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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

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OPP OFFICE OF PESTICIDE PROGRAMS
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

DATE: July 12, 2007

SUBJECT: PYROXSULAM: Report of the Cancer Assessment Review Committee

PC Code: 108702

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

Jessica Kidwell

TO: Kim Harper, Toxicologist (RAB2)
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The Cancer Assessment Review Committee met on June 6, 2007 to evaluate the carcinogenic potential of PYROXSULAM. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

Received in
EEB 7/24/2007

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

PYROXSULAM

PC CODE 108702

FINAL
July 12, 2007

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

PYROXSULAM CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Kimberly Harper, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Karlyn Bailey

Lori Brunsman, Statistician

William Burnam, Chair

Marion Copley

Kit Farwell

Nancy McCarroll

Robert Mitkus

Esther Rinde

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: PMRA (Canada) - Catherine Adcock, Deborah Ramsingh; Alan Levy (HED/RAB2)

PYROXSULAM CANCER ASSESSMENT DOCUMENT FINAL

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EXECUTIVE SUMMARY

On June 6, 2007, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of pyroxsulam. Pyroxsulam is being reviewed jointly by the US, Canada, and Australia; it is also under current review in the European Union.

Kimberly Harper of Registration Action Branch 2 presented the chronic toxicity/carcinogenicity study in F344 rats and the carcinogenicity study in CD-1 mice for pyroxsulam. In the chronic toxicity/carcinogenicity study, 65 Fischer 344 rats per sex were assigned nominal dose levels of 0, 10, 100 and 1000 mg/kg/day of Pyroxsulam for 104 weeks. Ten rats/sex/dose were necropsied at 12-months; an additional five rats/sex/dose were necropsied at 12 months for neurologic evaluation. In the carcinogenicity study, groups of 50 mice were assigned nominal dose levels of 0, 10, 100 and 1000 mg/kg/day of Pyroxsulam for 18 months. Ms. Harper also presented information on mutagenicity and structure activity relationships.

The CARC concluded the following:

Carcinogenicity

Rat

- There were no treatment-related tumor increases in male or female F344 rats.

- *Adequacy of the Dosing*: The CARC determined that dosing was adequate for the assessment of carcinogenic potential, even though there were few treatment related findings in this study, because the highest dose tested was the limit dose of 1000 mg/kg/day. Body weights were minimally reduced in the high dose females (4-7%) and body weight gains were decreased 8-10% throughout the study. The mean absolute and relative liver weights in females given 1000 mg/kg/day at 24 months were increased 6.1% and 10.9%, respectively. However, there were no corresponding histopathology findings that would explain the increased weights. There were no treatment related adverse effects on mortality, clinical signs, ophthalmology, hematology, clinical chemistry, or histopathology. The NOAEL was 1000 mg/kg/day for both sexes; the LOAEL was not observed in this study.

Mouse

- There was no treatment-related increase in tumor incidence in female CD-1 mice.

- In male CD-1 mice, the incidence of liver tumors for the 0, 10, 100, and 1000 mg/kg/day dose groups was as follows:

Adenomas: 5/49 (10%), 13/46 (28%), 9/49 (18%), 14/48 (29%)
Carcinomas: 1/49 (2%), 0/46 (0%), 2/49 (4%), 4/48 (8%)
Combined: 6/49 (12%), 13/46 (28%), 10/49 (20%), 15/48 (31%)

Male mice had a statistically significant trend for liver carcinomas at $p < 0.05$. There were statistically significant pair-wise comparisons of the 10 and 1000 mg/kg/day dose groups with the controls for liver adenomas, and liver adenomas and/or carcinomas combined, all at $p < 0.05$. The incidence rates for adenomas and combined adenomas/carcinomas exceeded the laboratory historical control range in both the low dose (10 mg/kg/day) and high dose groups (1000 mg/kg/day). The incidence rate for carcinomas in the high-dose group also exceeded the historical control range.

The CARC concluded, however, that the tumors in the low- and high-dose groups were not treatment-related due to the highly variable background levels of liver tumors in the CD-1 mouse, especially the males. A study published in 2005 by Charles River stated the historical control ranges for adenomas and carcinomas in male CD-1 mice from 52 separate studies were 3-28% and 2-16%, respectively. This indicates that liver tumors in male mice are fairly common and highly variable, suggesting that liver tumors in mice be held to a higher statistical standard of $p<0.01$, instead of $p<0.05$. The liver adenomas in the low- and high-dose groups in this study are at the high-end of the historical control range published by Charles River, but do not significantly exceed it. The historical control data also showed that liver tumors are more common in male mice than in female mice. Other points taken into consideration were 1) the lack of a clear dose response, 2) SAR – none of the other chemicals in this pesticide class are linked to liver tumors, 3) pyroxsulam is not mutagenic, 4) the mouse metabolism study indicated a dose-response in internal exposure, but there was no clear dose-response in tumors, 5) there was no increase in basophilic foci, which is more commonly linked to tumor formation than clear cell foci, and 6) there was no tumor response in female mice.

• *Adequacy of the Dosing:* Although there was little overt toxicity in either sex, other than the hepatotoxicity seen in males, the CARC determined that the dosing was adequate, but not excessive, for the determination of carcinogenic potential of pyroxsulam because the highest dose tested (1000 mg/kg/day) was the limit dose. The only effects related to treatment were in males and included increased absolute and relative liver weights (26.4% and 31.6%, respectively), increased liver masses in, increased number of foci of altered hepatocytes, and an increased incidence of tumors in males of the high dose. There were no effects on survival, clinical or ophthalmic examinations, body weights and body weight gains, food consumption, hematology, or clinical chemistry. There were no treatment related effects in female mice.

Mutagenicity

There is no mutagenicity concern for pyroxsulam

Structure Activity Relationship

As a whole, the triazolopyrimidine sulfonamide class of pesticides is not associated with liver tumors. Of the five chemicals that are currently registered in the US, four are classified as "not likely to be carcinogenic to humans." The fifth chemical, pensoxsulam, the most closely related to pyroxsulam, is classified as "suggestive, but not enough evidence to determine human significance" due to increased large granular lymphocytic leukemia in rats. Penoxsulam was not associated with liver tumors in rats or mice.

Classification and Quantification of Carcinogenic Potential

In accordance with EPA's *Final Guidelines for Carcinogen Risk Assessment (March 2005)*, the CARC classified pyroxsulam as ***"Not Likely To Be Carcinogenic To Humans."*** This decision was based on the following: 1) There are no treatment-related tumors in rats or mice. The liver tumors seen in male mice were not considered to be treatment-related. Liver tumors are very common and highly variable in CD-1 mice, especially males; 2) The SAR shows that six closely related chemicals are not associated with liver tumors; and 3) There is no mutagenicity concern.

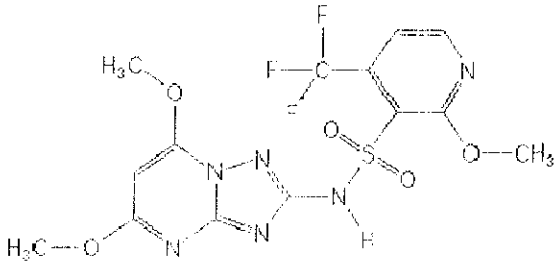
Quantification of carcinogenic potential is not required.

I. INTRODUCTION

On June 6, 2007, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of pyroxsulam. Pyroxsulam is being reviewed jointly by the US, Canada, and Australia; it is also under current review in the European Union.

II. BACKGROUND INFORMATION

Pyroxsulam is a new herbicide belonging to the triazolopyrimidine sulfonamide class of pesticides. Dow AgroSciences is currently seeking food uses on wheat, hay, and straw. (N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluromethyl)pyridine-3-sulfonamide), acts by inhibiting acetolactate synthase. This product is being developed as a systemic post-emergence broad-spectrum grass and broadleaf herbicide for use in wheat production systems (including durum). Dow AgroSciences is submitting two formulations containing pyroxsulam for registration in the U.S. GF-1674 is a 30 g/L oil dispersion with a 3:1 ratio of cloquintocet-mexyl to pyroxsulam; Dow states that this formulation will be for use on Spring wheat. GF-1274 is a 75 g/kg wettable granule that has a 1:1 ratio of cloquintocet-mexyl to pyroxsulam. The PC code is 108702.



III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in F-344 Rats

Reference: Stebbins, K. E., and K. J. Brooks (02 November 2005). XDE-742: Two-Year Chronic Toxicity/Oncogenicity and Chronic Neurotoxicity Study In Fischer 344 Rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Study ID: 031014, 02 November 2005. MRID 46908407. Unpublished

A. Experimental Design

The study design allocated groups of 65 Fischer 344 rats per sex to nominal dose levels of 0, 10, 100 and 1000 mg/kg/day of Pyroxsulam for 104 weeks. Ten rats/sex/dose were

necropsied at the 12-month mark: an additional five rats/sex/dose were necropsied at 12 months for neurologic evaluation

B. Discussion of Tumor Data:

There were no significant increases in tumors in the treated groups compared to controls.

C. Non-Neoplastic Lesions

There was a decrease in the incidence of basophilic foci of altered cells in hepatocytes of the high dose females; the decrease was not considered toxicologically adverse.

Table 1. Selected non-neoplastic histological findings

Sex	Males				Females			
Dose (mg/kg/day)	0	10	100	1000	0	10	100	1000
Number of Rats	50	50	50	50	50	50	50	50
Liver: Focus of basophilic hepatocytes; 1-5	25	15	18	17	2	1	4	21*
Liver: Focus of basophilic hepatocytes; 6-10	13	19	16	1*	7	8	9	14
Liver: Focus of basophilic hepatocytes; 11-20	4	3	0	0	18	23	17	4*
Liver: Focus of basophilic hepatocytes; 21 or more	0	0	0	0	19	14	14	0*

*Statistically identified by Yate's Chi-square test, alpha = 0.05, two-sided.

D. Adequacy of the Dosing for Assessment of Carcinogenicity:

There were no treatment related adverse effects on mortality, clinical signs, ophthalmology, hematology, clinical chemistry, or histopathology. Body weights were minimally reduced in the high dose females (4-7%) throughout the study, and body weight gains were decreased 8-10% throughout the study. The differences in BW/BWG as compared to controls were not more pronounced as the study progressed. The mean absolute and relative liver weights in females given 1000 mg/kg/day at 24 months were increased 6.1% and 10.9%, respectively. However, there were no corresponding histopathology findings that would explain the increased weights. The decrease incidence of basophilic foci of alteration is not generally associated with toxicity. Although there were few treatment related findings in this study, the highest dose tested was the limit dose of 1000 mg/kg/day. The CARC determined that the dosing was adequate for the assessment of carcinogenic potential.

2. Carcinogenicity Study in CD-1 Mice

Reference: Johnson, K.A., D.V.M., Ph.D. ; M. D. Dryzga, B.S. ; B. L. Yano, D.V.M., Ph.D. (15 December 2005). XDE-742: 18-Month Dietary Oncogenicity Study in CD-1 Mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Study ID: 031015, 15 December 2005. MRID 46908406. Unpublished

A. Experimental Design

The study design allocated groups of 50 mice to nominal dose levels of 0, 10, 100 and 1000 mg/kg/day of Pyroxsulam for 79 weeks. Actual doses were 0, 10, 100 and 932 mg/kg/day for males.

B. Discussion of Survival and Tumor Data

There were no compound-related tumors and no increased mortality in the female mice.

Only analyses of the males are presented in this document.

There were no statistically significant incremental changes in mortality with increasing doses of Pyroxsulam in male mice (Table 2).

Male mice had a statistically significant trend for liver carcinomas at $p < 0.05$. There were statistically significant pair-wise comparisons of the 10 and 1000 mg/kg/day dose groups with the controls for liver adenomas, and liver adenomas and/or carcinomas combined, all at $p < 0.05$. The statistical analyses of the tumors in the male mice were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 3) (Memo, L. Brunsman, 5/18/07, TXR# 0054586).

Historical control data is presented in Table 4. Out of 200 male CD-1 mice, 23 had a liver adenoma (incidence 12%); the range for the individual studies was 1-8 mice with liver adenomas per 50 mice or an incidence rate of 2-16%. Out of 200 male mice, 5 had a liver carcinoma (incidence rate 3%); the range of individual animals with a liver carcinoma (with or without metastasis) was 1-2 per 50 mice (incidence rate 2-4%). The overall incidence rate for combined liver tumors was 27/200 or 14%. The range for the individual studies was 3-10 per 50 mice or an incidence rate of 6-20%.

Table 2. Pyroxsulam – CD-1 (Crl:CD1(ICR)) Mouse Study (MRID 46908406)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks			
Dose (mg/kg/day)	1-26	27-52	53-79[f]	Total
0	0/50	1/50	9/49	10/50 (20)
10	1/50	3/49	6/46	10/50 (20)
100	0/50	2/50	8/48	10/50 (20)
1000	0/50	2/50	10/48	12/50 (24)

Table copied from Memo, L. Brunsman, 5/18/07, TXR# 0054586.
[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at week 79.
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Pyroxsulam – CD-1 (Crl:CD1(ICR)) Mouse Study (MRID 46908406)

Male Liver Tumor Rates[+]
and Fisher's Exact Test and Exact Test for Trend Results

	Dose (mg/kg/day)			
	0	10	100	1000
Adenomas (%)	5/49 (10)	13/46 (28)	9[a]/49 (18)	14/48 (29)
p =	0.06696	0.02300*	0.19363	0.01716*
Carcinomas (%)	1/49 (2)	0/46 (0)	2[b]/49 (4)	4/48 (8)
p =	0.02622*	1.00000	0.50000	0.17451
Combined (%)	6/49 (12)	13/46 (28)	10[c]/49 (20)	15[d]/48 (31)
p =	0.05737	0.04462*	0.20651	0.02067*

Table copied from Memo, L. Brunsman, 5/18/07, TXR# 0054586.
[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
[a]First adenoma observed at week 53, dose 100 mg/kg/day.
[b]First carcinoma observed at week 73, dose 100 mg/kg/day.
[c]One animal in the 100 mg/kg/day dose group had both an adenoma and a carcinoma.
[d]Three animals in the 1000 mg/kg/day dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Historical Control Values: Primary Hepatocellular Neoplasms in Male CD-1 Mice from 18-Month Dietary Oncogenicity Studies

Organ/Observation	Study			
	A	B	C	D
Liver (number examined)	50	50	50	50
Adenoma, hepatocyte, benign, primary - one	8	1	5	7
Adenoma, hepatocyte, benign, primary - two	0	1	0	1
Carcinoma, hepatocyte, malignant without metastasis - one	2	1	0	1
Carcinoma, hepatocyte, malignant with metastasis - one	1	0	0	0
Total Mice with Adenoma and/or Carcinoma	10	3	5	9

Study A necropsied 12/2001; Study B necropsied 05/2003; Study C necropsied 12/2003; Study D necropsied 04-05/2004.

C. Non-Neoplastic Lesions

Males in the high dose group had greater numbers of mice with foci of altered cells and a greater incidence and multiplicity of hepatocellular tumors – adenomas and/or carcinomas (summary in Table 4).

Foci of altered cells were categorized by the cytoplasmic staining of the majority of the cells in the focus. Apparent treatment-related increases in the numbers of clear (vacuolated) cell foci (statistically significant) and lesser increases in the numbers of mixed or eosinophilic cell foci occurred in males given 1000 mg/kg/day. Foci of altered cells are relatively uncommon in control CD-1 mice. Male mice given 1000 mg/kg/day that had hepatic foci of altered cells tended to have a multiplicity of the effects considered related to treatment, *i.e.*, either more than one subtype of focus of altered cells or a focus along with one or more hepatocelluar adenoma(s) and/or carcinoma(s). However, multiplicity was also found for one control male (#03A1389) which had three basophilic foci and one mixed cell focus of altered cells along with six hepatocellular adenomas. The incidence of foci of altered cells in the liver of male mice given 10 or 100 mg/kg/day and females from all dose levels was low and similar to controls.

Table 5. Non-neoplastic lesion in the liver of mice exposed to XDE-742.

	Dose Level (mg/kg/day)							
	Males				Females			
	0	10	100	1000	0	10	100	1000
Liver (number examined)	50	50	50	50	50	50	50	50
Focus of Altered Cells, hepatocyte, - basophilic, one or more	1	1	2	2	0	2	0	1
- clear, one or more	0	0	0	7*	0	0	0	0
- eosinophilic, one or more	0	0	1	3	1	0	1	1
- mixed, one	2	1	0	5	1	0	0	0
Number of Mice with Focus of Altered Cells, hepatocyte, any descriptor, any number, (total)	2	3	2	12*	2	3	2	2
Number of Mice with a Focus of Altered Cells, any descriptor, and a primary hepatocyte tumor (Adenoma and/or Carcinoma)[a]	1	0	1	7	0	0	0	0
Hyperplasia	0	0	0	0	1	0	0	0
Hypertrophy, centrilobular/midzonal (very slight-slight)	23	19	19	28	3	2	4	4
Necrosis, hepatocyte focal (very slight)	2	0	4	4	3	2	4	1
Vacuolization, hepatocyte centrilobular/midzonal	4	1	2	6	0	0	0	1

* Statistically significant difference by Yates Chi-Square, alpha = 0.05, two-sided.

[a] Not statistically analyzed.

Data obtained from Text Table 8 on page 35 and Table 26 on page 172 of the study report.

D. Adequacy of the Dosing

There were no effects on survival, clinical or ophthalmic examinations, body weights and body weight gains, food consumption, hematology, or clinical chemistry. The only effects related to treatment were increased absolute and relative liver weights in males of the high dose group (26.4% and 31.6%, respectively). Gross pathology examination showed an increased in the number of liver masses in the male mice of the high dose group. Microscopic examination of the tissues showed an increased number of foci of altered hepatocytes and an increased incidence of tumors. There were no treatment related effects in female mice. Although there was little overt toxicity in either sex, other than the hepatotoxicity seen in males, the CARC determined that the dosing was adequate, but not excessive, for the determination of carcinogenic potential of pyroxsulam because the highest dose tested (1000 mg/kg/day) is the limit dose.

IV. TOXICOLOGY

1. Metabolism

Rat (MRID 46908412): In a rat metabolism study (MRID 46908412), ^{14}C-pyroxsulam (^{14}C-XDE-742: batch no. DAS Inv# 1901; purity 99.5% a.i.: triazole-ring ^{14}C-labeled) was administered as an aqueous METHOCEL™ suspension by oral gavage to groups of three or four male Fischer 344 rats as a single nominal dose of 10 or 1000 mg pyroxsulam (XDE-742) per kg body weight. Another group of four male rats was administered 14 daily 10 mg/kg oral doses of unlabeled XDE-742 followed by a single 10 mg/kg triazole-ring ^{14}C-labeled XDE-742 on day 15. An additional group of four male Fischer 344 rats was administered a single oral nominal dose of 10 mg/kg of pyridine-ring ^{14}C-labeled XDE-742 (batch no DAS Inv# 1905; purity 100% a.i.) to determine if ring separation occurs during metabolism. In order to determine the biliary elimination of ^{14}C-XDE-742, three male rats were administered an intravenous (iv) emulsion of 10 mg/kg triazole-ring ^{14}C-labeled XDE-742.

The data indicate XDE-742 was rapidly absorbed and ^{14}C-XDE-742-derived radioactivity was rapidly excreted. Saturation of absorption was observed between the doses of 10 and 1000 mg XDE-742/kg leading to a decrease in the bioavailability of XDE-742. Between 85 and 90% of the XDE-742 dosed was essentially unchanged in the urine and feces. One major metabolite found at 4-16% of the administered dose in the urine and feces was 2'-demethyl-XDE-742. Volatile organics and CO_2 were negligible for the low dose groups of both ring ^{14}C-labels of XDE-742 (groups 1 and 5) and group 2 animals (high dose).

Based on the time to peak plasma or RBC radioactivity levels, ^{14}C-XDE-742 was rapidly absorbed and eliminated both by oral and iv routes. Following a single dose of ^{14}C-XDE-742 at 10 mg/kg, a mean peak plasma or RBC concentration was reached at 26-30 minutes and 6 minutes post-dosing for oral and iv routes, respectively. The mean $t_{½}$ of distribution was 1-1.3

hours and the mean $t_{½}$ of elimination was 11-14.5 hours for both oral and iv routes. The AUCs for RBCs were about a tenth of that obtained with plasma, suggesting little binding of XDE-742 with RBCs.

XDE-742 was rapidly excreted *via* the urine and feces with the majority of the radioactivity eliminated by 12 and 24 hr post-dosing, respectively, and with some dose dependency in the routes of excretion. At 48 hours post-dosing between 98 and 110% of the administered dose was recovered in the urine, feces, tissues, carcasses and cage wash for all dose groups. The urine accounted for 57-78% and 30% of the administered dose from all low dose groups and high dose group, respectively, following 48 hours post-dosing. The feces accounted for 45-51% and 69% of the administered dose from all low dose groups (except for iv dose group) and high dose group, respectively. Following the iv administration of XDE-742, the feces accounted for 17% of the administered dose. Based on this, one might conclude that at least 17% of the administered dose would be excreted via the biliary route. For all dose groups, radioactivity recovered in the tissues/carcasses and the cage wash accounted for less than 1% and 1-3% of the administered dose, respectively. Also, no remarkable differences in tissue distribution or bioaccumulation were seen for all dose groups.

Volatile organics and CO_2 in expired air were not quantifiable for the low dose groups of both ring ^{14}C-labels of XDE-742 (groups 1 and 5). Group 2 animals (high dose) had <0.005 and 0.001% of the administered dose detected in volatile organics and CO_2.
There were a total of 7 radioactive peaks detected at >0.05% of the administered dose in the excreta from the groups that were analyzed. Only parent XDE-742 and 2'-demethyl-XDE-742 (XDE-742-DM) were detected in all the matrices and ranged from 80-90% and 4-16% of the administered dose, respectively. In the urine, the parent XDE-742 and 2'-demethyl-XDE-742 (XDE-742-DM) ranged from 28-50 and 2-11% of the administered dose, respectively. In the feces, XDE-742 and 2'-demethyl-XDE-742 ranged from 34-62 and 2-7% of the administered dose, respectively. No other peaks accounted for >1.5% of the administered dose/group.
There were essentially no differences in the total radioactivity eliminated in the urine and feces between the two different ring ^{14}C-labels of XDE-742 when they were administered as a single oral dose. Also, there were no differences among the distribution of parent XDE-742 and 2'-demethyl-XDE-742 in the urine and feces. Four major peaks (4 in the urine and 2 in the feces, <1% of the administered dose each) unique to the metabolism of the triazole ^{14}C-labeled XDE-742 samples would be consistent with minimal ring cleavage occurring during the metabolism of XDE-742.

This metabolism study is classified acceptable/guideline and satisfies the guideline requirements for a metabolism study (OPPTS 870.7485 and OECD 417) in rats.

Mouse (MRID 46908413): In a mouse metabolism study (MRID 46908413), three groups of 40 male mice were administered a single oral dose of ^{14}C-pyroxsulam (triazole-ring ^{14}C-XDE-742; batch no. DAS Inv. 1901; purity 100% a.i) in a suspension of 0.5% METHOCEL™ at 10, 100, or 1000 mg/kg to provide data on plasma, RBC, and liver ^{14}C-time-course through 72 hours

post-dosing. Data from 4 mice per group were obtained at 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, and 72 hours post-dosing. In addition, limited plasma, RBC, and liver ^{14}C concentrations were generated from 12 female mice following a single oral gavage administration of 100 mg ^{14}C-XDE-742/kg for comparison. From these data, dose-related changes in test material absorption, distribution and elimination were estimated.

Orally administered ^{14}C-XDE-742 was rapidly absorbed without any apparent lag time with an absorption rate constant of 4.4, 2.6, and 0.7 per hour at the 10, 100 and 1000 mg/kg doses, respectively. Both plasma and RBC C_{max} occurred at 0.5, 1, and 1 hour post-dosing and liver C_{max} occurred at 0.5, 1, and 4 hours post-dosing for male mice dosed at 10, 100 and 1000 mg/kg, respectively. ^{14}C-XDE-742 cleared quickly from plasma, RBC and liver with $t_{½}$ (alpha phase) of 2, 2, and 3 h for the 10, 100, and 1000 mg/kg groups, respectively. Overall, the plasma, RBC, and liver AUC's increased by a factor of 6 from the 10 to 100 mg/kg dose groups, and by a factor of 4 to 5 from the 100 to the 1000 mg/kg dose groups indicating lower or less efficient absorption at the middle and high doses when compared to the low dose. Although the increases in AUC were less than dose proportional, significantly higher exposure of ^{14}C-XDE-742 with increasing dose was apparent (i.e., up to 30-fold from 10 to 1000 mg/kg).

Elimination of the absorbed radioactivity from plasma, RBC and liver followed a biexponential pattern comprising of a rapid (α) and a slow (β) phase. Most of the absorbed radioactivity was eliminated from the body via α elimination phase which resulted in a $t_{½}$ of 2-3 hours. The remaining radioactivity was eliminated slowly via the β elimination phase resulting in the terminal $t_{½}$ of 22-30 hours in plasma, 62-212 hours in RBC, and 32-307 hours in the liver for the males dosed at 10, 100 and 1000 mg/kg, respectively.

^{14}C-XDE-742 did not accumulate in the carcass or tissues 72 hours post-dosing in any of the dose groups. For all dose groups, radioactivity recovered in the tissues/carcasses and the cage wash accounted for less than 1% and 1-4% of the administered dose, respectively.

XDE-742 was rapidly excreted *via* the urine and feces with the majority of the radioactivity eliminated by 12 and 24 hr post-dosing, respectively, and with some dose dependency in the routes of excretion. At 72 hours post-dosing between 101 and 108% of the administered dose was recovered in the urine, feces, tissues, carcasses and cage wash for all dose groups. The major route of elimination of ^{14}C-XDE-742 was urine (56-61% of the administered dose) for the males dosed at 10 and 100 mg/kg and the females dosed at 100 mg/kg. For the single oral high dose (1000 mg/kg), 26% of the administered dose was eliminated in the urine. Between 77 and 84% of the radioactivity was eliminated in the urine (all groups) within 0-12 hours post-dosing. By 72 hours post-dosing, between 39 and 43% of the administered dose was eliminated in feces for the males dosed at 10 and 100 mg/kg and the females dosed at 100 mg/kg. For the 1000 mg/kg group, 77% of the administered dose was eliminated in the feces.

This metabolism study is classified acceptable/non-guideline. This study was conducted to provide data on plasma, RBC, and liver ^{14}C-time-course of ^{14}C-XDE-742 following single oral

gavage administrations to male and female mice for comparative purposes. This study was not designed to satisfy a metabolism guideline.

2. Mutagenicity

There is no mutagenic concern for XDE-742 at this time. This assessment of the **parent compound** is based on the following five acceptable/guideline genetic toxicology studies:

1. In an *in vitro* reverse gene mutation test with *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA98 and *Escherichia coli* strain WP2 *urv*A at concentrations up to 5000 µg/plate (limit concentration), XDE-742 was not mutagenic with or without metabolic activation (MRID 46908414).

2. In an *in vitro* mammalian cell gene mutation assay in Chinese hamster ovary cells at the HGPRT locus at concentrations up to 200 µg/mL (limit of solubility), XDE-742 was not mutagenic with or without metabolic activation (MRID 46908408).

3. In an *in vitro* chromosomal aberration assay using rat lymphocytes at concentrations up to 200 µg/ml (limit of solubility) in the presence and absence of metabolic activation, there was no evidence of increased chromosomal aberrations induced above background (MRID 46908409).

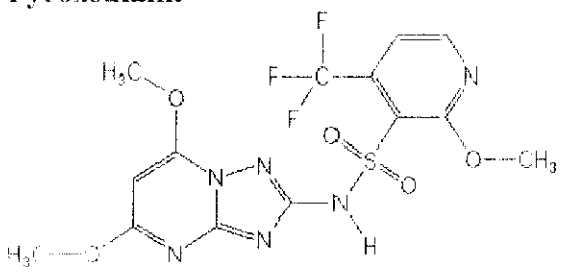
4. In an *in vivo* micronucleus assay performed in CD-1 mice, no increase in micronucleated polychromatic erythrocytes was seen following dosing up to the limit dose of 2000 mg/kg bw (MRID 46908410). No mortality was present at any dose.

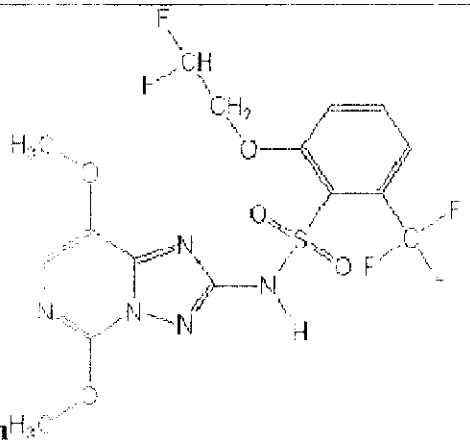
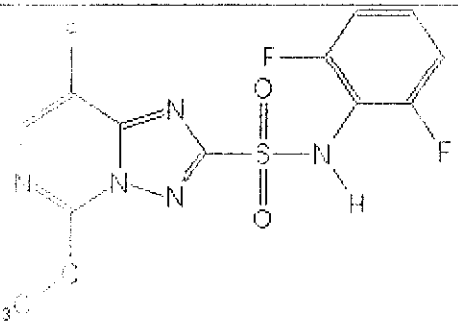
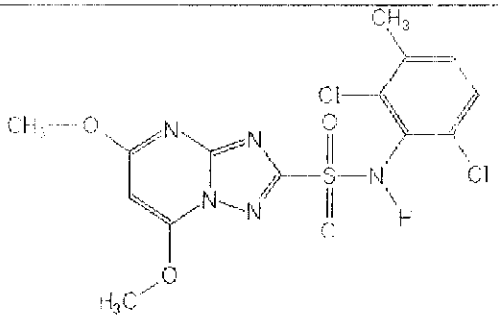
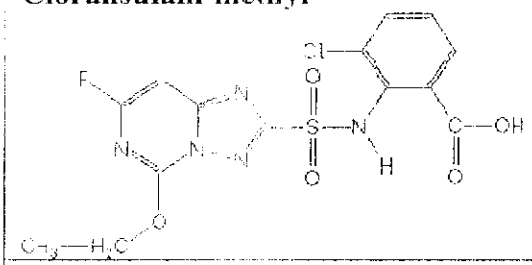
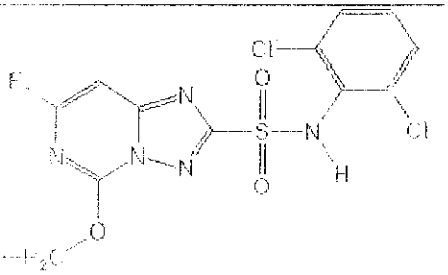
5. In an *in vivo/in vitro* measurement of unscheduled DNA synthesis using CD-1 mouse hepatocytes, no induction of UDS was observed at doses up to the limit dose of 2000 mg/kg bw. (MRID 47022001).

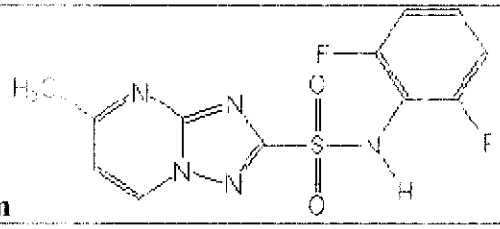
3. Structure-Activity Relationship

Pyroxsulam belongs to the triazolopyrimidine sulfonamide class of chemicals. There are six other chemicals in this class, five of which are currently registered in the US. None of the chemicals is considered mutagenic; and 4 of the 5 are considered "not likely to be carcinogenic to humans" or "evidence of non-carcinogenicity to humans." Penoxsulam appears to be its closest congener; its' cancer classification is "suggestive evidence but not enough to evaluate human significance," due to an increase in large granular lymphocytic leukemia compared to control.

Pyroxsulam:



Chemical/ Pesticide Class Structure	PC Code/ CAS#	Cancer Classification	Tumor Types	Muta.
 **Penoxsulam**	119031/ 219714-96-2	Suggestive evidence but not enough to evaluate human significance	Large granular lympho-cytic leukemia	Negative
 **Florasulam**	129108/ 145701-23-1	Not likely	None	Negative
 **Metosulam** not yet registered in US	NA/ 139528-85-1	NA	None	NA
Cloransulam-methyl 	129116/ 147150-35-4	Not likely	None	Negative
 **Diclosulam**	129122/ 20145701-21-9	Not likely	None	Negative

Chemical/ Pesticide Class Structure	PC Code/ CAS#	Cancer Classification	Tumor Types	Muta.
 **Flumetsulam**	129016/ 98967-40-9	Group E – Evidence of non-carcinogenicity to humans	None	Negative

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

28-Day Rats (MRID 46908349): In a 28-day oral toxicity study (MRID 46908349) [XR-742 (96.7% a.i., lot# 200100558-14B, TSN102505)] was administered to 5 Fischer 344 rats/sex/dose in their diet at dose levels of 0, 10, 100, 500, or 1000 mg/kg/day. Animals were observed daily for clinical signs and mortality. Detailed clinical observations, body weights, and food consumption were recorded twice during the first week and weekly thereafter. Ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, and gross pathology and histopathology were also examined.

There were no treatment related effects on mortality, clinical signs, or body weight and/or body weight changes throughout the treatment period. There were no effects observed in ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology at the end of the study.

The LOAEL was not observed. The NOAEL is 1000 mg/kg/day, the limit dose.

This 28-day oral toxicity study in the rat is acceptable/guideline; it is a range-finding study for the 90-day and 2-year rat studies.

90-Day Rats (MRID 46908350): Ten male and ten female Fischer 344 rats per group were given test diets formulated to supply 0, 10, 100, or 1000 milligrams XDE-742/BAS-770H per kilogram body weight per day (mg/kg/day) for at least 90 days. Parameters evaluated were daily observations, detailed clinical observations, ophthalmologic examinations, body weight, feed consumption, hematology, clinical chemistry, urinalysis, selected organ weights, and gross and histopathologic examinations. An additional ten male and ten female rats in the control and high-dose groups were held untreated for at least 28 days following the dosing period to assess recovery from treatment-related effects.

There were no treatment-related effects on feed consumption, ophthalmologic observations,

and hematologic parameters. A few males and up to 50% of females given 1000 mg/kg/day had treatment-related perineal urine soiling at various times during the study. Females given 1000 mg/kg/day had statistically identified decreases in mean body weights from test day 29 through the end of the 90-day dosing period. Males given 1000 mg/kg/day had a statistically identified lower alanine aminotransferase (ALT) value, and a statistically identified higher cholesterol concentration, that were interpreted to be treatment-related. Males and females given 1000 mg/kg/day also had a treatment-related lower concentration of protein in the urine, relative to controls. The alterations in ALT, cholesterol, and urine protein were interpreted to be of no toxicological significance. The only treatment-related change in male organ weights was a statistically identified higher relative liver weight for the 1000 mg/kg/day group. Females given 1000 mg/kg/day had statistically identified lower absolute heart, ovary, and thymus weights, and statistically identified higher relative kidney, liver, and brain weights. The alterations in these female organ weights were reflective of the treatment-related lower body weights at the 1000 mg/kg/day dose level. There were no treatment-related gross or histopathologic effects.

Following a 28-day recovery period, the ALT value for males given 1000 mg/kg/day was still lower than controls but not statistically identified, following the 28-day recovery period. There was complete recovery of all other treatment-related effects.

The effects observed at 1000 mg/kg/day were not considered to be toxicologically significant and, therefore, **the NOAEL for this study is 1000 mg/kg/day. A LOAEL was not observed.**

This 90-day oral toxicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rat.

90-Day Mice (MRID 46908351): Ten male and ten female CD-1 mice per group were given test diets formulated to supply 0, 10, 100, or 1000 milligrams XDE-742/BAS-770H per kilogram body weight per day (mg/kg/day) for at least 90 days. Parameters evaluated were daily observations, detailed clinical observations, ophthalmologic examinations, body weight, feed consumption, hematology, clinical chemistry, selected organ weights, gross and histopathologic examinations.

There were no treatment-related effects on body weight, feed consumption, ophthalmology, clinical observations or hematologic parameters. Females given 1000 mg/kg/day had statistically-identified increased serum cholesterol (29.9% greater than controls), which was at the high-end of the historical control range (5/10 females had cholesterol levels in excess of the historical control average). Males at 1000 mg/kg/day also had increased cholesterol (22.3%) that was not statistically identified likely due to one high dose male that had higher cholesterol levels than all the others (242 compared to <200 mg/dL). Half (5/10) of the high-dose males had cholesterol levels outside the historical control range. The only other finding was a statistically-identified increase in absolute and relative liver weights for the 1000 mg/kg/day group males (18.3% and 12.3% higher than controls, respectively). The absolute and relative liver weights of females given 1000 mg/kg/day were 7.7% and 5.0% greater than controls.

respectively, and were not statistically identified. Taken together, the increased cholesterol levels in males and females and the increased liver weights in males could indicate hepatic disease, however, there was no corroborating evidence of gross or histopathological changes in the liver. Therefore, these effects were not considered adverse.
The LOAEL was not observed. The NOAEL is 1000 mg/kg/day.

This study is acceptable and satisfies the guideline requirement for a Subchronic Oral Toxicity [feeding] CD-1 Mice; OPPTS 870.3100 (rodent); OECD 408, EEC, Part B.26, JMAFF (Subchronic Oral Toxicity Study).

b) Chronic Toxicity

Rats (MRID 46908407): This study was conducted to evaluate the potential chronic toxicity and oncogenicity of XDE-742 (N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide) to rats. Groups of 65 male and 65 female Fischer 344 rats were fed diets formulated to provide 0, 10, 100, or 1000 mg/kg/day. Ten rats/sex/dose were necropsied after one year (chronic toxicity group), five rats/sex/dose were necropsied after one year (chronic neurotoxicity group), and the remaining 50 rats/sex/dose were fed the respective diets for up to two years and necropsied (oncogenicity group). The chronic neurotoxicity study has been previously reported.

There were no treatment related adverse effects on mortality, clinical signs, ophthalmology, hematology, clinical chemistry, histopathology.

Females given 1000 mg/kg/day had treatment-related statistically identified lower mean body weights at most time-points when compared to controls. At 12 and 24 months, body weight gains for females given 1000 mg/kg/day were 7.8% and 6.7% lower than controls, respectively. The decrement in body weight gain was interpreted to be a non-adverse effect, because the lower weights did not worsen during the second year of the study, and the body weights at most time-points throughout the study were within historical control ranges. Feed consumption for females administered 1000 mg/kg/day was statistically identified as lower than controls between test days 8 through 84. This decrement in feed consumption was interpreted to be treatment-related, and corresponded to the lower body weights. For the remainder of the study, the feed consumption of females given 1000 mg/kg/day was comparable to controls at most time-points. There were no treatment-related effects on body weights or feed consumption of females given 10 or 100 mg/kg/day, nor of males from any dose group.

Treatment-related changes in organ weights consisted of higher mean absolute (4.1%) and relative (8.8%) liver weights in males given 1000 mg/kg/day at 12 months only, and higher mean absolute (6.1%) and relative (10.9%) liver weights in females given 1000 mg/kg/day at 24 months. The higher relative liver weights were statistically identified as different from controls. The liver weight changes were interpreted to be non-adverse, based on the lack of any corresponding clinical pathologic or histopathologic liver effects.

A LOAEL was not observed in this study. The no-observed-adverse-effect level (NOAEL) was 1000 mg/kg/day for both sexes.

This chronic/carcinogenicity study in the rats is acceptable and satisfies the guideline requirement for a chronic/carcinogenicity study (OPPTS 870.4300); OECD 453 in rats.

Mice (MRID 46908406): In a carcinogenicity study (MRID 46908406) pyroxsulam (98.0% a.i., E0952-52-01/TSN103826)] was administered to 50 CD-1 mice/sex/dose in their diet at nominal dose levels of 0, 10, 100, or 1000 mg/kg bw/day) for 18 months. Animals were evaluated by daily cage side observation and periodic handheld detailed clinical examination. Body weight and food consumption were measured weekly for the first 13 weeks and monthly thereafter. Ophthalmic examinations were conducted pre-exposure and prior to necropsy. All mice had a complete necropsy examination with white blood cell (WBC) and differential WBC counts and weights of selected organs at the scheduled necropsy. Tissues were examined histopathologically from all control and high-dose group mice, as well as all mice that died or were euthanized in moribund condition. The kidneys, liver, lungs, ovaries, and all relevant gross lesions from the low- and intermediate-dose groups at the terminal necropsy were also examined histopathologically.

There were no effects of XDE-742 consumption with regards to survival, clinical examinations, body weights and body weight gains, or food consumption. There were no effects related to treatment for either ophthalmic examinations or total or differential WBC counts.

Treatment-related effects occurred in the liver of male mice given 1000 mg/kg/day, with the mean absolute and relative liver weights increased by 26.4% and 31.6%, respectively, increased incidence of liver masses at necropsy, histopathologically increased incidence of foci of altered cells (hepatocytes), and increased incidence and numbers of hepatocellular adenomas and carcinomas, although the tumor incidences were not statistically identified. There was a tendency of affected mice to have both foci of altered cells and multiple tumors (adenomas and/or carcinomas).

Male mice given 10 mg/kg/day had a slightly increased incidence and number of liver adenomas that was not considered dose related because it was not accompanied by increased organ weight or alterations in histopathology as was the high dose group. There were no effects on males or females at 100 mg/kg/day.

The **LOAEL is 1000 mg/kg/day,** based on the increase in mean absolute and relative liver weights and the increased incidence of foci of altered cells (hepatocytes). The **NOAEL is 100 mg/kg/day.**

This carcinogenicity study in mice is acceptable/guideline and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in rats.

5. Mode of Action Studies:

No mode of action studies were submitted for this chemical.

V. Committee's Assessment of the Weight-of-the-Evidence

1. Carcinogenicity

Rat

•There were no treatment-related tumor increases in male or female F344 rats.

•*Adequacy of the Dosing*: The CARC determined that the dosing was adequate for the assessment of carcinogenic potential even though there were few treatment related findings in this study because the highest dose tested was the limit dose of 1000 mg/kg/day. Body weights were minimally reduced in the high dose females (4-7%) throughout the study, and body weight gains were decreased 8-10% throughout the study. The mean absolute and relative liver weights in females given 1000 mg/kg/day at 24 months were increased 6.1% and 10.9%, respectively. However, there were no corresponding histopathology findings that would explain the increased weights. There were no treatment related adverse effects on mortality, clinical signs, ophthalmology, hematology, clinical chemistry, histopathology. The NOAEL was 1000 mg/kg/day for both sexes; the LOAEL was not observed in this study.

Mouse

• There was no treatment-related increase in tumor incidence in female CD-1 mice.

• In male CD-1 mice, the incidence of liver tumors for the 0, 10, 100, and 1000 mg/kg/day dose groups was as follows:

Adenomas: 5/49 (10%), 13/46 (28%), 9/49 (18%), 14/48 (29%)
Carcinomas: 1/49 (2%), 0/46 (0%), 2/49 (4%), 4/48 (8%)
Combined: 6/49 (12%), 13/46 (28%), 10/49 (20%), 15/48 (31%)

Male mice had a statistically significant trend for liver carcinomas at $p < 0.05$. There were statistically significant pair-wise comparisons of the 10 and 1000 mg/kg/day dose groups with the controls for liver adenomas, and liver adenomas and/or carcinomas combined, all at $p < 0.05$. The incidence rates for adenomas and combined adenomas/carcinomas exceeded the laboratory historical control range in both the low dose (10 mg/kg/day) and high dose groups (1000 mg/kg/day). The incidence rate for carcinomas in the high-dose group also exceeded the historical control range.

The CARC concluded, however, that the tumors in the low- and high-dose groups were not treatment-related due to the highly variable background levels of liver tumors in the CD-1 mouse, especially the males. A study published in 2005 by Charles River stated the historical control ranges for adenomas and carcinomas in male CD-1 mice from 52 separate studies were 3-28% and 2-16%, respectively. This indicates that liver tumors in male mice are fairly common and highly variable, suggesting that liver tumors in mice be held to a higher statistical standard of $p<0.01$, instead of $p<0.05$. The liver adenomas in the low- and high-dose groups in this study are at the high-end of the historical control range published by Charles River, but do not significantly exceed it. The historical control data also showed that liver tumors are more common in male mice than in female mice. Other points taken into consideration were 1) the lack of a clear dose response, 2) SAR – none of the other chemicals in this pesticide class are linked to liver tumors, 3) pyroxsulam is not mutagenic, 4) the mouse metabolism study indicated a dose-response in internal exposure, but there was no clear dose-response in tumors, 5) there was no increase in basophilic foci, which is more commonly linked to tumor formation than clear cell foci, and 6) there was no tumor response in female mice.

- *Adequacy of the Dosing:* Although there was little overt toxicity in either sex, other than the hepatotoxicity seen in males, the CARC determined that the dosing was adequate, but not excessive, for the determination of carcinogenic potential of pyroxsulam because the highest dose tested (1000 mg/kg/day) was the limit dose. The only effects related to treatment were in males and included increased absolute and relative liver weights (26.4% and 31.6%, respectively), increased liver masses in, increased number of foci of altered hepatocytes, and an increased incidence of tumors in males of the high dose. There were no effects on survival, clinical or ophthalmic examinations, body weights and body weight gains, food consumption, hematology, or clinical chemistry. There were no treatment related effects in female mice.

2. Mutagenicity

There is no mutagenicity concern for pyroxsulam

3. Structure Activity Relationship

As a whole, the triazolopyrimidine sulfonamide class of pesticides is not associated with liver tumors. Of the five chemicals in that are currently registered in the US, four are classified as "not likely to be carcinogenic to humans." The fifth chemical, penoxsulam, the most closely related to pyroxsulam, is classified as "suggestive, but not enough evidence to determine human significance" due to increased large granular lymphocytic leukemia in rats. Penoxsulam was not associated with liver tumors in rats or mice.

VI. Classification of Carcinogenic Potential

In accordance with EPA's *Final Guidelines for Carcinogen Risk Assessment (March 2005)*, the CARC classified pyroxsulam as ***"Not Likely To Be Carcinogenic To Humans."*** This decision was based on the following:

i) There are no treatment-related tumors in rats or mice. The liver tumors seen in male mice were not considered to be treatment-related. Liver tumors are very common and highly variable in CD-1 mice, especially males.
ii) The SAR shows that six closely related chemicals are not associated with liver tumors.
iii) There is no mutagenicity concern.

[**Note:** While the majority (n=7) voted for *"Not Likely To Be Carcinogenic To Humans"*, several CARC members (n=3) voted for *"Suggestive Evidence of Carcinogenic Potential"*. This "Suggestive" classification was based on the following: 1) The liver tumors in male mice were considered to be treatment-related since there was a significant trend for carcinomas and there were significant pair-wise comparisons at the 10 and 1000 mg/kg/day dose groups for adenomas and combined at $p<0.05$; 2) The incidences of liver tumors at all dosed groups exceeded the laboratory historical control data; and 3) The incidence of foci of altered hepatocytes (mainly clear cell foci) was increased at the high dose.]

VII. Quantification of Carcinogenic Potential

Quantification of carcinogenic potential is not required.

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Chemical: Pyroxsulam

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