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DATA EVALUATION RECORD

STUDY IDENTIFICATION:

Das, Y. T. 1992. Metabolism of [Thienyl-3-^{14}C] SAN 582 H Under Anaerobic Aquatic Soil Conditions. Study performed by Innovative Scientific Services, Inc., Piscataway, N. J. for Sandoz Crop Protection Corporation. MRID No. 423672-01.

TYPE OF STUDY: Anaerobic Aquatic Metabolism (162-3)

REVIEWED BY:

George Tompkins, Entomologist
Review Section 1, EFGWB, EFED

Signature: George Tompkins
Date: NOV 24 1992

APPROVED BY:

Paul J. Mastradone, Section Chief
Review Section 1, EFGWB, EFED

Signature: Paul J Mastradone
Date: NOV 24 1992

CONCLUSIONS:

1. EFGWB concludes that the study submitted is acceptable and satisfies data requirements for anaerobic aquatic metabolism.

2. Based on the results of the study SAN 582 H degraded under anaerobic non-sterile conditions at 25^{0}C with a half-life of 36 days, and at 5^{0}C with a half-life of 292 days. Under sterile conditions at 25^{0}C SAN 582 H degraded with a half-life of 377 days and at 5^{0}C with a half-life of 1484 days.

3. When SAN 582 H was incubated at 25^{0}C under non-sterile conditions the parent degraded to reach a low of 0.4% of applied dose by day 270. The primary metabolites were M3 (dechlorinated parent, see Figure 4 for structures) reaching a maximum of 20.6% of the applied radioactivity by day 90, M11 (the hydroxylated derivative of the dechlorinated parent) reaching a maximum of 7.0% of the applied by 90 days, PL 3688 (the methylthio derivative of the dechlorinated parent) reaching a maximum of 4.9% of the applied by day 90, M13 (the sulfoxide of PL 3688) reaching a maximum of 12.4% of the applied by day 120, M10 (the sulfone of PL 3688) reached a maximum of 9.8% of the applied by day 90. A polar component reached a maximum of 22.3% of the applied dose by day 60 and this component appeared to be a complex between M3 and some soil constituents. The deaminated form of the M3-Cysteine conjugate, N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-2(thioethylenecarboxy)-acetamide, reached a maximum concentration of 4.6% of applied dose by 90 days.

At 5^{0}C under non-sterile conditions the metabolic pattern

was similar, but at a slower rate. At day 360 the following concentrations were reached: parent SAN 582 H was 41.8% of applied, M3 was 16.8%, M11 was 2.1%, M13 was 8.7%, M10 was 2.8%, PL 3688 was 3.4%. The polar component (M3 complex) reached a maximum of 11.8% of applied dose by day 90.

4. Under sterile conditions at both 25^{0}C and 5^{0}C there was some breakdown of parent SAN 582 H but no significant levels of metabolites from microbial activity were observed.

MATERIALS AND METHODS:

[Thienyl-3-^{14}C]SAN 582 H (specific activity 43 uCi/mg, radiochemical purity of the combined shipments was 98.8%) and analytical reference SAN 582 H (99.6% pure) were used in the study. The lake sediment (silt loam containing 38% sand, 51% silt, 11% clay, pH 7.1, organic matter 5.7%, and CEC of 6.9 meq/100 g) and water were collected from Dryden Lake, Tompkins County, New York on 29 June 1990. The sediment was obtained from the top 3-inch crust (Horizon A) and the water from the standing depth of ca. 3 feet. The sediment and water were passed through a 2 mm sieve and suitable aliquots of the sediment and water were analyzed for their characteristics (Tables I and II). A biological incubator was used to hold the test vessels and was maintained at 25$\pm$1^{0}C under dark conditions.

Individual 40-ml borosilicate glass bottles (test vessels) were used to contain the sediment and water. Each test vessel was provided with an airtight teflon-lined silicone septum and an open-top plastic screw cap. Each test vessel contained 3 g of lake sediment (based on dry weight) and a total of 30 ml of natural lake water. The test vessels were individually wrapped with aluminum foil to protect them from light. The control test vessels were sterilized by autoclaving. The following numbers of test vessels were utilized for the analyses: 26 non-sterile at 25^{0}C, 8 sterile at 25^{0}C, 16 non-sterile at 5^{0}C and 8 sterile at 5^{0}C. Additionally, 8 non-sterile vessels at 25^{0}C, 4 sterile vessels at 25^{0}C, and 4 non-sterile vessels and 4 sterile at 5^{0}C were utilized as surrogates for anaerobicity measurements and microbiological assays.

Anaerobic conditions were established and maintained by flushing the test vessels with nitrogen for ca. 30 min/day for 3 weeks prior to dosing and at least once every week thereafter. The test vessels remained saturated with nitrogen throughout the study period and were checked for anaerobicity at the beginning and at the end of the studies, using additional (surrogate) test vessels. Measurements for anaerobicity were made at day 0 and at day 360 using a platinum combination electrode in conjunction with a digital multimeter to measure the oxidation-reduction potential (ORP) relative to normal hydrogen electrode (E_{nhe}).

[^{14}C]SAN 582 H was isotopically diluted with analytical grade [^{12}C]SAN 582 H at an approximate ratio of 1:5 (^{14}C:^{12}C). A

dosing solution was prepared in acetonitrile. The concentration of diluted [^{14}C]SAN 582 H in the solution was determined by LSC to be 3.0 ug/ul (61,559 dpm=1 ug of SAN 582 H). To the water layer in each vessel 100 ul (299.3 ug of SAN 582 H) of the dosing solution was added making a concentration of 10 ppm.

Duplicate test vessels were taken from the non-sterile 25^{0}C test at 0, 1, 3, 7, 14, 21, 30, 60, 90, 120, 180, 270, and 360 days. Duplicate sterile test vessels from the 25^{0}C test were taken at 0, 90, 180, and 360 days. Duplicate non-sterile test vessels from the 5^{0}C test were taken at 0, 3, 14, 21, 30, 90, 180 and 360 days and duplicate sterile vessels from the 5^{0}C test were taken at 0, 90, 180, and 360 days.

Radioactivity measurements from soil extracts and volatile trapping solutions were determined by LSC. The headspace of each test vessel was flushed out into a series of traps comprising of ethylene glycol. 1.0 N sulfuric acid, and 1.0 N sodium hydroxide, with each kind alternating with an empty trap. The soil in the test vessels were subjected to a methanol-water mixture (90:10, v/v) extraction procedure. Aliquots were assayed by LSC. Following the methanol-water extraction, the soil was subjected to alkaline hydrolytic extraction using aqueous 1.0 N sodium hydroxide solution. After completing the extractions the sediment residue was dried at room temperature and its unextractable radioactivity measured by combustion analysis. Quantification of parent and metabolites was based on HPLC using analytical reference standards for comparison. The identities of the parent and metabolites was confirmed by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS).

REPORTED RESULTS:

1. The anaerobic aquatic half-life of SAN 582 H under non sterile conditions was 36 days at 25^{0}C, and 292 days at 5^{0}C. Under sterile conditions the anaerobic aquatic half-life of SAN 582 H was 377 days at 25^{0}C and 1484 days at 5^{0}C.

2. When SAN 582 H was incubated at 25^{0}C under non sterile conditions the parent concentration reached a low of 0.4% of applied dose by day 270. The primary metabolite was M3, the dechlorinated parent, reaching a maximum of 20.6% of the applied dose by day 90. Other metabolites were M11 (the hydroxylated derivative of the dechlorinated parent) which reached a maximum of 7.0% of applied by 90 days; PL 3688 (the methylthio derivative of the dechlorinated parent) which reached a maximum of 4.9% of the applied by day 90; M13 (the sulfoxide of PL 3688) reached a maximum of 12.4% of the applied by day 120; M10 (the sulfone of PL 3688) which reached a maximum of 9.8% of the applied by day 90. A [polar component reached a maximum of 22.3% of the applied dose by 60 days and this component appeared to be a complex between M3 and some soil constituents. The deaminated form of the

M3-Cysteine conjugate, N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-2-(thioethylenecarboxy)-acetamide, reached a maximum concentration of 4.6% of applied dose by 90 days.

At 5°C under non sterile conditions the metabolic pattern was similar, but at a much slower rate. At day 360 the following concentrations were reached: parent SAN 582 H was 41.8% of applied, M3 was 16.8%, M11 was 2.1%, M13 was 8.7%, M10 was 2.8%, PL 3688 was 3.4%. The polar component (M-3 complex) reached a maximum of 11.8% of applied dose by day 90.

3. Under sterile conditions at both 25°C and 5°C there was some breakdown of the parent but no significant levels of metabolites from microbial activity were observed. At day 360 the following concentrations were reached: parent SAN 582 H was 50% of applied, M13 was 2.4%, M10 was 1.7%, M11 was 1.8%, M3-Cys was 0.8%, M3 was 0.6%, PL 3688 was <0.1%, and the polar component reached a maximum of 25.5% of the applied dose.

4. The mean redox potential (E_{nhe}) values were -272 (day 0) and -269 (day 360) under non sterile conditions at 25°C, -262 (day 0) and -266 (day 360) under non sterile conditions at 5°C, -274 (day 0) and -268 (day 360) under sterile conditions at 25°C, and -264 (day 0) and -272 (day 360) under sterile conditions at 5°C (Table VI). These values indicate that anaerobic conditions were maintained throughout the study.

5. The material balances ranged from 94.4.0-107.4.% in the tests under all test conditions. The mean material balance under non sterile conditions was 99.7±1.8% at 25°C and 99.7±2.2% at 5°C. Under sterile conditions the mean material balance was 100.2±3.7% at 25°C and 101.1±1.4% at 5°C.

DISCUSSION:

1. In the non sterile 25°C tests the radioactivity in the water layer decreased steadily to 24.3% of the applied dose by 360 days. The radioactivity in the methanol:water extraction (Extract I) of the soil increased to a maximum level of 24.2% of the applied dose by 14 days and subsequently decreased to 10.2% of applied by 360 days. The radioactivity in the alkaline hydrolytic extraction (Extract II) of the soil increased to a maximum level of 39.0% of applied dose by day 90 and subsequently decreased to 25.4% of applied dose by day 270. The unextractable radioactivity reached a maximum level of 38.4% of applied by day 360. No significant radioactivity (<0.1%) was found in the volatile traps.

At 5°C under non sterile conditions the metabolic pattern was similar to that of the 25°C tests but at a slower rate. The radioactivity in the water layer dropped to 38.1% of applied dose by day 360. In Extract I the radioactivity increased to a maximum level of 27.0% by day 90 and decreased to 19.9% of applied by day 360. The radioactivity in Extract II increased to 24.0% by day 360. The unextractable radioactivity reached a maximum level of

14.1% of applied dose by day 360.

2. Under sterile conditions at both 25^{0}C and 5^{0}C there was some breakdown of the parent and the contributing process for this degradation is unknown. No significant levels of metabolites related to microbial activity were present in the sterile tests.

3. The radiochemical purity of the labeled SAN 582 H was listed on page 24 as being 98.8%. However, in Figure 1 on page 91, the the radiochemical purity is listed as 97%. Although it is believed not to influence the results, this discrepancy is noted.

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