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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361



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

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THROUGH: Richard Loranger, Branch Senior Scientist
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And

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Registration Division (7505P)

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 | -- | -- | -- |
| <p>The overall data submission is of high quality and acceptable for placement in to full review</p> <p>- Indicates study passed the screen for the parameter specified</p> <p>a. GLP/Compliance statement present</p> <p>b. Test article, including stability, homogeneity, concentration, purity</p> <p>c. Dosing adequacy (including appropriate levels and numbers of animals) and route of administration</p> <p>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.</p> <p>e. Control data including (as applicable) historical controls and positive controls</p> <p>x Indicates the study did not pass the screen for the parameter specified, or the information is not available.</p> <p>N/A Not Applicable.</p> | | | | | | | |

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 021117. 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: 021111. 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 Aktiengesellschaft. 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 Aktiengesellschaft. 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 | Stebbins, K.; Dryzga, M. (2004) XDE-742: One-Year Dietary Toxicity Study in Beagle Dogs. Project Number: 031012. Unpublished study prepared by Dow Chemical, USA. 339p. |
| 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 | Woolhiswe, M.; Wiscinski, 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) XDE-742/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 (Sprague-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 revertant 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 <i>in vitro</i> 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 C _{max} values, which resulted in a t _{1/2} of 2-3 hours. The remaining radioactivity was eliminated slowly via the slow elimination phase, resulting in the terminal t _{1/2} 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

HED File Code:

Memo Date: 7/31/1997

File ID: DPD237724

Accession #: 000-00-0113

HED Records Reference Center
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