12/2/91
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DATA EVALUATION RECORD

STUDY 1

CHEM 109801 **Iprodione** §161-1

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41885401
Das, Y.T. 1990. *Hydrolysis of [Phenyl(U)-^{14}C]iprodione in aqueous solutions buffered at pH 5, 7, and 9.* ISSI Laboratory Project No. 89100. Rhône-Poulenc Study No. EC-89-050. Unpublished study performed by Innovative Scientific Services, Inc., Piscataway, NJ, and submitted by Rhône-Poulenc Ag Company, Research Triangle Park, NC.

DIRECT REVIEW TIME = 4

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DATE: December 2, 1991.

CONCLUSIONS:

Degradation - Hydrolysis:

1. The submitted study is acceptable and can be used to fulfill the Hydrolysis (161-1) data requirement.

2. Phenyl ring-labeled [^{14}C]iprodione hydrolyzed with half-lives of 131 days, 4.7 days, and 27 minutes in sterile aqueous buffered solutions adjusted to pH 5, 7, and 9, respectively, that were incubated in the dark at 25 °C. The degradates, 3-(isopropylcarbamoyl)-5-(3,5-dichlorophenyl)hydantoic acid (RP-35606) and 1-(3,5-dichlorophenyl)carbamoyl-3-isopropyl-hydantoin (RP-30228) were identified.

3. No additional data on the hydrolysis of iprodione are required at this time.

METHODOLOGY:

Phenyl ring-labeled [^{14}C]iprodione (uniformly labeled, radiochemical purity 97.3%, specific activity 3.3 mCi/mMol, Rhône-Poulenc), dissolved in acetone, was added at 11.0-12.3 ppm to sterile aqueous 0.01 M buffer solutions adjusted to pH's 5 (acetate), 7 (potassium phosphate), and 9 (sodium borate); the final concentration of the co-solvent (acetone) was 0.17%. Aliquots (3 mL) of the test solutions were transferred to Teflon vials that were sealed and incubated at 25 ± 1 °C in the dark. Duplicate vials of the pH 5 solutions were removed for analysis at 0, 1, 3, 7, 14, 21, and 30 days posttreatment; duplicate vials of the pH 7 solutions were removed at 0, 5.3, 17, 40.4, 76, and 124.7 hours; and duplicate vials of the pH 9 solutions were removed at 0, 14-15, 29, 45-50, 60-65, and 107-121 minutes.

Immediately after sampling, an aliquot (100 µL) of each test solution was analyzed for iprodione and its degradates using reverse-phase HPLC on a ODS-120T column eluted with acetonitrile:water (6:4, v:v) containing 0.01% acetic acid with flow-through UV (254 nm) and radioactivity detectors. Identifications of the degradates were made by comparison to the retention times of unlabeled reference standards. Additional aliquots (10 µL) of the test solutions were analyzed for total radioactivity using LSC.

Degradate identifications were confirmed using LC/MS in the positive ion discharge mode. An aliquot of the pH 5 solution sampled at 30 days posttreatment was partitioned twice with methylene chloride; organic phases were combined. The remaining aqueous phase was lyophilized; the resulting residue was redissolved in methanol, then combined with the organic phase, concentrated under a stream of nitrogen, and analyzed by LC/MS. Because of the rapid hydrolysis of iprodione with increasing pH, additional pH 7 and 9 solutions were prepared, treated, and incubated as described above then sampled at 2 hours (pH 7) or 15 minutes (pH 9) posttreatment prior to extraction and LC/MS analysis.

DATA SUMMARY:

Phenyl-ring labeled [^{14}C]iprodione (uniformly labeled, radiochemical purity 97.3%), at 11.0-12.3 ppm, hydrolyzed with calculated half-lives of 131 days, 4.7 days, and 27.2 minutes in sterile aqueous buffered solutions that were incubated in the dark at 25 °C for 30 days (pH 5), 5.2 days (pH 7), or 107-121 minutes (pH 9), respectively. The major degradates were 3-(isopropyl-carbamoyl)-5-(3,5-dichlorophenyl)hydantoic acid (RP-35606), and 1-(3,5-di-chlorophenyl)carbamoyl-3-isopropylhydantoin (RP-30228).

In the pH 5 solution at 30 days posttreatment, iprodione comprised 80.4-82.8% of the applied radioactivity, and RP-35606 had increased to 10.8-11.9% (Table V).

In the pH 7 solution at 5.2 days posttreatment (124.7 hours), iprodione comprised 40.2-41.9% of the applied radioactivity, RP-35606 comprised 4.6-5.5% (maximum 9.8-10.4% at 1.7 days), and RP-30228 had increased to 44.3-47.0% (Table VI).

In the pH 9 solution at 107-121 minutes posttreatment, iprodione comprised 3.4-5.6% of the applied, RP-35606 had increased to 1.4-1.7%, and RP-30228 had increased to 90.7-93.3% (Table VII).

Three unidentified [^{14}C]compounds were detected in the pH 7 solution at maximums of 9.2, 2.1, and 2.0% of the applied. Unidentified "other" radioactivity, described as the sum of several insignificant radioactive areas, in the pH 5, 7, and 9 solutions, was detected at maximums of 9.0, 3.8, and 4.0% of the applied, respectively. During the study, material balances ranged from 95.6 to 103.4% of the applied (Table II).

During the study, the pH's of the test solutions ranged between 5.00-5.09, 6.99-7.09, and 8.99-9.10 (Table III).

COMMENTS:

1. The study author reported a calculated half-life of 153.5 hours (6.4 days) for iprodione in the pH 7 solution. The Dynamac reviewer calculated a half-life of 113.5 hours (4.7 days). It appears that the reported 153.5 hours is a typographical error, because the slope of the line, intercept, and correlation coefficient calculated by the Dynamac reviewer concurred with that calculated by the study author. The Dynamac reviewer also confirmed the half-lives calculated by the study author for iprodione in the pH 5 and 9 solutions. Therefore, in this review, a half-life of 4.7 days (113.5 hours) was reported for iprodione in the pH 7 solution.

2. It is not clear if the solutions or the glassware were adequately sterilized. Apparently the buffer solutions were not sterilized after the final pH adjustment, and although the solutions were made with sterile water, it is unlikely that the chemicals used were sterile. Likewise, it is possible that the 80% methanol solution with low-temperature oven drying was inadequate to completely sterilize the glassware. Autoclaving and/or filter-sterilization would be more appropriate sterilization methods.

The use of a microscope is inadequate to determine the sterility of a solution because a microbial population of approximately 10^6 bacteria/mL is required to visualize contamination. A more appropriate method to determine the sterility of the solutions would be to culture the microorganisms from aliquots of the solutions. (Greenberg, A.E., R.R. Trussell, and L.S. Clesceri. 1985. *Standard Methods For the Examination of Water and Wastewater.* Sixteenth Edition. American Public Health Association)

3. The statistical estimate of the hydrolytic half-life of iprodione in the pH 5 solution that was reported in this study is of limited value because the calculations involve extrapolation beyond the experimental time limits of the study. Data are often incapable of accurately predicting trends outside of their range because differences are magnified and reactions which are linear within the scope of the experiment may become curvilinear.