DATA EVALUATION RECORD

STUDY 1

CHEM 122990 Mesotrione §161-1
CAS No. 104206-82-8
FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 44373529
Miles, P. D. and S. P. Powell. 1995. ZA1296: Aqueous hydrolysis in pH 4, 5, 7, and 9 solutions at 25°C and 50°C. Laboratory Project ID: 94JH098. Unpublished study performed by Zeneca Limited, Bracknell, UK; and submitted by Zeneca, Inc., Wilmington, DE.

DIRECT REVIEW TIME = 29 Hours

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CONCLUSIONS

Degradation - Hydrolysis

1. This study is scientifically valid ***(acceptable)***, and ***satisfies*** EPA Subdivision N Guideline requirements for hydrolysis.

2. Radiolabeled [^{14}C]mesotrione at a nominal concentration of 1 ug/mL was hydrolytically stable in sterile pH 5, 7, and 9 aqueous buffer solutions incubated in darkness at 25 ± 1 °C for up to 30 days. Following the incubation period, 96.9%, 97.4%, and 97.1% (reviewer-calculated means for the two radiolabels) of the applied radioactivity was present as parent compound, respectively, in the pH 5, 7 and 9 systems.

   Additionally, using a method similar to that for the 25 °C study, during a 5-day test period at 50 °C mesotrione was also hydrolytically stable at pH 4, 7, and 9.

3. The registrant should consider the critical elements in the Comments Section. Although not crucial in this instance, these may impact the acceptability of future submissions.

METHODOLOGY

Cyclohexanedione ring-labeled [^{14}C]mesotrione {ZA1296; 2-[4-(methylsulphonyl)-2-nitrobenzoyl]-1,3 cyclohexanedione; radiochemical purity 98.2%, specific activity 36.6 Ci/mol; p. 10} or uniformly phenyl ring-labeled [^{14}C]mesotrione {radiochemical purity 97.8%, specific activity 30.4 Ci/mol}, dissolved in acetonitrile (<1% by volume; p. 9), was directly injected at a nominal application of 1 µg/mL through autoclaved septa into autoclaved amber vials containing autoclaved pH 5 (acetate), pH 7 (acetate), and pH 9 (borate) 0.01 M aqueous buffer solutions (pp. 11, 12). The test vials were placed in a water bath preheated to 25°C; the temperature of the water bath was measured at each sampling interval using an electronic thermometer (Appendix 10, p. 37). The vials were incubated in darkness at 25 ± 1°C for up to 30 days. A single test vial (for each radiolabel) was removed for analysis at 0, 5, 12, 19, 23, and 30 days posttreatment (p. 13). The pH of the test systems remained constant throughout the incubation period (Appendix 3, p. 27). The sterility of the test solutions was confirmed at the beginning, middle, and end of the study using nutrient agar plates (p. 15).

At each sampling interval, aliquots of the test solutions were analyzed for total radioactivity by LSC (p. 13). Additional aliquots of each solution were analyzed by normal phase TLC on Kieselgel 60 F-254 plates developed with the following solvent systems: (1) toluene:methanol:triethylamine (6:3:1, v:v:v); (2) toluene:dioxane:ethanol:triethylamine (3:3:3:1, v:v:v:v); (3) chloroform:tetrahydrofuran:formic acid (20:20:1, v:v:v); and (4) chloroform:methanol:water:formic acid (20:7:1:1, v:v:v:v; p. 14).

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Additional aliquots of each solution were also analyzed by reverse-phase TLC on $KC_{18}F$ plates developed with methanol:water:acetic acid (50:50:1, v:v:v). Samples were co-chromatographed with nonradiolabeled reference standards; the visualization method was not reported. Radiolabeled areas on the plates were quantified by radioimage scanning.

DATA SUMMARY

Radiolabeled [^{14}C]mesotrione (radiochemical purities of cyclohexanedione and phenyl labels, respectively, 98.2% and 97.8%), at a nominal concentration of 1 µg/mL, was hydrolytically stable in sterile pH 5, 7, and 9 aqueous buffer solutions incubated in darkness at 25 ± 1°C for up to 30 days. Following the incubation period, 96.9%, 97.4%, and 97.1% of the applied radioactivity was present as parent compound, respectively, in the pH 5, 7 and 9 systems (reviewer-calculated means for the two radiolabels; Tables 1, 2; p. 17). An unidentified minor degradate was present at 2.2% of the applied radioactivity (in unspecified samples); tabular data were not reported (p. 15).

Material balances in the cyclohexanedione-label study for the pH 5, pH 7, and pH 9 buffer systems were 94.5-102.9%, 100.0-103.0%, and 96.8-100.5%, respectively, throughout the incubation period (Table 1, p. 17). Material balances in the phenyl-label study for the pH 5, pH 7, and pH 9 buffer systems were 101.8-105.8%, 103.0-105.6%, and 102.1-106.9%, respectively, throughout the incubation period (Table 2, p. 17).

COMMENTS

1. Replicate test vials were not utilized in this study. Individual test vials were analyzed at each sampling interval for each radiolabel. The use of single test samples is generally not considered to be good laboratory practice; at a minimum, duplicate test vials are necessary for each label in order to accurately determine the decline of the parent compound and the formation and decline of the degradates. Data on the hydrolytic degradation of the parent compound for each label may serve as replicate data in determination of half-lives if the treatment rates are the same and similar degradation patterns are observed. The parent compound was stable and data were generally not variable over time at each pH. Therefore, it is unlikely that a new study would provide additional information on the hydrolysis of mesotrione in these systems.

2. The solubility of the test compound in each of the three buffer systems was not reported. The solubility in water was reported as 8.1×10^3 ppm at pH 5.5, and 1.2×10^5 ppm at pH 7.0 (unspecified temperatures, p. 10).

3. Method detection limits were not reported. Limits of detection and quantitation should be reported to allow the reviewer to evaluate the adequacy of the method for the

determination of parent and degradates in the test system.

4. An additional study was conducted with pH 4 (acetate), pH 7 (acetate), and pH 9 (borate) 0.01 M aqueous buffer solutions at 50°C for 5 days using a method similar to that described previously for the 25°C study (pp. 9, 11, 12). The parent compound was hydrolytically stable in all three buffer systems which were incubated for up to 5 days at 50°C (Tables 3, 4; p.18).

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