Data Evaluation Report on the hydrolysis of XDE-742 (pyroxsulam)

PMRA Submission Number 2006-4727; EPA MRID Number 46908326; APVMA ATS 40362

Data Requirement:	PMRA DATA CODE:	8.2.3.2
	EPA DP Barcode:	332118
	OECD Data Point:	IIA 2.9.1, IIA 7.5
	EPA Guideline:	Subdivision N, §161-1 Hydrolysis Studies

Test material:	^{14}C-XDE-742-TP and ^{14}C-XDE-742-PYR (for purity, see: 1. Test Material)
Common name:	XDE-742 (pyroxsulam)
Chemical name:	
IUPAC:	N-(5,7-dimethoxy[1,2,4]triazolo[1,5-α]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide
CAS name:	N-(5,7-dimethoxy[1,2,4]triazolo[1,5-α]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide
CAS No:	422556-08-9
Synonyms:	INV1901 (TP), INV1905 (PYR)
Smiles string:	c1(c(ccnc1OC)C(F)(F)F)S(Nc2nn3c(n2)nc(cc3OC)OC)(=O)=O

Primary Reviewer:	J. Catherine Evans (#1638) PMRA	**Date:** December 13, 2006
Secondary Reviewers:	Dr. Hemendra Mulye (#213) PMRA	**Date:** January 11, 2007
	Greg Orrick USEPA E Bell for Greg Orrick	**Date:** May 16, 2007 October 25, 2007
	David McAdam AUS DEW D Murphy for David McAdam	**Date:** 30 May 2007 November 2, 2007
	Émilie Larivière PMRA Émilie Larivière	**Date:** 19 October 2007 October 19, 2007

Company Code	DWE
Active Code	JUA
Use Site Category	13,14
EPA PC Code	108702

2070876

CITATION: Yoder, R. N., 2005, Hydrolysis of XDE-742 at pH 5, 7, and 9, Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268, 040008, M. D. Culy, May 21, 2004.

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EXECUTIVE SUMMARY: Hydrolysis of radiolabelled XDE-742 (labelled at a. the triazole ring and b. the pyridine ring) at 0.1 mg a.i/L was studied in the dark at 20 °C in sterile aqueous buffered solutions at pH 5 (sodium acetate buffer), pH 7 (TRIS buffer) and pH 9 (sodium tetraborate buffer) for 32 days. The experiment was conducted in accordance with US EPA Subdivision N, Section 161-1 and SETAC Part 1 Section 9, and to meet the GLP standards, the US EPA Good Laboratory Practice Standards, 40 CFR Part 160. Samples were analysed at 0, 4, 7, 14, 21 and 32 days without extraction, and the XDE-742 residues were analysed by LSC and HPLC-radiochromatography (HLPC-RAM). There were no transformation products observed.

The radioactivity balance was 100.1 ± 0.6 %, 99.2 ± 1.0 % and 99.6 ± 0.9 % of the applied at pH 5, pH 7 and pH 9, respectively. At test termination, the concentration of the parent compound was 100 % in all three pH systems. There was no unidentified radioactivity and sample pH did not change throughout the study.

The half-life (lives)/ DT50 (50% decline times) of XDE-742 could not be determined in any of the three buffer systems studied as the parent compound was stable to hydrolysis.

This study is classified as acceptable and satisfies the guideline requirement for a hydrolysis study.

RESULTS SYNOPSIS:
XDE-742 was stable to hydrolysis at pH 5, 7, and 9 at 20 °C.

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: This study was designed to fulfill U.S. Environmental Protection Agency (EPA) requirements for hydrolysis as outlined in US EPA Subdivision N, Section 161-1 and the requirements of European Commission Directive 91/414/EEC, Annex II, Points 2.9.1 and 7.2.1.1, Canada PMRA DACO Number 8.2.3.2, SETAC Part 1 Section 9, and OECD 111. Deviations from OECD guidelines were that the preliminary Tier 1 test at 50 °C for the OECD guideline was omitted, a pH 5 study was performed instead of a pH 4 study and test solutions were not sparged to remove oxygen. These did not affect the validity of the study.

COMPLIANCE: This study was also conducted to meet Good Laboratory Practices standards, 40 CFR Part 160. Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

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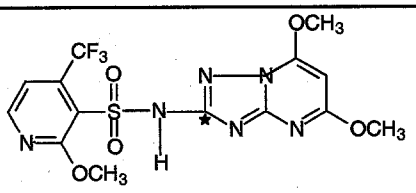
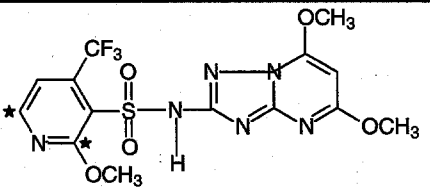
A. MATERIALS:

1. Test Material XDE-742

Chemical Structure: (stars denote postitions of radiolabel)		
Inventory #:	INV1901	INV1905
Description:	^{14}C-TP-XDE-742 (Phase not given, XDE-742 solid at 20 °C)	^{14}C-PY-XDE-742 (Phase not given, XDE-742 solid at 20 °C)
Analytical purity:	not given	not given
Radiochemical purity:	98.3%	98.4%
Specific activity:	36.6 mCi/mmole	43.7 mCi/mmole
Storage conditions:	-20 °C (stable)	-20 °C (stable)

Physico-chemical properties of XDE-742:

Parameter	Values	Comments
Water solubility (all at 20 °C) purified water (unbuffered) pH 4 (phosphate) buffer pH 7 (phosphate) buffer pH 9 (phosphate/ tetraborate) buffer	 62.6 mg/L 16.4 mg/L 3.20 x 10^3 mg/L 1.37 x 10^4 mg/L	strong pH influence on solubility Very soluble in water Turner, B. J. "Determination of Water Solubility for XDE-742" NAFST806, unpublished report of Dow AgroSciences LLC, 22-December-2004.

Vapour pressure/volatility	1 x 10^{-7} Pa at 20 °C (<10^{-9} torr)	Low volatility Madsen, S. "Determination of the Surface Tension, Density, and Vapour Pressure of the Pure Active Ingredient XDE-742," DERBI 144723, unpublished report of Dow AgroSciences LLC, 09-October-2003.
UV absorption "Neutral" aqueous solution (2< pH< 12)	λmax = 297 nm ε = 8000 L/(mol*cm)	will not affect hydrolysis conducted in dark
pKa	4.67 at 20 °C	Sheets, J. J., Gast, R. E., Hanley, T. R., Krieger, M., Mayes, M. A. "Early Stage Registration Assessment of X666742: Phase I Weed Management Sulfonamide for European and Canadian Cereal Markets," DERBI No 79155, unpublished report of Dow AgroSciences LLC, 28 September 2000.

log Kow pH 4 (phosphate) buffer pH 7 (phosphate) buffer pH 9 (phosphate/ tetraborate) buffer	 1.08 -1.01 -1.60	trend consistent with solubility results Turner, B. J., "Determination of Octanol/Water Partition Coefficient for XDE-742," NAFST807, 2004, unpublished report of Dow AgroSciences LLC.
Stability of compound at room temperature, if provided	N/A	

2) Buffer Solution: Buffer solutions were made with HPLC grade water as follows:

Table 1: Description of buffer solutions.

pH	Type and final molarity of buffer	Composition
5	0.01 M acetate	0.41 g sodium acetate in water, pH adjusted with 2N HCl, made up to 0.5 L
7	0.01 M TRIS (THAM)	0.61 g tris(hydroxymethyl) aminomethane in water, pH adjusted with 2N HCl, made up to 0.5 L
9	0.01 M borate	1.91 g sodium tetraborate in water, pH adjusted with 2N HCl, made up to 0.5 L

B. EXPERIMENTAL CONDITIONS

1) Preliminary Study: no preliminary studies were conducted.

2) Experimental conditions

Table 2: Experimental parameters

Parameters	Details
Duration of the study	32 days

Test concentrations (mg a.i./L) nominal: measured:		 0.1 mg/L 0.10 mg/L (pH 5 and 7), 0.11 mg/L (pH 9)
No. of replications		1 sample from each of two radiolabels per time
Preparation of test medium	volume used/treatment	15 mL
	method of sterilization	autoclave at 121 °C for 20 min
	co-solvent (type/concentration)	acetone (0.3%)
Test apparatus (type/material/volume)		24-mL centrifuge tubes with Teflon-lined screw caps, closed system, with no volatile traps.
Is there any indication of the test material adsorbing to the walls of the test apparatus?		No indication of material adsorption to walls, solubility and material balance indicate that sorption is unlikely to have been significant.
Experimental conditions (temperature in °C, lighting)		maintained in dark incubator at 20 ± 1°C

3). Supplementary Experiments: none

4). Sampling:

Table 3: Sampling details.

Criteria	**Details**
Sampling intervals for the parent/transformation products	0, 4, 7, 14, 21 and 32 days after treatment
Sampling method	Total radioactivity of 1-mL aliquots assayed by LSC 300-µL injection volume analyzed by HPLC-RAM
Sampling methods for the volatile compounds, if any	none, not applicable
Sampling intervals/times for pH measurement and sterility check	each day of sample analysis
Sample storage before analysis	pH, sterility check and LSC performed on the day of sampling, HPLC samples refrigerated and analyzed up to one week after sampling

C. ANALYTICAL METHODS:

Total ^{14}C measurement was determined by liquid scintillation counter on triplicate aliquots. No extraction or cleanup methods were used, however at times when HPLC analysis could not be performed on the day of sampling, the pH of the pH 9 samples was adjusted to a pH of about 7 using 1 or 2 N HCl.

Triplicate aliquots were analyzed by HPLC-RAM. Samples were separated by reverse-phase HPLC (Zorbax SB-C-18 column, gradient elution from 95%:5% A:B to 5%:95% A:B, where A is water +1% acetic acid and B is acetonitrile + 1% actetic acid) equipped with a Gilson fraction collector set for 0.1 min fractions. The radiolabel in the fractions was counted on a 96-well TopCount LSC, generally for 5 minutes. LSC counts were then used to construct the radiochromatogram. A direct count of the sample injected was also made in order to determine chromatographic recovery. No transformation products were detected.

The quantitation limits of radioactivity (Currie, 1968) for aqueous samples and HPLC analyses were less than or equal to 0.6% of the applied radiocarbon. Detection limits for the parent compound for each pH and radiolabel are below:

Limits of Detection and Quantitation as Percent of Applied Radioactivity:

		pH 5		pH 7		pH 9	
Sample Type	Radiolabel	LOD	LOQ	LOD	LOQ	LOQ	LOQ
Aqueous Phase	TP	0.05	0.21	0.05	0.21	0.05	0.20
Aqueous Phase	PY	0.04	0.17	0.04	0.16	0.04	0.16
HPLC Analyses	TP	0.12	0.56	0.12	0.55	0.12	0.54
HPLC Analyses	PY	0.10	0.44	0.10	0.44	0.10	0.44

II. RESULTS AND DISCUSSION:

A. TEST CONDITIONS: The pH and sterility of each sample was assessed at each sampling time. Sample pH did not change (remained within 0.1 pH unit) over the study and sterility was maintained in all samples reported. Incubator temperature (nominally set to 20 °C) was monitored using a Camille system which reported if any temperatures were out of the acceptable range for more than one hour, however the study does not indicate whether any deviations occurred during the 32 day test period or provide any details of the temperature range.

B. MASS BALANCE:
Radiocarbon recovery/material balance averaged 100.1 % ± 0.6 %, 99.2 % ± 1.0 % and 99.6 % ± 0.9 % at pH 5, 7 and 9, respectively. Material balance ranged from 101.0 to 99.1, 100.1 to 96.3 and 100.7 to 97.3, respectively for pH 5, 7 and 9.

Hydrolysis Radioactive Material Balance (Expressed as Percent of Applied Radiocarbon)—in Sterile Buffer at pH 5, 7 and 9:

DAT	Label	pH 5	pH 7	pH 9
0	TP	100.0	100.1	100.2
0	Py	101.0	99.9	100.5
4	TP	100.6	99.9	100.7
4	Py	99.7	100.1	99.9
7	TP	99.5	98.6	99.5
7	Py	99.6	98.9	99.7
14	TP	100.7	99.7	97.3
14	Py	100.3	96.3	99.8
21	TP	100.5	99.1	99.5
21	Py	100.1	98.9	99.8
32	TP	99.7	99.0	99.1
32	Py	99.1	99.3	99.2
Average		100.1	99.2	99.6
SD		0.6	1.0	0.9
Maximum		101.0	100.1	100.7
Minimum		99.1	96.3	97.3

C. TRANSFORMATION OF PARENT COMPOUND: Greater than 99% of the applied ^{14}C was associated with the parent compound at test termination. There was no transformation of the parent compound observed at any tested pH and thus no hydrolysis pathway could be constructed and no half-life could be determined for XDE-742 for the tested pH range.

III. STUDY DEFICIENCIES: No deficiencies were noted.

IV. REVIEWER'S COMMENTS: The results of the temperature monitoring were not provided in the study, so it is not possible to ascertain whether incubator temperature was maintained within the allowable limits. This does not affect the results of the study as the parent compound was stable at all pHs tested.

Australian Reviewer's Comments: Agree with the above comments from the Canadian reviewer and the study is acceptable. The deviation from OECD guidelines are noted (study conduct at pH 5 rather than pH 4) but this do not effect the results of the study as there was no hydrolysis.

V. REFERENCES:

Turner, B. J., "Determination of Water Solubility for XDE-742", 2004, NAFST806, unpublished report of Dow AgroSciences, LLC.

Madsen, S., "Determination of the Surface Tension, Density, and Vapour Pressure of the Pure Active Ingredient XDE-742," NAFST814, 2003, unpublished report of Dow AgroSciences LLC.

Sheets, J. J., Gast, R. E., Hanley, T. R., Krieger, M., Mayes, M. A. "Early Stage Registration Assessment of X666742: Phase I Weed Management Sulfonamide for European and Canadian Cereal Markets," DERBI No 79155, unpublished report of Dow AgroSciences LLC, 28 September 2000.

Turner, B. J., "Determination of Octanol/Water Partition Coefficient for XDE-742," NAFST807, 2004, unpublished report of Dow AgroSciences LLC.

Currie, L. A. "Limits for Qualitative Detection and Quantitative Determination-Application to Radiochemistry", Anal. Chem. 1968, 40, 586-593.