DATA EVALUATION RECORD

STUDY 6

CHEM 129016 XRD-498 §162-3

STUDY ID 41931733

Wolt, J.D.; Schwake, J.D.; Batzer, F.R.; Brown, S.M.; McKendry, L.H.; Miller, J.R.; Roth, G.A.; and Stanga, M.A. ANAEROBIC AQUATIC METABOLISM OF XRD-498 [N-(2,6-DIFLUOROPHENYL)-5-METHYL-(1,2,4)TRIAZOLO (1,5-a)PYRIMIDINE-2-SULFONAMIDE. Preformed and Submitted by DowElanco; Midland, MI under Dow Protocol No. 89080; Study completed on 14 June 1991; Received by EPA 19 June 1991.

DIRECT REVIEW TIME = 1.6 day

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CONCLUSIONS:

The anaerobic aquatic metabolism study is not acceptable to meet Subdivision N Data Requirement for the following reasons:

The metabolite (degradate [12]), which reached a maximum concentration of 52% of applied radioactivity by day 360 posttreatment, was only tentatively identified. The identity of this metabolite must be confirmed.

The registrant must satisfactorily address the deficiency above for the study to fulfill the data requirement. If the registrant does not address the above deficiency, a new anaerobic metabolism study is required to fulfill the data requirement.

This study covered both the aniline and the pyrimidine labelled XRD-498. However, the data was so similar that it is treated as one set of data. The XRD-498 labelled materials had a half-live of 183 days when applied to clay soil at 26°C and 75% of 1/3 bar moisture. There was one anaerobic metabolite which was greater than 10% of applied radioactivity and/or 0.01 ppm. The metabolite was tentatively identified as [N-(2,6-difluorophenyl)-4,5,6,7-tetrahydro-5-hydroxy-5-methyl-(1,2,4)triazolo(1,5-a)pyrimidine-2-sulfonamide] (See Table VI). No anaerobic half-life for the metabolite was calculated due to the continued formation up to 360 days posttreatment. Under aerobic conditions this metabolite exhibited a half-life of 2 days in comparison to an aerobic soil metabolism half-life of ≈80 for XRD-498. Therefore, XRD-498 under anaerobic conditions appears to be persistent.

MATERIALS AND METHODS:

Test Material: XRD-498-^{14}C labelled in the 5th position of the pyrimidine with a specific activity 10.9 mCi/mmole and labelled uniformly in the aniline ring with a specific

activity of 28.0 mCi/mmol. The radiochemical purity was 99%.

Standards: Standards were prepared from a 99.7% pure batch.

Stock Solution: The appropriate aliquot of ^{14}C-XRD-498 in acetone was delivered to 0.005 N NaOH solution and the acetone evaporated under a stream of N_2 gas. Spiking solution were prepared such that a 500 μL aliquot or 250 μL aliquot delivered to 50 gms of soil resulted in an application of 0.2 ppm.

After analysis, the actual rates of application were found to be 0.18, 0.22, 0.19, and 0.20 ppm for the pyrimidine W, pyrimidine W_{11}, aniline W, and aniline W_{11} samples, respectively

Soil: See Table I

Sampling: 0, day 30, day 60, day 180, and day 360.

Test System: See Figure 2

METHODOLOGY:

Sediment was separated from water at the time of study initiation, by decantation of water following sediment settling. Samples of sediment were analyzed for air dry and oven dry moisture content. Biometer flasks (see Figure 2) received 100 mL water + 50 gms. sediment. Additionally, the repeat study (W_{11}) received 0.5 gms finely ground alfalfa per reaction flask to serve as a carbon source for micobial oxidation (enhancing microbial activity will reduce the redox potential). The biometer flasks were held in a dark incubator at ≈25°C for 8 days prior to spiking of test material for the initial test (W); while in the repeat study a 32 day incubation period was allowed to enhance microbial activity.

One hundred mL of 0.2N NaOH was added to the volatile reservoir at the time of sample spiking. Aliquots of test solution were delivered to the surface water of each flask. A sweep of N_2 gas was delivered to the water surface to distribute the test material and to flush the headspace in each biometer flask. Each flask was then sealed and returned to incubators where they were maintained in the dark until sacrificed.

At each sampling interval, dissolved O_2 and pH (W_{11} samples) of the water phase was measured and the color of the sediment phase was noted. Caustic trapping solution was recovered and analyzed for $^{14}CO_2$. Sediment and water were transferred to 250 mL volume, capped, tared centrifuged tubes. The sediment was then separated from water by centrifugation at ≈4000 rpm for ≈30 minutes. The water phase was decanted into a 50 mL plastic bottle. The sediment + entrained water was retained in the centrifuge tubes.

Sample intervals were at 0, 30, 60, 180, and 360 days posttreatment.

Extractions of sediment samples were determined manually and robotically using acidified acetone (acetone/acetic acid/water 18:1:1 v/v/v). Approximately 15 g samples of moist soil were weighed into centrifuge tubes to which 15 mL of acidified acetone solution was added. These were centrifuged for ≥1 hour at low setting. The samples were then centrifuged at

1600 rpm and the water decanted to 50 mL volumetric flasks. Extractions with 15 mL aliquots of acidified acetone was repeated twice and the centrifuged extracts were decanted and combined with previous fractions. Aliuots of these extractions were used for LSC and HPLC/fractional LSC.

Non-extractable bound residues were determined by combustion and trapping of evolved $^{14}CO_2$. Triplicate determinations were performed. Approximately 1 g samples of the extracted sediment were weighed on to a glass boat for combustion. The CO_2 was trapped in a scintillation vial. ^{14}C activity was determined by LSC.

DATA SUMMARY:

Distribution of applied ^{14}C for any sampling interval was no different for ^{14}C-aniline and ^{14}C-pyrimidine-XRD-498. A calculated half-life of 183 days for XRD-498 was reported (See Table VI). One metabolite, [N-(2,6-difluorophenyl)-4,5,6,7-tetrahydro-5-hydroxy-5-methyl-(1,2,4)triazolo(1,5-a)pyrimidine-2-sulfonamide], was addressed which reached a maximum concentration of 52% of applied radioactivity at termination of test period (day 360 post-treatment). Total radioactivity associated with other peaks average ≤4% of applied radioactivity at any sampling interval. The half-life for the major degradate (called degradate [12] tentatively identified above) was not determined since no decline within the 360 day test period was observed.

Volatilization was minimal in the strongly anaerobic system. The average activity in the caustic traps was ≤3% of applied radioactivity for any sampling interval. Average bound residue increased from 7% to 15% of applied radioactivity over 180 days and a decline to 11% of applied radioactivity by 360 days (see Table VI). Recovery of applied mass average 96 ± 9% for all treatment and sample intervals.

COMMENTS:

1. The half-life of XRD-498 was estimated through modeling data for average recovery of applied ^{14}C-XRD-498 with time (Table VI) (an apparent first order decay). The data was subjected to simulation modeling using SimuSolv software. The model accounted for 84% of the variation in average values of XRD-498 observed. A half-life of 187 days for XRD-498 was determined.

   Data for average recovery of applied ^{14}C within time were subjected to more extensive simulation modeling using SimuSolv software. First order rates were assumed for both the parent and major degradate. This model accounted for 94% of the variation in data for XRD-498 and 98% of the variation in data for the degradate. The half-life was calculated to be 183 days for XRD-498.

2. Two studies were addressed in the submission. The weakly anaerobic study was used only for comparison of data. The confirmed study (strongly anaerobic) was used for the fulfillment of the data requirement.

3. The major metabolite, which reached 52% of applied by day 360 post-treatment, was only tentatively identified.

4. Based on the aniline and pyrimidine labelled XRD-498 exhibiting no difference (within analytical variability) the two were averaged and one half-life calculated.

5. Storage stability data indicated that there was little effect of storage on the distribution of radiocarbon (see Appendix K) in water and sediment samples.

6. The correlation coefficients reported for the first order anaerobic half-lives were 0.83 and 0.93.

7. The redox potential data was not furnished.

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