UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

DATE: November 17, 2006

MEMORANDUM

SUBJECT: Pyroxsulam: New Chemical Screen of Submitted Toxicology Studies.
PC Code: 108702 DP Barcode: 332276

FROM: Kim Harper/Alan Levy Alan C. Levy
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THROUGH: Richard Loranger, Branch Senior Scientist
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And

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The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) screen the study data for all new active ingredients submitted under the Pesticide Registration Improvement Act (PRIA). The following memorandum contains the results of the Registration Action Branch 2 (RAB2) screen of the toxicology study data for the new active ingredient (a.i), pyroxsulam, triazolopyrimidine herbicide. This new active ingredient is part of a trilateral review with Canada (PMRA) and Australia (APVMA). HED/OPP will conduct primary review of the mammalian toxicology data. The proposed use is for the control of grass and

broadleaf weeds in wheat. This screen was performed in accordance with screening criteria based on the 870 series guidelines for toxicology studies. The preliminary toxicity profile is attached, and is based on the registrant-suggested study results (i.e., No Observed Adverse Effects Levels, or NOAELs, and Lowest Observed Adverse Effect Levels, or LOAELs). Study profile summaries were provided by the registrant for each study, but these have not been included in the screen. In summary, the submitted studies are adequate for review for the proposed Section 3 registration. Additional details are provided in the attached tables.

Table 1. Toxicology Data Requirements Screening Results

Chemical: Pyroxsulam [N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide]

PC Code(s): 108702 Food Use: X Non-Food Use: _____

Guideline	Study Title	MRID	GLP[a]	Test Article[b]	Dosing[c]	Animal Observations[d]	Control Data[e]
870.3100 XDE-742/ BAS-770H	90-Day Dietary Toxicity Study with a 28-Day Recovery in Fischer 344 Rats.	46908350	–	–	–	–	–
870.3100 XDE-742/ BAS-770H	90-Day Dietary Toxicity Study In CD-1 Mice.	46908351	–	–	–	–	
870.3150 XDE-742/ BAS-770H	90-Day Dietary Toxicity Study in Beagle Dogs.	46908352	–	–	–	–	–
870.3700	Oral Prenatal Developmental Toxicity Study of XDE-742 in Rabbits.	46908354	–	–	–	–	–
870.3700	Oral Gavage Developmental Toxicity Study in CRL (CD (SD) Rats XDE-742	46908355	–	–	–	–	–
870.3700	A Range-Finding and 28-Day Toxicity Study in Dogs XR-742	46908401	–	–	–	–	–
870.3800	Maternal Toxicity Study in Wistar Rats (Range-Finding) Oral Administration (Gavage). XDE-742/BAS 770H	46908402	Not GLP	–	–	Limited; Acceptable for Range-Finding	–
870-3800	One-Generation Reproduction Toxicity Study in Wistar Rats (Range-Finding) Oral Administration (Diet).XDE-742/BAS 770H	46908403	Not GLP	–	–	Limited; Acceptable for Range-Finding	– No Historical
870.3800	Two-Generation	46908404	–	–	–	–	–

Guideline	Study Title	MRID	GLP[a]	Test Article[b]	Dosing[c]	Animal Observations[d]	Control Data[e]
	Dietary Reproductive Toxicity Study in CD Rats. XDE-742						No Historical
870.4100	One-Year Dietary Toxicity Study in Beagle Dogs. XDE-742	46908405	--	--	--	--	--
870.4200	18-Month Dietary Oncogenicity Study in CD-1 Mice. XDE-742	46908406	--	--	--	--	--
870.4300 XDE-742	Two-Year Chronic Toxicity/ Oncogenicity and Chronic Neurotoxicity Study in Fischer 344 Rats. XDE-742	46908407	--	--	--	--	--
870-530	Evaluation of XDE-742 in the Chinese Hamster Ovary Cell/Hyposanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay.	46908408	Y	XDE-742	Up to limit of solubility	XDE-742 is not mutagenic under experimental conditions in the *CHO/HGPRT* gene mutation assay	Y
870-5375	Evaluation of XDE-742 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes.	46908409	Y	XDE-742	Up to limit of solubility	XDE-742 was non-genotoxic under experimental conditions	Y
870-5395	Evaluation of XDE-742 in the Mouse Bone Marrow Micronucleus Test.	46908410	Y	XDE-742	500 1000 2000 mg/kg/ day	Did not induce a sig. increase in MN-PCE	Y

Guideline	Study Title	MRID	GLP[a]	Test Article[b]	Dosing[c]	Animal Observations[d]	Control Data[e]
870-6200	Chronic Neurotoxicity Study in Fischer 344 Rats XDE-742	46908411	–	–	–	–	Includes Positive Control Data
870.5100	Salmonella *Typhimurium*/ Escherichia coli Reverse Mutation Assay with XDE-742/BAS-770H	46908414	Y	XDE-742 BAS 770H	Up to limit of solubility	Test substance is not mutagenic under experimental conditions in bacterial rverse mutation assay	Y
870.7485	Metabolism and Pharmacokinetics of (Carbon 14) XDE-742 in Male Fischer Rats Following Single and Repeated Oral Administration.	46908412	–	–	–	–	–
870.7485	Pharmacokinetics of (Carbon 14)-XDE-742 in CD-1 Mice Following Single Oral Gavage Administration.	46908413	–	–	–	–	–
870.3050 XR-742	28-Day Dietary Toxicity Study in Fischer 344 Rats XR-742	46908349	–	–	–	–	–
	XDE-742/ BAS 770H Maximization Test in Guinea Pigs.	46908347	–	–	–	–	–
	GF-1674: Local Lymph Node Assay in BALB/cAnNCrl	46908348	–	–	–	–	–

Guideline	Study Title	MRID	GLP[a]	Test Article[b]	Dosing[c]	Animal Observations[d]	Control Data[e]
870.3200	XDE-742/ BAS 770H Dermal Test Study in Wistar Rats Application. 2-Wk. Pilot Study	46908353	Not Audited by QUA	No Concen-tration or Homo-Geneity			
	Oral Dose Range-Finding Prenatal Developmental Toxicity Study of XDE-742 in Rabbits.	46908415	--	No Homo-Geneity, Concen-tration or Stability	--	--	--
	The overall data submission is of high quality and acceptable for placement in to full review						

- Indicates study passed the screen for the parameter specified

a. *GLP/Compliance statement present*

b. Test article, including stability, homogeneity, concentration, purity

c. Dosing adequacy (including appropriate levels and numbers of animals) and route of administration

d. *Animal parameters* observed, including (as applicable) body weight, food consumption, survival, hematology, clinical chemistry, urinalysis, histopathology, necropsy findings, study-specific parameters such as tumors, *developmental toxicity*, etc.

e. Control data including (as applicable) historical controls and positive controls

x Indicates the study did not pass the screen for the parameter specified, or *the information is not available.*

N/A Not Applicable.

Conclusions:

The toxicology studies submitted to support the tolerance petition for the new active ingredient, pyroxsulam were screened for completeness and general acceptability. These studies have passed the screen and are eligible for complete reviews, including hazard characterization and hazard identification for risk assessment. A Cancer Assessment Review Committee (CARC) meeting may be needed to address significance of the slightly increased incidence of liver adenomas in male mice observed in the mouse cancer study.

Bibliography of Submitted Toxicology Studies for Pyroxsulam	
46908350	Stebbins, K.; Dryzga, M.; Brooks, K..; et. al (2003) XDE-742/BAS-770H: 90-day Dietary Toxicity Study with a 28-Day Recovery in Fischer 344 Rats. Project Number 02117. Unpublished study prepared by Dow Chemical, USA. 382p.
46908351	Johnson, K.; Dryzga, M.; Brooks, K. (2003) XDE-742/BAS-770H: 90-Day Dietary Toxicity Study in CD-1 Mice. Project Number: 021106. Unpublished study prepared by Dow Chemical, USA. 288p.
46908352	Stebbins, K.; Baker, P. (2003) XDE-742/BAS-770H: 90-Day Dietary Toxicity Study in Beagle Dogs. Project Number: 02111. Unpublished study prepared by Dow Chemical, USA, 231p.
46908354	Sloter, E. (2005) Oral Prenatal Developmental Toxicity Study of XDE-742 in Rabbits: Final Report Project Number: WIL/406015. 041145. Unpublished study prepared by WIL Research Laboratories, Inc. 366p.
46908355	Carney, E.; Tornesi B. (2005) XDE-742: Oral Gavage Developmental Toxicity Study in CRL: CD(SD) Rats. Project Number 051053. Unpublished study prepared by Dow Chemical, USA. 372p.
46908401	Merriman, T. (2002) XR-742: A Range-Finding and 28-Day Dietary Toxicity Study in Dogs: Final Report. Project Number 3504/175, 011062. Unpublished study prepared by Springborn Laboratories, Inc. (SLI). 268p.
46908402	Schneider, S. (2004) XDE-742/BAS 770H: Maternal Toxicity Study in Wistar Rats (Range-Finding) Oral Administration (Gavage). Project Number: 10R0298/03022. Unpublished study prepared by BASF Aktiengesellshaft. 75p.
46908403	Schneider, S. (2004) XDE-742/BAS 770H – One Generation Reproduction Toxicity Study in Wistar Rats (Range-Finding) Oral Administration (Diet). Project Number: 15R0298/03023, 03023F0F, 03023F0M. Unpublished study prepared by BASF Aktiengesellschcaft. 192p.
46908404	Carney, E.; Zablontny, C.; Stebbins, K. (2005) XDE-742; Two Generation Dietary Reproductive Toxicity Study in CD Rats. Project Number: 041012. Unpublished study prepared by Dow Chemical, USA. 1189p.
46908405	Strebbins, K.; Dryzga, m. (2004) XDE-742: One-Year Dietary Toxicity Study in Beagle Dogs. Project Number: 031012. Unpublished study prepared by Dow Chemical, USA. 339.\p.
46908602	Stebbins, K.; Dryzga, M. (2005) Study Profile Template (SPT) for XDE-742: One-Year Dietary Toxicity Study in Beagle Dogs. Project Number: 0310012/SPT. Unpublished study prepared by Dow Chemical Co. 22p.
46908406	Johnson, K.; Dryzga, M.; Yano, B. (2005) XDE-742: 18-Month Dietary Oncogenicity Study in CD-1 Mice. Project Number: 031015. Unpublished study prepared by Dow Chemical, USA. 1054 p.
46908408	Seidel, S.; Schisler, M.; Grundy, J. (2004) Evaluation of XDE-742 in the Chinese Hamster Ovary Cell/Hyposanthine-Guanine-Phosphoribosyl Transfearse (CHO/HGPRT) Forward Mutation Assay. Project Number: 041003. Unpublished study prepared by Dow Chemical, USA. 25p.
46908409	Charles, G.; Schisler, M. (2004) Evaluation of XDE-742 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes. Project Number: 041005. Unpublished study prepared by Dow Chemical Co., USA. 31p.
46908410	Spencer, P.; Grundy, J. (2004) Evaluation of XDE-742 in the Mouse Bone Marrow Micronucleus Test. Project Number: 041004. Unpublished study prepared by Dow Chemical, USA. 42p.
46908411	Maurissen, J.; Andrus, A.; Yano, F., et al (2005) XDE-742: Chronic Neurotoxicity Study in Fischer 344 Rats. Project Number: 031014. Unpublished study prepared by Dow Chemical Co, USA. 376p.
46908412	Hansen, S.; Clark, A.; D.; et al (2005) XDE-742: Metabolism and Pharmacokinetics of (Carbon 14) – XDE-742 in Male Fischer 344 Rats Following Single and Repeated Oral Administration. Project Number 041019. Unpublished study prepared by Dow Chemical, USA, 83p.
46908413	Hansen, S.; Clark, A.; Saghir, S. (2006) XDE-742: Pharmacokinetics of (Carbon 14)-XDE-742 in CD-1 Mice Following Single Oral Gavage Administration. Project Number: 061017. Unpublished study prepared by Dow Chemical Co., USA 89p.
46908349	Stebbins, K.; Day, S. (2001) XR-742: 28-Day Dietary Toxicity Study in Fischer 344 Rats. Project Number: 011044. Unpublished study prepared by Dow Chemical Co., USA. 299p.

Bibliography of Submitted Toxicology Studies for Pyroxsulam	
46908347	Gamer, A.; Leibold, E. (2004) XDE-742/BAS 770H – Maximization Test in Guinea Pigs. Project Number: 30H0298/032101. Unpublished Study prepared by BASF Aktiengesellschaft, 42p.
46908348	Woollhiswe, M.; Wiescinski, C.; Anderson, L. (2005) GF-1674: Local Lymph Node Assay in Balb/cAnNCrl Mice. Project Number 051168. Unpublished study prepared by Dow Chemical, USA, 26p.
46908353	Kasper, U., (2004) XDE-742/BAS 770H – Dermal Test Study in Wistar Rats Application for 2 Weeks., 60p.
46908414	Engelhardt, G., et al., (2003) Salmonella Typhimurium/Escherichia Coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test) with XDE-742/BAS 770H, 60p.
46908415	Sloter, E.D., (2005) Oral Dose Range-Finding Prenatal Developmental Toxicity Study of XDE-742 in Rabbits, 279p.

Pyroxsulam Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Range-finding	28-Day dietary toxicity (Fischer rat) XDE-742	46908349 (2001) Non-guideline 0, 10, 100, 500, or 1000 mg/kg/day	NOAEL (M&F) = 1000 mg/kg/day LOAEL (M&F) = not observed
Range-finding	28-Day dietary toxicity (Beagle dog) XR-742	46908401 (2002) Non-guideline 0, 3000, 10000, or 30000 ppm M: 0, 85, 421, or 868 mg/kg/day F: 0, 169, 333, 1004 mg/kg/day	NOAEL = 868/1004 mg/kg/day LOAEL = not observed
870.3100	90-Day oral toxicity (CD-1 mouse) XDE-742/BAS-770H	46908351 (2003) Acceptable/guideline 0, 10, 100, or 1000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on increased serum cholesterol (M&F, 22.3 and 29.9%, respectively) and increased liver weights (M&F).
870.3100	90-Day oral toxicity (Fischer rat) XDE-742/BAS-770H	46908350 (2003) Acceptable/guideline 0, 10, 100, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not observed
870.3150	90-Day oral toxicity (Beagle dog) XDE0742/BAS-770H	46908352 (2003) M: 0, 10.9, 91.3, and 884.1 mg/kg/day F: 0, 10.4, 98.6, and 1142.4 mg/kg/day	NOAEL = 91.3/98.6 mg/kg/day, M/F, respectively LOAEL = 884.1/1142.4 mg/kg/day (M/F, respectively) based on decreased body weights (up to 31%) in both sexes, increased liver weights in both sexes, hepatocellular hypertrophy, and increased cholesterol and alkaline phosphatase activity
870.3200	14-Day dermal toxicity (Wistar rat) XDE-742/BAS-770H	46908353 (2004) Non-guideline 0 or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not observed

Pyroxsulam Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (Sprague-Dawley rat) XDE-742	46908355 (2005) 0, 100, 300, or 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not observed
870.3700b	Prenatal developmental in (New Zealand White rabbit) XDE-742	46908354 (2005) 0, 30, 100, or 300 mg/kg/day	**Maternal** NOAEL = 300 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 300 mg/kg/day LOAEL = not observed
870.3800	Reproduction and fertility effects (Spague-Dawley rat) XDE-742	46908404 (2005) 0, 100, 300, or 1000 mg/kg/day	**Parental/Systemic** NOAEL = 1000 mg/kg/day LOAEL = not observed **Reproductive** NOAEL = 1000 mg/kg/day LOAEL = not observed **Offspring** NOAEL = 1000 mg/kg/day LOAEL = not observed
870.4100b	Chronic toxicity (Beagle dog) XDE-742/BAS-770H	46908405 (2004) M: 0, 13.2, 93.0, or 619.6 mg/kg/day F: 0, 17.1, 88.7, and 589.1 mg/kg/day	NOAEL = 619.6/589.1 mg/kg/day LOAEL = not observed
870.4300	Chronic/Carcinogenicity (Fischer rat) XDE-742	46908407 (2005) 0, 10, 100, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not observed **no evidence of carcinogenicity**
870.4300	Carcinogenicity (CD-1 mouse) XDE-742	46908406 (2005) 0, 10, 100, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not observed **Slight increase in liver adenomas/carcinomas in male mice**
Gene Mutation 870.5300	Forward gene mutation in CHO	46908408 (2004) Tested up to limit of solubility	XDE-742 was not mutagenic under the test conditions.
Gene Mutation 870.53	Reverse gene mutation in CHO	46908414 (2004) Tested up to 2000 mg/plate	XDE did not induce an increase in revertent colonies above background levels in the presence or absence of S9 activation under experimental conditions.

Pyroxsulam Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Cytogenetics 870.5375	Chromosomal aberration assay XDE-742/BAS-770H	46908409 (2004) Tested up to limit of solubility	XDE-742 was considered to be non-genotoxic in this *in vitro* chromosomal aberration assay using rat lymphocytes.
Other Effects 870.5395	Bone marrow micronucleus test	46908410 (2004) 0, 500, 1000 or 2000 mg/kg	Under experimental conditions, XDE-742 was considered negative in the mouse bone marrow micronucleus test.
870.6200b	Chronic neurotoxicity screening battery (Fischer rat) XDE-742	46908411 (2005) Non-guideline 0, 10, 100, and 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not observed
870.7485	Metabolism and pharmacokinetics (Fischer rat) XDE-742	46908412 (2005) 0, 10, or 1000 mg/kg	XDE was rapidly absorbed and excreted, essentially unchanged in urine and feces. Only one metabolite was present at >5%, and that was 2'-demethyl-XDE-742. Plasma concentrations peaked ½ hour post dosing; by 48 hours post dose, there were no remarkable differences in distribution or bioaccumulation. Urine and feces were the primary routes of elimination. There was some dose dependency in absorption and route of elimination.
870.7485	Metabolism and pharmacokinetics (CD-1 mice) XDE-742	46908413 (2006) 0, 10, 100, or 1000 mg/kg	Elimination of the absorbed radioactivity from plasma, RBC, and liver followed a biexponential pattern comprising of a rapid and a slow phase. Almost all of the absorbed radioactivity was eliminated from the body via rapid phase elimination, accounting for an average of >98% from the Cmax values, which resulted in a t1/2 of 2-3 hours. The remaining radioactivity was eliminated slowly via the slow elimination phase, resulting in the terminal t1/2 of males of 23-30 hours in plasma, 62-212 hours in RBC, and 31-307 hours in the liver for the low to high doses, respectively.

13544

R138171

Chemical: Sethoxydim

PC Code:
121001

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