630 as described; the bottles were wrapped in aluminum foil and placed in a constant temperature room maintained at 25 ± 1 C. Duplicate aliquots of all irradiated solutions were collected after 0, 1, 2, 3, 7, 14, 21/22, and 30 days posttreatment; duplicate aliquots of the irradiated pH 7 and 9 solutions were also collected after 4 (pH 7 only) and 8 hours, and 1.25 days. Duplicate aliquots of the dark control solutions were collected after 0, 7, 14, 21, and 30 days posttreatment. The pH of the solutions was measured at each sampling interval.

The samples were extracted twice with ethyl acetate, and aliquots of the extracted water and the ethyl acetate extracts were analyzed for total radioactivity using LSC. If an extracted water sample contained [^{14}C]residues at >0.004 ppm (approximately 7% of the applied), the extracted water sample was acidified (pH 3), then again extracted with ethyl acetate; aliquots of the acidified extracted water layer and the ethyl acetate extract were analyzed using LSC. The three ethyl acetate extracts from each sample were combined and concentrated to near dryness on an evaporator under a stream of nitrogen, and the resulting residues were redissolved in methanol:ethyl acetate (1:1, v:v).

Aliquots of the concentrated extract solutions were analyzed by normal-phase TLC on silica gel plates developed in hexane:ethyl acetate:acetic acid (100:50:0.75, v:v:v; TLC System 1) and on silica gel plates developed in toluene:hexane (2:1, v:v; TLC System 3). The pH 5 and 9 solutions were also analyzed by reverse-phase TLC on C-18 plates developed in methanol:water:acetic acid (150:50:0.5, v:v:v; TLC System 2). [^{14}C]Compounds on the plates were located using autoradiography and identified by comparison with unlabeled reference standards of AC-303630, CL-303268, CL-303793, CL-312094, CL-322116, CL-322118, CL-325008, CL-325157, CL-325195, and CL-357806, which were cochromatographed with the samples and visualized under UV light. Zones of radioactivity were scraped from the plates, mixed with water and liquid scintillation cocktail, and analyzed using LSC. Aliquots of the 30-day, pH 5 and 9 irradiated samples were also analyzed using reverse-phase HPLC on a Supelco ID LC-8-DB column eluted with acetonitrile:water:acetic acid (60:40:0.01; v:v:v); the column was equipped with UV (260 nm) and radiometric detection. The identities of the [^{14}C]compounds were confirmed by comparison with the retention times of unlabeled standards of AC-303630, CL-303268, CL-312094, and CL-325195.

In order to generate sufficient material to identify the major [^{14}C]degradate, analytical grade AC-303630 or [^{13}C]AC-303630:analytical grade AC-303630:phenyl ring- or pyrrole-labeled [^{14}C]AC-303630 (25:25:0.05, v:v:v) were dissolved at 10 ppm in water:acetonitrile (350:150 and 350:200, respectively; v:v) and irradiated as described for 31 days. After concentration and purification, the [^{14}C]compound of interest was analyzed using normal- and reverse-phase TLC, HPLC, NMR, and GC/MS.

DATA SUMMARY

Phenyl ring-labeled [$\text{U-}^{14}\text{C}$]AC-303630 or pyrrole-labeled [$2\text{-}^{14}\text{C}$]AC-303630 [4-bromo-2-(4-

chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile; radiochemical purities $\geq 97\%$], at 0.065 ppm, photodegraded with registrant-calculated half-lives of 5.1-5.4, 6.9-8.1, and 4.8-4.9 days in sterile, aqueous pH 5, 7, and 9 buffer solutions, respectively, that were continuously irradiated for 30 days at 25 ± 1 C using a filtered xenon arc lamp (Tables XIV-XIX). The lamp had an emission spectrum comparable to natural sunlight and an initial intensity of 0.25 watts/m² at 340 nm; 24 hours of artificial irradiation appeared to be approximately equivalent to 1 day of sunlight in June (Figure 1). One degradate,

2-bromo-4-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-4-carbonitrile (CL-357806),

was identified in the irradiated solutions. Several minor photodegradates were isolated, each at $< 10\%$ of the applied (refer to Appendices 7-12). In the dark control solutions for both label positions, [¹⁴C]AC-303630 did not degrade under similar incubation conditions.

In the pH 5 irradiated solutions for both label positions, [¹⁴C]AC-303630 was 97.3-98.8% of the applied immediately posttreatment, 57.2-67.6% at 2 days, 43.9-58.8% at 3 days, 13.6-36.7% at 7 days, and 1.0-4.0% at 30 days posttreatment (TLC System 1; Tables XIV and XV). CL-357806 increased to 54.8-68.4% of the applied at 21 days posttreatment, and was 50.4-56.2% at 30 days (Table XX). Uncharacterized [¹⁴C]residues remaining in the buffer solution after extraction totaled a maximum 5.9% of the applied in the solution treated with phenyl ring-labeled [¹⁴C]AC-303630 and 6.9% in the solution treated with pyrrole-labeled [¹⁴C]AC-303630 (Tables IIIb and IXb). For the solutions treated with phenyl ring-labeled [¹⁴C]AC-303630, the material balances were 89.4-107.2% of the applied through 21 days posttreatment with no pattern of decline, and 81.0-86.2% at 30 days (Table IIIb). For the solutions treated with pyrrole-labeled [¹⁴C]AC-303630, the material balances were 94.3-103.8% of the applied through 3 days posttreatment with no pattern of decline, and 90.9-95.0% at 7 through 30 days (Table IXb).

In the pH 7 irradiated solutions for both label positions, [¹⁴C]AC-303630 was 98.8-99.2% of the applied immediately posttreatment, 62.8-81.7% at 4 days, 43.2-63.7% at 7 days, 29.5-39.7% at 14 days, and 4.1-11.4% at 30 days (TLC System 1; Tables XVI and XVII). CL-357806 increased to 57.0-67.0% of the applied at 30 days posttreatment (Table XXI). Uncharacterized [¹⁴C]residues remaining in the buffer solution after extraction totaled a maximum 7.4% of the applied in the solution treated with phenyl ring-labeled [¹⁴C]AC-303630 and 7.2% in the solution treated with pyrrole-labeled [¹⁴C]AC-303630 (Tables Vb and XIb). For the solutions treated with phenyl ring-labeled [¹⁴C]AC-303630, the material balances were 85.0-109.2% of the applied through 3 days posttreatment with no pattern of decline, and 87.5-95.7% at 4 through 30 days (Table Vb). For the solutions treated with pyrrole-labeled [¹⁴C]AC-303630, the material balances were 95.0-113.0% of the applied through 30 days posttreatment with no pattern of decline (Table XIb).

In the pH 9 irradiated solutions for both label positions, [¹⁴C]AC-303630 was 97.3-97.9% of the applied immediately posttreatment, 54.8-66.9% at 4 days, 37.8-56.6% at 7 days, 11.9-22.4% at 14 days, and 1.1-1.7% at 30 days (TLC System 1; Tables XVIII and XIX). CL-357806 increased to 61.6-73.3% of the applied at 14 through 30 days posttreatment (Table XXII). Uncharacterized

[¹⁴C]residues remaining in the buffer solution after extraction totaled a maximum 11.1% of the applied in the solution treated with phenyl ring-labeled [¹⁴C]AC-303630 and 13.3% in the solution treated with pyrrole-labeled [¹⁴C]AC-303630 (Tables VIIb and XIIIb). For the solutions treated with phenyl ring-labeled [¹⁴C]AC-303630, the material balances were 95.3-103.2% of the applied through 30 days posttreatment with no pattern of decline (Table VIIb). For the solutions treated with pyrrole-labeled [¹⁴C]AC-303630, the material balances were 93.3-101.0% of the applied through 30 days posttreatment (Table XIIIb).

In the dark controls for all treatment combinations, [¹⁴C]AC-303630 was $\geq 97.6\%$ of the recovered at all sampling intervals (TLC System 1; refer to Appendices 7-12). During the study, material balances were 88.7-110.9% of the applied with no pattern of decline (Tables II, IV, VI, VIII, X, and XII).

COMMENTS

1. Tables XIV and XV, and Tables XVIII and XIX, in which the concentrations of the parent compound in solution and the data used for the linear regression calculations for the pH 5 and 9 irradiated buffer solutions are reported, contain incorrect and misleading information. The concentrations of parent as determined by both TLC Systems 1 and 2 are reported and averaged ("Average, % Purity" in data column 3). However, on page 17 of the text, the study author stated that TLC system 2 failed to separate the parent compound from the major degradate, so that the data were of little use. The reported effective parent concentrations (final column) in Tables XIV, XV, XVIII, and XIX reflect only the data from TLC System 1, not the data from TLC System 2 or the Average concentrations.

In addition, in Tables XVI and XVII, in which the concentrations of the parent compound in solution and the data used for the linear regression calculations for the pH 7 irradiated buffer solutions are reported, the concentrations of parent reported as being determined by TLC System 2 were, in fact, determined by TLC System 3. TLC System 3 did adequately separate the parent compound for the major degradate, and it is valid to average the data from TLC Systems 1 and 3. The pH 7 samples were not analyzed using TLC System 2. As with the pH 5 and 9 data tables, the reported effective parent concentrations (final column) reflect only the data from TLC System 1, not the data from TLC System 2 or the Average concentrations.

The concentrations of parent compound in the three buffer solutions as determined in TLC Systems 1, 2, and 3 are clearly detailed in Appendices 7-12.

2. The initial intensity of the xenon arc lamp was set at 0.25 watts/m² at 340 nm. This was reported to be comparable to mid-autumn sunlight in Princeton, New Jersey (Figure 1). Also, it was stated that "The samples were irradiated continuously over the course of the experiment, which approximates a single day irradiation during the summer" [page 12]. Based on the relative intensities diagramed in Figure 1, this was interpreted to mean that 1 day of artificial light was equivalent to 1 day of summer sunlight, not that 30 days of

continuous irradiation were equal to 1 day of summer sunlight. That this was indeed the case was verified by FAX (attached) from registrant representative Zareen Ahmed on 30 Sep 96.

3. In several cases, the concentration of [^{14}C]residues in the extract and extracted water fractions following acidification and extraction was significantly greater than the concentration of [^{14}C]residues remaining in the water prior to acidification. For example, 3.3-6.6% of the applied radioactivity remained in the ethyl acetate-extracted pH 5 solutions at 30 days posttreatment (phenyl ring-labeled [^{14}C]AC-303630, Table IIIb). When the extracted aqueous solutions were acidified and again extracted with ethyl acetate, the concentration of [^{14}C]residues in the extract was 3.3-3.9%, and the concentration of [^{14}C]residues remaining in the acidified water were 4.9-5.9% (total 8.2-9.8%).
4. The results of the study were not presented in a clear, concise fashion, and considerable time was required on the part of the reviewer to leaf through numerous tables and appendices to find information needed to critique the study. Many of the data tables were difficult to interpret, and data for a given set of samples were scattered throughout the 253-page document. In some tables, the source of the data was incorrectly identified and calculations were incorrect (refer to Comments 2 and 3). Often, there was no logical column-to-column progression within a table. The concentrations of parent compound and the major degradates were presented in different tables, and quantitative information about unidentified radioactivity (needed to determine if all compounds present at >10% of the applied were identified) was provided only in the appendices.
5. The molarity of the acetic acid used to make the pH 5 buffer solution was not specified. There was no evidence that "concentrated acetic acid" was, in fact, glacial acetic acid.
6. It was reported that no change in pH of the test solutions occurred during the course of the study; no data were provided to support this statement.
7. It was reported that the sterility of the test solutions was confirmed from sterility assays of the 0- and 30-day samples. No additional information was provided.
8. A diagram of the photolysis apparatus was not provided. An adsorption spectrum of AC-303630 in the buffer solutions was not provided.
9. The study author concluded that [^{14}C]CL-357806 is a regioisomer of AC-303630, and stated that the rearrangement involves a [2+2] cycloaddition, a 1,3-sigmatropic shift of the N-C2 bond, followed by a reverse [2+2]cycloaddition [page 19].
10. The solubility of AC-303630 in deionized water, and in pH 4, 7, and 10 buffers at 25 C was reported to be 0.12-0.14 mg/L.
11. Dynamac Corporation of Rockville, MD, provided the technical bulk of this report.

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Pages 6 through 37 are not included.

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- ☐ A draft product label.
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American Cyanamid Co. Agricultural Research Division, P.O. Box 400, Princeton, NJ 08543-0400

FAX

Date:

9/30/96

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To

Mr. Alex Clem

EFED

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CC:

From: U.S. Plant Federal Registrations

✓ Arthur, Jack (609)716-2214

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Overholt, Janet (609)716-2410

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REMARKS:

☐ Urgent☐ For your review☐ Reply ASAP☐ Please comment

Alex:

Enclosed are the answers to the questions you had regarding the study on the aqueous photolysis of Ac 303,630. Please call me if you have any further questions.

Sincerely, Zareen Ahmed

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Pages _____ through _____ are not included.

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- ☐ Identity of product impurities.
- ☐ Description of the product manufacturing process.
- ☐ Description of quality control procedures.
- ☐ Identity of the source of product ingredients.
- ☐ Sales or other commercial/financial information.
- ☐ A draft product label.
- ☐ The product confidential statement of formula.
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