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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0050702

**MEMORANDUM**

DATE: March 24, 2004

SUBJECT: **PENOXSULAM:** Report of the Cancer Assessment Review Committee
PC Code: 119031

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

TO: Alan Levy, Toxicologist (RAB2)
William Cutchin, Risk Assessor (SIMB)
Health Effects Division (7509C)

Joanne Miller, PM
Philip Errico, Reviewer
Herbicide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on February 18, 2004 to evaluate the carcinogenic potential of Penoxsulam. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo
W. Burnam

# *CANCER ASSESSMENT DOCUMENT*

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
**PENOXSULAM**

PC Code 119031

FINAL REPORT

March 24, 2004

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

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DATA PRESENTATION: William Burnam

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

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

Karl Baetcke

Marion Copley

Vicki Dellarco

Abdallah Khasawinah

Nancy McCarroll

Tim McMahon

Esther Rinde

Jess Rowland

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John Pletcher, Consulting Pathologist See page iiia

Lori Brunsman, Statistical Analysis

OTHER ATTENDEES: P.V. Shah (HED/RAB1)

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PENOXSULAM CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: William Burnam

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

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

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## EXECUTIVE SUMMARY

On February 18, 2004, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Penoxsulam.

Dr. William Burnam of the Immediate Office described the 2-year chronic toxicity/ carcinogenicity study in Fischer 344 rats and the 18-month carcinogenicity study in CD-1 mice by detailing the experimental design, reporting on survival and body weight effects, treatment related non-neoplastic and neoplastic lesions, statistical analysis of the tumor data, the adequacy of the dose levels tested, as well as the structure activity relationship data and the mutagenicity studies.

Penoxsulam was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for two years. An additional ten rats/sex/group were treated at the same dosages and necropsied after one year of treatment. Penoxsulam was administered to groups of 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, or 375 mg/kg/day (male mice) or 0, 10, 100, or 750 mg/kg/day (female mice) for 18 months.

**The CARC concluded that Penoxsulam showed evidence of carcinogenicity based on the following:**

- Male Fischer 344 rats had a significant increasing trend at $p<0.05$, and there were significant pair-wise comparisons ($p < 0.01$) of all dose groups with the controls, for large granular lymphocyte leukemia (also known as mononuclear cell leukemia (MNCL)). The incidence of MNCL in male rats was 12/49 (24%), 30/49 (61%), 29/49 (59%), and 30/49 (61%) for the control, 5, 50, and 250 mg/kg/day dose groups, respectively. The incidence in the low-, mid-, and high-dose groups exceeded the laboratory historical control mean (28.5%) and range (16-40%). Although both the incidence of MNCL and the staging of MNCL were increased over controls, there was no dose-response within the treatment groups as the doses increased from 5 to 250 mg/kg/day. **Therefore, the CARC considered the MNCL to be treatment-related.**

- Although MNCL is recognized as a common neoplasm in Fischer rats, the mechanism of producing MNCL is not completely understood. Therefore, the significance of MNCL and its biological relevance for human cancer risk remains uncertain and cannot be discounted.

- No treatment-related tumors were seen in female Fischer 344 rats.

- The high dose (250 mg/kg/day) in the chronic toxicity/carcinogenicity study was **adequate** in male and female rats to assess the carcinogenicity of penoxsulam based

primarily on decreased body weight/body weight gain and the effects on the urinary system. In males at 250 mg/kg/day, the findings in the urinary system included chronic progressive glomerulonephropathy (CPGN), crystals in the renal pelvis, increased incidence and severity of hyperplasia of the renal pelvic epithelium. In the urinary bladder, a significant increase in the incidence and/or severity of the following was observed in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only).

- Penoxsulam administered to male CD-1 mice at up to 375 mg/kg/day and to female CD-1 mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females.

- In male mice, the highest dose tested (375 mg/kg/day) was **inadequate** for carcinogenicity testing because no adverse effect was observed at this dose. In female mice, the highest dose tested (750 mg/kg/day) was considered **adequate** for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this determination was provided in the 90-day subchronic oral study in mice.

- There is no concern for mutagenicity of penoxsulam.

- Penoxsulam is a member of the triazolopyrimidine sulfonamide chemistry family, which includes chloransulam-methyl, diclosulam, and flumetsulam. These pesticides were negative for MNCL.

- No mode of action data were available for penoxsulam.

In accordance with the EPA Proposed Guidelines for Carcinogen Risk Assessment (July 1999), the Committee classified Penoxsulam as **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"** and, therefore, quantification of human cancer risk is not required.

Note: **Although dosing in male mice was not considered to be adequate, the CARC concluded that an additional mouse carcinogenicity study was not required.** This was based on the following: 1) no treatment-related effects were seen up to the limit dose of a 1000 mg/kg/day in a subchronic mouse study; 2) no hyperplasia was seen in the mouse carcinogenicity study at 350 mg/kg/day in males and 750 mg/kg/day in females; 3) no structural alerts were seen with the SAR data; 4) rat data indicate saturation of absorption at 250 mg/kg/day; and 5) no mutagenic activity. Based on these data, the CARC determined that a repeat of the male mouse cancer study would have no impact on the regulation of penoxsulam.



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## I. INTRODUCTION

On February 18, 2004, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Penoxsulam.

## II. BACKGROUND INFORMATION

Penoxsulam (2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluromethyl)benzenesulfonamide), also known as XDE-638, is a new active ingredient systemic post-emergence herbicide chemical. Penoxsulam is a member of the triazolopyrimidine sulfonamide chemistry family. Its mode of action in susceptible weeds is by inhibition of acetolactate synthase (ALS), an enzyme required for the biosynthesis of certain amino acids necessary for plant growth. Section 3 registrations and permanent tolerances for penoxsulam are being requested by Dow AgroSciences LLC (Indianapolis, Indiana). The available toxicology data base for penoxsulam contains all the studies routinely required for registration of a food use chemical and establishment of permanent tolerances.

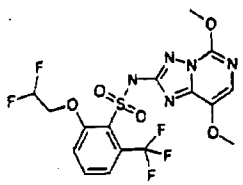

**Figure 2**
Penoxsulam

Registrations have been requested for technical grade penoxsulam, which contains 97.5% active ingredient, and for GF-881, a liquid manufacturing use concentrate containing 50% active ingredient. Penoxsulam is proposed to be used in the U.S. in a liquid formulation GF-443 SC SF (containing 21.7% active ingredient) and in 2 granular formulations GF-947 SF and GF-947 CA (both containing 0.24% active ingredient) for the selective control of various weeds in dry-seeded and water-seeded rice in the southern United States and California. Formulations of penoxsulam will be applied by ground equipment and/or aerially. Permanent tolerances have been requested for residues of penoxsulam (expressed as parent only) in/on rice grain, straw, hulls, bran, and polished rice (PP 3F06542). At this time, no residential uses have been proposed for penoxsulam.



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## III. EVALUATION OF CARCINOGENICITY STUDIES

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

References: Johnson, K.A., M.D. Dryzga and K.E. Stebbins (2002) XDE-638: Two-year chronic toxicity/oncogenicity and chronic neurotoxicity study in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID 991244, November 14, 2002. MRID 45830901. Unpublished.

Hardisty, J.F. (2002) Pathology peer review and pathology working group (PWG) review of large granular lymphocyte leukemia (LGL) in a two-year chronic toxicity/oncogenicity and chronic neurotoxicity study of XDE-638 in Fischer 344 rats. The Dow Chemical Company, Toxicology Research Laboratories, H&ES, Midland, MI. EPL Project No. 368-002, November 5, 2002. MRID 45830913. Unpublished.

A. Experimental Design

In a combined chronic toxicity/carcinogenicity study (MRID 45830901, 45830913) penoxsulam (97.7% a.i.) was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for two years. An additional ten rats/sex/group were treated at the same dosages and necropsied after one year of treatment.

B. Discussion of Mortality and Tumor Data

Survival Analyses

The statistical evaluation of mortality indicated a statistically significant increasing trend with increasing doses of penoxsulam in male rats. See Table 1 for male mortality test results. There were no treatment-related effects on mortality in females.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program (Memo, J. Kidwell, 1/29/04, TXR No. 0052326).



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Table 1. Penoxsulam - Fisher 344 Rat Study
(Memo, J. Kidwell, 1/29/04, TXR No. 0052326)

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

Weeks

| Dose (mg/kg/day) | 1-26 | 27-52 | 53[i] | 53-78 | 79-106[f] | Total |
|---|---|---|---|---|---|---|
| 0 | 0/60 | 0/60 | 10/60 | 1/50 | 11/49 | 12/50 (24)* |
| 5 | 0/60 | 1/60 | 10/59 | 0/49 | 10/49 | 11/50 (22) |
| 50 | 0/60 | 0/60 | 10/60 | 1/50 | 21/49 | 22/50 (44)* |
| 250 | 0/60 | 0/60 | 10/60 | 2/50 | 18/48 | 20/50 (40) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105/106.

( )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 $p < 0.01$.



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Tumor Analyses

No treatment-related tumors were seen in female rats. Male rats had a significant increasing trend at $p<0.05$, and there were significant pair-wise comparisons ($p < 0.01$) of all dose groups with the controls, for large granular lymphocyte leukemia (See Table 2) .

Table 2. Penoxsulam - Fisher 344 Rat Study (PWG Diagnoses)
(Memo, J. Kidwell, 1/29/04, TXR No. 0052326)

Male Large Granular Lymphocyte Leukemia Tumor Rates[+] and Peto's Prevalence Test Results
Dose (mg/kg/day)

| Dose | 0 | 5 | 50 | 250 |
|---|---|---|---|---|
| Leukemia (%) | 12/49 (24) | 30/49 (61) | 29/49 (59) | 30/49 (61) |
| p = | 0.03567* | 0.00010** | 0.00014** | 0.00038** |

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First leukemia observed at week 78, dose 250 mg/kg/day.

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 $p < 0.01$.

The histopathology slides were reviewed by an external Pathology Working Group (PWG) to establish consensus diagnoses. The incidence in all groups of treated males exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%). The PWG concluded that the LGL leukemia in males was not treatment-related for the following reasons: the increased incidence was limited to one sex and one species; there was no dose-dependency in the frequency of LGL leukemia in males; no other tumors were induced in males or females; the increased frequency of LGL leukemia in treated males occurred primarily after life-time exposure to penoxsulam; *in vitro* and *in vivo* studies showed no evidence of genotoxicity; carcinogenicity studies conducted in F344 rats with other chemicals in this class (triazolopyrimidines) have been negative for LGL leukemia. The study report states that LGL leukemia (also termed mononuclear cell leukemia or Fischer rat leukemia) is the most common

neoplastic cause of mortality in male Fischer rats. It is characterized by early involvement of the spleen and liver with later dissemination to lymph nodes, bone marrow, peripheral blood and other organs. The lungs and brain are frequently involved.

The laboratory's historical control range for LGL leukemia from eight carcinogenicity studies (seven dietary, one inhalation) necropsied between February 1994 and February 1997 was16-40% (8/50-20/50) with a mean of 28.5% (Table 2 of the DER Appendix). For females, the mean was 17.8% and the range was 10-28% (5/50-14/50) rats/group. All studies were 24 months in duration and the animal supplier, feed and housing were similar to the current study. Incidences per study were included with the PWG report (MRID 45830913).

Data from the National Toxicology Program (NTP) historical control database report a mean of 50.5% (range 32-74%) for males and 28.1% (range 14-52%) for females for two-year feeding studies (Haseman et al 1998, see Attachment 4). These are from a much larger historical control database of approximately 27 feeding studies.

There are some conflicting views on the significance of MNCL for human risk assessment for this pesticide and in general. The Pathology Working Group (PWG) has indicated that penoxsulam is associated with an increase in MNCL and its severity at all doses, but within the treated groups, there is no dose-response as the doses increase from 5 to 250 mg/kg/day. They also contend that this tumor type in this strain of rat is of "questionable biological relevance" for humans. Other opinions from scientists with the National Toxicology Program (NTP) indicate that the relevance to humans of this tumor type cannot be dismissed. The publication by Caldwell (1999) offers another opinion about these tumors.

Although MNCL is recognized as a common neoplasm in Fischer rats, the mechanism of producing MNCL is not completely understood. Therefore, the significance of MNCL and its biological relevance for human cancer risk remains uncertain and cannot be discounted.

C. Non-Neoplastic Lesions

a. Non-neoplastic: In the **interim sacrifice groups**, an increase in the severity of chronic progressive glomerulonephropathy (CPGN) was observed in males at 250 mg/kg/day (Table 3). Very slight glomerulonephropathy (<25% involvement) was found in 7/10 controls and 9/10 and 7/10 of the low- and mid-dose groups, respectively. All males given 250 mg/kg/day had glomerulonephropathy, with 4/10 graded very slight and 6/10 graded as slight (26-50% involvement). There was no treatment-related effect on the incidence or severity of glomerulonephropathy in females.

An increased incidence of splenic extramedullary hematopoiesis was observed in males at 250 mg/kg/day; however, the degree was only very slight. Females were not affected.



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| TABLE 3: Histopathologic effects in interim sacrifice groups[a] | | | | |
|---|---|---|---|---|
| Organ/Lesion | Dosages (mg/kg/day) | | | |
| | 0 | 5 | 50 | 250 |
| | MALES | | | |
| **Kidney** (number of animals examined) | 10 | 10 | 10 | 10 |
| Chronic Progressive Glomerulonephropathy<br>Any grade<br>Very slight<br>Slight | 7 (1.00)[b]<br>7<br>0 | 9 (1.00)[b]<br>9<br>0 | 7 (1.00)[b]<br>7<br>0 | 10 (1.60)[b]<br>4<br>6 |
| **Spleen**<br>Number of animals examined<br>Extramedullary Hematopoiesis - very slight | 10<br>3 | 10<br>5 | 10<br>5 | 10<br>7 |
| | FEMALES | | | |
| **Kidney** (number of animals examined) | 10 | 10 | 10 | 10 |
| Chronic Progressive Glomerulonephropathy<br>Very slight<br>Slight | 1<br>0 | 2<br>0 | 2<br>0 | 1<br>0 |

[a] Data extracted from Text Table 9 (page 55) and Table 97 (pages 311-323) of MRID 45830901.
[b] Average severity grade calculated by reviewer based on 1= very slight; 2= slight.

In the **main study groups**, most of the histopathologic findings were observed in the kidney, liver and adrenal of male rats and the urinary bladder of both sexes.

Urinary system findings: In the kidney, there was an increase in the severity of CPGN in all groups of treated males (Table 4). An increase in the severity of CPGN at 5 mg/kg/day was not considered treatment-related. Data on the severity of CPGN in historical control males from seven two-year studies with dietary exposure and one with inhalation exposure were submitted (Table 5). The studies were conducted between February 1994 and February 1997. Each study contained 50 rats/group. The animal supplier, feed and housing conditions were similar to the current study.

An increased incidence of crystals in the renal pelvis was observed in males at 250 mg/kg/day; the unilateral incidence was significantly increased. The study report states that the crystals stained pale pink with hematoxylin and eosin stain, had an ill-defined particulate appearance and faint concentric rings. Eleven of the rats with crystals were necropsied prior to the scheduled termination. The study report indicates that the crystals are consistent with those reported in the 4-week study by Stebbins *et al* (1998).

The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more



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common finding. In females, the only histopathologic finding in the kidney was a slight increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased.

In the urinary bladder, a significant increase in the incidence and/or severity of the following was observed in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only). Rats with urinary bladder calculi had greater degrees of mucosal hyperplasia with ½ males having severe diffuse hyperplasia with inflammation and 6/6 females having moderate diffuse hyperplasia. The other male at 250 mg/kg/day with calculi at necropsy had acute transmural necrosis of the bladder which was considered the primary cause of death.

Miscellaneous Findings: Regenerative hepatocyte hyperplasia, slight and moderate combined, was increased in males at all dose levels but not in a dose-responsive manner (Table 4). Evaluation of individual rats with this diagnosis showed that, with one exception, the effect was secondary to LGL leukemia with hepatic infiltration of malignant lymphocytes causing degeneration of some hepatocytes and regeneration of the remaining viable cells. The one exception had hepatic disease secondary to atrial (heart) thrombosis. All male rats also had some degree of biliary hyperplasia with or without inflammation but the incidence of severe grade was increased in animals treated at 5 and 250 mg/kg/day. These effects were also secondary to hepatic involvement by leukemic cells.

An increase in hyperplasia of the adrenal medulla was observed in all groups of treated males but the change was significant only at 250 mg/kg/day (Table 4). Data were submitted to demonstrate that the incidence of adrenal medullary hyperplasia was lower in the study control animals than in historical control rats. In eight 24-month studies (7 dietary and 1 inhalation) which included 50 male rats/group, 32% of the control group had adrenal hyperplasia (focal and multifocal combined).

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| TABLE 4: Histopathologic effects in the main study groups[a] | | | | |
|---|---|---|---|---|
| **Organ/Lesion** | **Dosages (mg/kg/day)** | | | |
| | **0** | **5** | **50** | **250** |
| **KIDNEY** (number of animals examined) | **MALES** | | | |
| | 50 | 50 | 50 | 50 |
| Chronic Progressive Glomerulonephropathy | 50 (1.54)[b] | 49 (2.16)[b] | 50 (1.88)[b] | 50 (2.76)[b] |
| Any grade | 33 | 13* | 21* | 5* |
| Very slight | 11 | 20 | 15 | 13 |
| Slight | 2 | 11* | 13* | 21* |
| Moderate | 4 | 5 | 1 | 11 |
| Severe | | | | |
| Crystals, Pelvis, Unilateral | 0 | 0 | 1 | 10* |
| Bilateral | 0 | 0 | 0 | 4 |
| Hyperplasia, Pelvic Epithelium, Multifocal | | | | |
| Any grade | 11 | 11 | 16 | 29* |
| Very slight | 9 | 8 | 10 | 10 |
| Slight | 1 | 2 | 5 | 16* |
| Moderate | 1 | 1 | 1 | 3 |
| **URINARY BLADDER** (number of animals examined) | 50 | 50 | 50 | 50 |
| Crystals, Lumen | 0 | 1 | 0 | 14* |
| Hyperplasia, Mucosa, Multifocal, Any grade | 4 | 0 | 3 | 21* |
| Very slight | 4 | 0 | 2 | 13* |
| Slight | 0 | 0 | 1 | 8* |
| **LIVER** (number of animals examined) | 50 | 50 | 50 | 50 |
| Hepatocyte, hyperplasia; regenerative; | | | | |
| Any grade | 2 | 10* | 17* | 10* |
| Slight | 1 | 4 | 10* | 2 |
| Moderate | 1 | 6 | 7 | 8 |
| Bile duct, hyperplasia; with or without inflammation; multifocal | | | | |
| Any grade | 50 | 50 | 50 | 50 |
| Very slight | 7 | 5 | 8 | 14 |
| Slight | 29 | 24 | 22 | 20 |
| Moderate | 14 | 15 | 17 | 8 |
| Severe | 0 | 6* | 3 | 8* |
| **ADRENAL** (number of animals examined) | 50 | 50 | 50 | 50 |
| Hyperplasia; medulla; unilateral or bilateral; focal or multifocal | 8 | 17 | 15 | 22* |

| TABLE 4: Histopathologic effects in the main study groups[a] | | | | |
|---|---|---|---|---|
| **Organ/Lesion** | **Dosages (mg/kg/day)** | | | |
| | **0** | **5** | **50** | **250** |
| | **FEMALES** | | | |
| **Kidney** (number of animals examined) | 50 | 50 | 50 | 50 |
| Hyperplasia, Pelvic Epithelium, Multifocal | 8 | 7 | 11 | 15 |
| Any grade | 6 | 6 | 10 | 9 |
| Very slight | 2 | 1 | 1 | 6 |
| Slight | | | | |
| **URINARY BLADDER** (number of animals examined) | 48 | 49 | 50 | 50 |
| Crystals, Lumen | 2 | 1 | 3 | 21* |
| Hyperplasia, Mucosa, Multifocal, Any grade | 2 | 1 | 5 | 31* |
| Very slight | 2 | 1 | 4 | 24* |
| Slight | 0 | 0 | 1 | 7* |
| Hyperplasia, Mucosa, Diffuse, Any grade | 1 | 0 | 0 | 11* |
| Slight | 1 | 0 | 0 | 4 |
| Moderate | 0 | 0 | 0 | 7* |
| **LIVER** (number of animals examined) | 50 | 50 | 50 | 50 |
| Hyperplasia; regenerative; hepatocyte | 2 | 2 | 2 | 2 |
| Any grade | 0 | 1 | 1 | 0 |
| Slight | 2 | 1 | 1 | 2 |
| Moderate | | | | |
| Hyperplasia; with or without inflammation; bile duct; multifocal | 42 | 41 | 42 | 35 |
| Any grade | 42 | 40 | 42 | 35 |
| Very slight | 0 | 1 | 0 | 0 |
| Slight | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | | | | |

[a] Data extracted from Table 102 (pages 360-398) of MRID 45830901.
[b] Average severity grade calculated by reviewer based on 1=very slight, 2=slight, 3=moderate and 4=severe.
* Statistically different from controls by Yates Chi Square Test, alpha=0.05



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**TABLE 5: Kidney histopathology grades of CPGN of control male Fischer 344 rats on two-year studies[a,b,c]**

| Chronic Progressive Glomerulonephropathy (Grade) | | | | | |
|---|---|---|---|---|---|
| **Study** | **Very Slight** | **Slight** | **Moderate** | **Severe** | **Very Severe** |
| A | 9 | 14 | 15 | 7 | – |
| B | 14 | 17 | 14 | 3 | 2 |
| C | 10 | 25 | 8 | 4 | – |
| D* | 6 | 15 | 20 | 9 | – |
| E | 12 | 15 | 16 | 6 | – |
| F | 18 | 21 | 9 | 2 | – |
| G | 12 | 21 | 13 | 4 | – |
| H# | 0 | 14 | 28 | 8 | – |

[a] Data extracted from Text Table 14 (page 64) of MRID 4583090

[b] Data reflect number of animals having the specified observation. All studies consisted of 50 rats/group and lasted for 24 months.

[c] Average severity score calculated by reviewer = 2.34 based on 1=very slight, 2=slight, 3=moderate and 4=severe.

* Histopathology conducted by Pathology Associates, Inc. Nomenclature for the grades of nephropathy were minimal, mild, moderate and marked.

# Exposure for study was via inhalation. All other studies were dietary route.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose (250 mg/kg/day) in the chronic toxicity/carcinogenicity study was **adequate** in male and female rats to assess the carcinogenicity of penoxsulam based primarily on decreased body weight/body weight gain and the effects on the urinary system. A metabolism study suggests that saturation of absorption occurred at a dose level of 250 mg/kg/day. A higher dose may have produced more precipitation of the test material and exacerbated the irritative urinary tract effects. In addition, there was increased mortality in the males at the two higher doses, although this occurred late in the study.

At 250 mg/kg/day, body weights for males were decreased 2-4% from control values during the first year, decreased 3-6% from control values during the second year, and decreased 6.2% at 24 months. Body weights were also lower in females at 250 mg/kg/day, although the differences from control were not statistically significant as frequently as in male rats. At 250 mg/kg/day, body weights for females were decreased 2-4% from control values during the first year, decreased 2-4% from control values during the second year, and decreased 3.3% at 24 months. Body weight gains were also decreased at 250 mg/kg/day during Day 1-8 (11% and 17%, males and females, respectively) and Days 1-92 (6% and 5%, males and females, respectively). Overall (Day 1-731/732) body weight gain was decreased in males (10%) and females (6%) at 250 mg/kg/day. Histopathologic findings were observed in the kidney of male rats and the urinary bladder of both sexes at the high dose of 250 mg/kg/day. In males at 250 mg/kg/day, the findings in the urinary system included chronic progressive glomerulonephropathy (CPGN), crystals in the renal pelvis, increased incidence and severity of hyperplasia of the renal pelvic epithelium. In the urinary bladder, a significant increase in the incidence and/or severity of the following was observed in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only).

Additional support for this determination was provided in the 90-day toxicity study in rats with dose levels of 0, 5, 50, 250, or 500 mg/kg/day. In males, decreased body weight/body weight gains and decreased RBC parameters were seen at 250 and 500 mg/kg/day. In females, increased incidences of mineralization and hyperplasia of the pelvic epithelium in the kidneys was seen at 500 mg/kg/day.



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2. Carcinogenicity Study in Mice

Reference: Yano, B.L. and S.J. Day (2002) Revised report for : XDE-638: oncogenicity study in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project Study ID 001032R, October 11, 2002 (original report), October 31, 2002 (revised report). MRID 45830915. Unpublished

A. Experimental Design

In a carcinogenicity study (MRID 45830915), penoxsulam (97.7% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, or 375 mg/kg/day (male mice) or 0, 10, 100, or 750 mg/kg/day (female mice) for 18 months.

B. Discussion of Survival and Tumor Data

There were no treatment-related effects on mortality. Penoxsulam administered to male mice at up to 375 mg/kg/day and to female mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females.

C. Non-Neoplastic Lesions

In association with the increased liver weight, microscopic examinations revealed hepatocyte hypertrophy in the centrilobular and midzonal regions of the hepatic lobule. Incidences and severity are summarized in Table 6. Hypertrophy ranged from very slight to severe in males administered 100 or 375 mg/kg/day. This effect involved 29/50 and 35/50 males in the 100 and 375 mg/kg/day groups vs 14/50 in the control group. For males, incidences and severity in the control and 10 mg/kg/day group were similar. Only very slight to slight hypertrophy was observed in 28/50 females in the 750 mg/kg/day group. Incidences in the lower female dose groups were only slightly increased over the control value. In all groups with hepatocellular hypertrophy, the cytoplasm had an increased eosinophilic staining. The study authors considered the increased eosinophilic staining of the cytoplasm to be a compensatory change consistent with the induction of hepatocellular enzymes and smooth endoplasmic reticulum. In males, the areas of altered staining were said to contain small lipid vacuoles. Although not clearly stated, it is assumed that lipid vacuoles were observed in males in both the 100 and 375 mg/kg/day groups. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group.

| TABLE 6: Microscopic liver lesions in mice administered XDE-638 for 18 months | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Lesion** | **Males (mg/kg/day)** | | | | **Females (mg/kg/day)** | | | |
| | **0** | **10** | **100** | **375** | **0** | **10** | **100** | **750** |
| **Hepatocyte hypertrophy** | | | | | | | | |
| **very slight** | 10 | 8 | 14 | 7 | 1 | 1 | 3 | 12* |
| **slight** | 3 | 5 | 13* | 11* | 0 | 1 | 1 | 16* |
| **moderate** | 0 | 0 | 1 | 9* | 0 | 0 | 0 | 0 |
| **severe** | 1 | 0 | 1 | 8* | 0 | 0 | 0 | 0 |
| **Dilitation or cystic spaces–peliosis** | | | | | | | | |
| **very slight** | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| **slight** | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Data obtained from text table 6, page 28, MRID 45830915.
*Statistically significantly different from the control, $p<0.05$.

D. Adequacy of Dosing for Assessment of Carcinogenicity

In male mice, the highest dose tested (375 mg/kg/day) was **inadequate** for carcinogenicity testing because no adverse effect was observed at this dose. In female mice, the highest dose tested (750 mg/kg/day) was considered **adequate** for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this determination was provided in the 90-day subchronic oral study in mice (MRID 45830905). In this study treatment-related toxicologically significant adverse effects were not observed at the highest dose tested in males (1027 mg/kg/day) or in females (1029 mg/kg/day). All treatment-related effects observed in the 90-day subchronic study were essentially the same liver effects as in the 18-month carcinogenicity study and were considered to be adaptive rather than adverse effects.

**Although dosing in the males was not considered to be adequate, the CARC concluded that an additional mouse carcinogenicity study was not required.** This was based on the following:1) no treatment-related effects were seen up to the limit dose of a 1000 mg/kg/day in a subchronic mouse study; 2) no hyperplasia was seen in the mouse carcinogenicity study at 350 mg/kg/day in males and 750 mg/kg/day in females; 3) no structural alerts were seen with the SAR data; 4) rat data indicate saturation of absorption at 250 mg/kg/day; and 5) no mutagenic activity. Based on these data, the CARC determined that a repeat of the male mouse cancer study would have no impact on the regulation of penoxsulam.

# IV. TOXICOLOGY

## 1. Metabolism

In a metabolism/disposition study (MRID 45830927), Fischer 344 rats (four/sex/group) were given single or 15 multiple oral low doses (5 mg/kg) or a single high dose (250 mg/kg) of $^{14}$C-XDE-638 (Penoxsulam). Both a triazole ring label (Lot no. F-458-159, INV 1456, 28.9 mCi/mmol, >99% radiochemical purity) and phenyl ring label (Lot no. F-458-183A, INV 1475, 24.6 mCi/mmol, >98.4% radiochemical purity) were utilized along with non-labeled XDE-638 (Lot no. N D05167938, TSN101773, chemical purity 97.5%). An additional group of three male and three female rats were fitted with bile duct cannulae and biliary elimination monitored over 24 hours following an oral dose of 5 mg/kg. Absorption, distribution, metabolism and kinetic parameters were evaluated for the single and multiple low dose and the high-dose groups.

Overall recovery of administered radioactivity was an acceptable 91-107%. Dose confirmation revealed that dosing was within 13% of the target doses, and results of homogeneity and stability assessments were acceptable.

Absorption of the test article was rapid. Urinary, fecal and biliary excretion data revealed that absorption of a single low dose was 81-88% and that much of the radioactivity in the feces was the result of biliary contributions of absorbed radioactivity. Biliary excretion was greater for males (55.8% of dose) than for females (14.1% of dose). Data on plasma kinetics supported the contention that absorption was saturated at the 250 mg/kg dose. Both the $C_{max}$ and AUC values were indicative of substantially decreased absorption at the higher dose. Essentially identical elimination kinetics were observed at both dose levels. Maximum plasma concentration ($C_{max}$) and whole body clearance (Cl) data also supported observed gender-related variability in disposition of the test article.

**Urine and feces were major excretory routes. Both gender and dose affected excretion pattern. Following a single low dose (5 mg/kg), excretion of radioactivity over 168 hours was primarily via the urine in females (69% vs 36% for males) and via the feces in males (55% vs 20% for females).** Elimination patterns were similar for the repeated (15-day) low dose. Excretion in urine was more prominent following a single low dose (36% and 69% males and females, respectively) and in feces more prevalent at the high dose (70% and 87% for females and males, respectively). The shift in excretory route was greater for males (3.8-fold) than for females (2.5-fold) and was consistent with saturated absorption. Most urinary excretion (>90%) occurred within 36 hours for the low-dose group and within 48 hours for the high-dose group. Fecal excretion was essentially complete within 72 hours regardless of dose. Excretion profiles following the repeated low dose regimen were similar to that for the single low dose. Label position (triazole vs phenyl) did not significantly alter the disposition of the test article. Tissue burdens assessed at various times after dosing revealed that at sampling times equivalent



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to $C_{max}$ (0.5 hrs) and ½ $C_{max}$ (3 hrs), most radioactivity was associated with the gastrointestinal tract and organs/tissues associated with initial absorption, metabolism and elimination (e.g., liver). Assessment of tissue and carcass burdens at 7 days post dose showed that radioactivity was negligible (~0.69% and <1.9% of the low and high doses, respectively) and, therefore, there was no evidence of sequestration.

Analysis of metabolite profiles revealed up to 17 urinary components, 37 fecal components, and 19 biliary fractions in pooled samples, but most represented <1% of the administered dose. Parent compound was the most prevalent urinary component in both the low- and high-dose groups. Metabolite profiles of pooled fecal samples also revealed numerous components, most of which represented <1% of the administered radioactivity. Saturated absorption was also reflected in that greater amounts of parent compound occurred in the feces of the high-dose group (67-80% of administered dose) than in the low-dose group (3-12%). A 2-hydroxyphenyl derivative was detected in the urine and accounted for ~1.3-2.9% (low dose) and <1.0% (high dose) of administered radioactivity; in the feces it represented <1.05% of the administered dose. A glucuronide conjugate was also identified primarily in the bile. Unidentified components with retention times of 22.9 and 24.0 minutes represented 5.6 and 6.2%, respectively of the administered dose in feces of low-dose males. The absence of radioactivity in expired air precluded the formation of volatile metabolites or carbon dioxide. Metabolite profiles of the pooled bile samples also revealed numerous metabolites. The presence of parent compound in the bile (~9.4% and 4.8% of the administered dose for males and females, respectively) in conjunction with reduced urinary excretion of radioactivity in bile-cannulated rats were indicative of potential enterohepatic circulation. Only minor ring cleavage was observed. The investigators proposed a metabolism pathway specifying various Phase I (O-dealkylation and hydroxylation products) and Phase II (conjugation products) metabolites.

The results of this study showed that $^{14}$C- XDE-638 (Penoxsulam) orally administered to male and female rats underwent fairly rapid but incomplete absorption which became dose-limited at or below a dose of 250 mg/kg. Although widely distributed among tissues, there was no evidence of sequestration or bioaccumulation. Excretion was primarily via the urine and feces, with unabsorbed test article accounting for much of the fecal radioactivity especially for the high-dose group. A large number of metabolites were detected in urine, feces, and bile. Minor qualitative, gender-related differences were observed. Most metabolites represented only a small portion (<1%) of the administered dose. Minor qualitative and quantitative differences in metabolite profiles observed for the phenyl and triazole labels provided information on biotransformation supportive of the proposed metabolism scheme.

This metabolism study in the rat (MRID 4583027) is classified **Acceptable/Guideline** and satisfies the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The studies provide data consistent with Tier 1 requirements as well as Tier 2 ancillary studies.



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**2. Mutagenicity**

Technical grade penoxsulam did not demonstrate any mutagenic potential in a battery of mutagenicity studies. There is no concern for mutagenicity resulting from exposure to penoxsulam. The mutagenicity studies are acceptable and satisfy the 1991 revised Guideline requirements for mutagenicity studies.

Results were negative in the presence or absence of rat S-9 activation in a reverse gene mutation study using *Salmonella typhimurium/Escherichia coli* and in a forward gene mutation study using CHO cells at the HGPRT locus up to the limit dose or an insoluble level, respectively. In an *in vitro* chromosomal aberration study in primary rat lymphocytes, penoxsulam was negative when tested to insoluble concentrations with or without rat S-9 activation. Similarly, penoxsulam was negative up to the limit dose in an *in vivo* micronucleus study in mice using bone marrow cells.

In addition, GF-443, a formulated product containing 21.9% penoxsulam, did not demonstrate any mutagenic potential in two mutagenicity studies. Results were negative up to the limit dose without or with rat S-9 activation in a reverse gene mutation study using *Salmonella typhimurium/Escherichia coli* and in an *in vivo* micronucleus study, also tested up to the limit dose, in mouse bone marrow cells.

(i) In a reverse gene mutation assay in bacteria (MRID 45830921, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to XDE-638 up to concentrations of 1000 µg/plate without mammalian metabolic activation (S9-mix) and 5000 µg/plate with S9-mix. There was no evidence of induced mutant colonies over background.

(ii) In a reverse gene mutation assay in bacteria (MRID 45830922, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to GF-443 (Lot No. E-828-59, 21.9% a.i.) at concentrations up to 5000 µg/plate with and without mammalian metabolic activation (S9-mix). **There was no evidence of induced mutant colonies over background.**

(iii) In a mammalian cell gene mutation assay at the HGPRT locus (MRID 45830923), Chinese hamster ovary CHO-K1-BH4 cells cultured *in vitro* were exposed to XDE-638 , up to concentrations of 1500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix) for four hours. **There was no evidence of induced mutant colonies over background.**

(iv) In a mammalian cell cytogenetics assay (Chromosomal aberrations) (MRID 45830924), primary rat lymphocytes in whole blood culture were exposed to XDE-638 up to



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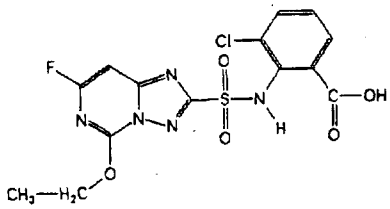
concentrations of 1500.0 µg/mL for four hours with and without metabolic activation (S9-mix) and harvested 20 hours post-treatment. **There was no evidence of chromosome aberrations induced over background.**

(v) In a CD-1 mouse bone marrow micronucleus assay (MRID 45830925), XDE-638 was tested to the limit dose of 2000 mg/kg/day. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.**

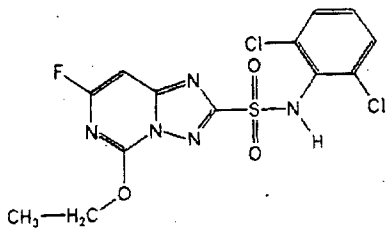
## 3. Structure-Activity Relationship

Penoxsulam is a member of the triazolopyrimidine sulfonamide chemistry family. Some toxicity information and structures of related triazolopyrimide herbicides[1] (chloransulam-methyl, diclosulam, Flumetsulam) are presented below. [Note: These 3 chemicals all have the triazolopyrimidine group attached directly to the sulfur and, thus, can truly be called triazolopyrimidine sulfonamides. Penoxsulam is actually a benzene sulfonamide (i.e., the benzene ring is attached to the sulfur). They are still sufficiently similar from a structural perspective to be grouped.] Some, but not all, are registered in the U.S. These U.S. registered pesticides were negative for MNCL.

Chloransulam-methyl (PC 129116) was tested for chronic/cancer in the Fischer 344 rat and was negative up to the highest dose tested of 375 mg/kg/day. Mice were also negative up the limit dose of 1000 mg/kg. It was not mutagenic.



Diclosulam (PC 129122) was negative in the Fischer 344 rat at doses up to 400 mg/kg/day and was negative in mice up to 500 mg/kg. It was not mutagenic.



[1]Hanley and Billington. 2001.Toxicology of Triazolopyrimidine Herbicides. Chapter 75. *Handbook of Pesticide Toxicology*. Volume 2.



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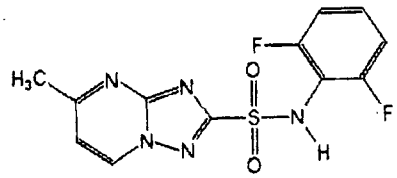
Flumetsulam (PC 129016) was not carcinogenic in the Fischer rat or the mouse up to the limit dose of 1000 mg/kg.



There was no mention of MNCL in any triazolopyrimide herbicide data base. In most species, the target organ was the kidney.

## 4. Subchronic and Chronic Toxicity

### b) Subchronic Toxicity

Rat

In a 90-day oral toxicity study (MRID 45830906) penoxsulam (97.5%), was administered to 10 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 5, 50, 250 or 500 mg/kg/day. Recovery groups receiving 0 or 500 mg/kg/day during the study were maintained for an additional four weeks on the control diet. In a 4-week dietary toxicity study (MRID 45830903), penoxsulam was administered to 5 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day.

No animals died during the 90-day study. The only treatment-related clinical sign was perineal urine soiling (more prevalent in females than males) that was not considered to be a toxicologically significant adverse effect. Body weights were reduced in males at 500 and 250 mg/kg/day. At 500 mg/kg/day, body weights were decreased 4-5% from control values during the study and were decreased 5% at termination of the study. At 250 mg/kg/day, body weights were decreased 3-8% from control values during the study and were decreased 7% at termination of the study. Body weight gains were also reduced in males at 500 and 250 mg/kg/day. The overall body weight gains were decreased 9% at 500 mg/kg/day and 12% at 250 mg/kg/day compared to controls at termination of the study. Average daily feed consumption was reduced in males at 500 and 250 mg/kg/day throughout the duration of the study. At 500 mg/kg/day, overall feed consumption (days 1-92) was decreased 6%. At 250 mg/kg/day, overall feed consumption was decreased 8%.

In males at 500 mg/kg/day, statistically significant decreases in red blood cell counts (decreased 5%), hemoglobin (decreased 8%) and hematocrit (decreased 7%) were observed. Also, in males at 250 mg/kg/day, statistically significant decreases in hemoglobin (decreased 4%) and hematocrit (decreased 4%) were observed. Although possibly treatment-related, increases in total protein, albumin and serum cholesterol observed in the 500 and 250 mg/kg/day males are considered to be of equivocal toxicological significance.

Increased liver weights observed in males and females at 250 and 500 mg/kg/day are considered to be adaptive responses, rather than adverse effects, as there were no microscopic correlates except for slight hypertrophy in the 500 mg/kg/day males. Microscopic kidney changes were seen in the females at 500 mg/kg/day (mineralization and hyperplasia of the pelvic epithelium) and are considered to be treatment-related. These effects may be related to the sex-related difference in metabolism in which elimination of XDE-638 was found to be primarily fecal in males and urinary in females.

**In male rats, the LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain, decreased feed consumption, and decreased RBC parameters. In male rats, the NOAEL is 50 mg/kg/day. In female rats, the LOAEL is 500 mg/kg/day based on increased incidences of mineralization and hyperplasia of the pelvic epithelium in the kidneys. In female rats, the NOAEL is 250 mg/kg/day.**

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 rats.

In a previous 4-week dietary toxicity study (MRID 45830903)(see summary in Appendix to DER), rats receiving 500 and 1000 mg/kg/day had decreased body weights (males and females), decreased body weight gains (males and females), decreased feed consumption (males and females), decreased RBC parameters (males and females), increased kidney weights (females), and histopathology in the kidneys of females (crystals in the pelvis and inflammation and hyperplasia of the pelvic epithelium). The LOAEL for this study is 500 mg/kg/day and the NOAEL is 100 mg/kg/day. This 4-week dietary toxicity study in the rat is **Acceptable/Non-Guideline as a range-finding study.** It does **not** satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

Mouse

In a 90-day subchronic oral toxicity study (MRID 45830905), penoxsulam (97.5% a.i.) was administered to 10 CD-1 mice/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day (actual doses were 0, 10.2, 101.8, 511.3 and 1027 mg/kg bw/day, respectively for males and 0, 10.4, 103.7, 524.1 and 1029 mg/kg bw/day, respectively for females).

There were no compound-related effects on mortality, body weights, food consumption, clinical signs, ophthalmologic examinations, or hematology. A slight increase in alkaline phosphatase activity in males at 500 and 1000 mg/kg/day was considered to be of only minimal toxicologic significance. Alanine aminotransferase and aspartate aminotransferase were not affected. There were increases in absolute (33-41%) and relative (32-48%) liver weights at 500 and 1000 mg/kg/day in males. There were also increases in absolute (32%) liver weight at 1000 mg/kg/day and in relative (11-29%) liver weights at 500 and 1000 mg/kg/day in females. Histopathological findings revealed a dose-related increase in the occurrence of hepatocellular hypertrophy in the livers of males at ≥100 mg/kg/day and in the livers of females at ≥500 mg/kg/day. Electron microscopic examination of liver samples from two males given 1000 mg/kg/day showed an increase in smooth endoplasmic reticulum. Although treatment-related, the increases in liver weight, hepatocellular hypertrophy and smooth endoplasmic reticulum observed in the male and female mice in this study are not considered to be adverse findings. Rather, they are considered to be adaptive responses indicating a stimulation of the liver



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microsomal enzyme system by the test material. Electron microscopic examination of the two male mice also revealed cytoplasmic inclusions consistent with lipid accumulation, but which were not considered to be of toxicologic concern.

**The NOAEL for the male and female mice in this study is the highest dose tested viz. 1027 mg/kg/day for males and 1029 mg/kg/day for females (actual doses). A LOAEL was not observed in this study (>1027 mg/kg/day for males and >1029 mg/kg/day for females). Dosing in this study is adequate since the limit dose for subchronic feeding studies is 1000 mg/kg/day.**

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

**c) Chronic Toxicity**

Rat

In a combined chronic toxicity/carcinogenicity study (MRID 45830901, 45830913) penoxsulam ( 97.7% a.i.) was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for two years. An additional ten rats/sex/group were treated at the same dosages and necropsied after one year of treatment. Another five rats/sex/group were treated at the same dosages and examined for neurological effects as part of a chronic (one-year) neurotoxicity study (reported separately in MRID 45830912).

There was no treatment-related increase in mortality. An increase in perineal urine soiling, particularly in females, at 50 and 250 mg/kg/day, while treatment-related, was not considered to be a toxicologically significant adverse effect. Statistically significant decreases in body weight and body weight gain in males and females at 250 mg/kg/day, although of relatively small magnitude, were considered to be toxicologically significant. Slight but statistically significant decreases in RBC parameters (RBC counts, HGB and HCT) in males at 250 mg/kg/day were also considered to be toxicologically significant. There were no ophthalmoscopic effects due to treatment.

Blood urea nitrogen (BUN) was significantly increased (11-44%) at 18 and 24 months in males at 250 mg/kg/day. Urine volume was increased in males and females at 250 mg/kg/day (26-175% in males and 38-103% in females) throughout the study. Specific gravity was decreased in treated males with statistical significance achieved at 12, 18 and 24 months for the 250 mg/kg/day group. The urinary system effects were not considered toxicologically significant in males or females at 5 and 50 mg/kg/day due to the small magnitude of the changes.

In the interim sacrifice animals, the only gross change considered treatment-related was perineal



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urine soiling which was present in 9/10 males and 7/10 females at 250 mg/kg/day, as compared to 2/10 male and 1/10 female control rats. Four of ten female rats at 50 mg/kg/day also had perineal soiling. Male rats at 250 mg/kg/day had increased absolute and relative kidney weights, approximately 11% and 15%, respectively, and an increase in the severity of chronic progressive glomerulonephropathy (CPGN).

In the main study groups, the incidences of the following gross pathology findings were increased: calculi in the pelvis and bilateral roughened surface of the kidney in males at 250 mg/kg/day; enlarged spleen (with probable lymphoid tumor) in all treated males (no dose response); and urinary bladder calculi in males and females at 250 mg/kg/day. Terminal body weight was significantly decreased (7%) in males at 250 mg/kg/day. There was a statistically significant increase (11-20%) in the absolute and relative kidney weights of males at 250 mg/kg/day.

Microscopic examination of the kidney showed an increase in the severity of CPGN at all dose levels in males; the increase in severity at 5 and 50 mg/kg/day was not dose related and therefore was considered an incidental finding. The incidence of crystals in the renal pelvis was significantly increased in males at 250 mg/kg/day. The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more common finding. In females, the only histopathologic finding in the kidney was a slight increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased. In the urinary bladder, there was a significant increase in the incidence and/or severity of the following in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only).

**The LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain (males and females), decreased RBC parameters (decreased RBC count, HGB and HCT in males), clinical pathology changes ( increased BUN in males, increased urine volume in males and females, and decreased specific gravity in males), increased absolute and relative kidney weights (males), increased incidence of renal pelvis crystals (males), increased incidence of bladder crystals and calculi (males and females), hyperplasia of the renal pelvis epithelium (males and females) and bladder mucosa (males and females), and increased severity of chronic progressive glomerulonephropathy (males). The NOAEL is 50 mg/kg/day.**

Mouse

In a carcinogenicity study (MRID 45830915), penoxsulam (97.7% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, or 375 mg/kg/day (male

mice) or 0, 10, 100, or 750 mg/kg/day (female mice) for 18 months.

There were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmologic examinations, hematology, or gross pathology. Treatment-related effects were limited to the liver. Absolute and relative liver weights were increased by 12% in males administered 375 mg/kg/day and relative liver weight was increased by 11% in males administered 100 mg/kg/day (all $p<0.05$). Absolute and relative liver weights were marginally increased in females at 750 mg/kg/day and 100 mg/kg/day (non-significant). Microscopically, changes in the liver included hepatocellular hypertrophy in males administered 375 or 100 mg/kg/day and in females administered 750 mg/kg/day. The hepatocellular hypertrophy in males and females was associated with increased eosinophilic staining properties, and along with the increased liver weights was considered to be an adaptive change resulting from induction of the liver microsomal enzyme system by the test material. This change was not considered to be an adverse effect.

The affected hepatocytes in male mice administered 375 and 100 mg/kg/day were said to contain clear cytoplasmic vacuoles, but there was no quantitative description of the incidence or severity of these vacuoles. Based on the information presented in this study, the clear cytoplasmic vacuoles are not considered to be of toxicological significance. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group. Because of the severity of this lesion (very slight/slight) and its low frequency (4/50), it also is not considered to be of toxicological significance.

**The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 375 mg/kg/day for males and 750 mg/kg/day for females. A LOAEL was not observed in this study for the male or female mice (>375 mg/kg/day for males and >750 mg/kg/day for females).**

## V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

### 1. Carcinogenicity

*Rat*

- Male Fischer 344 rats had a significant increasing trend at $p<0.05$, and there were significant pair-wise comparisons ($p < 0.01$) of all dose groups with the controls, for large granular lymphocyte leukemia (also known as mononuclear cell leukemia (MNCL)). The incidence of MNCL in male rats was 12/49 (24%), 30/49 (61%), 29/49 (59%), and 30/49 (61%) for the control, 5, 50, and 250 mg/kg/day dose groups, respectively. The incidence in all dose groups exceeded the laboratory historical control mean (28.5%) and range (16-40%). Although both the incidence of MNCL and the staging of MNCL were increased over controls, within the treatment groups there was no dose-response as the doses increased from 5 to 250 mg/kg/day. **The CARC considered the MNCL to be treatment-related.**

- Although MNCL is recognized as a common neoplasm in Fischer rats, the mechanism of producing MNCL is not completely understood. Therefore, the significance of MNCL and its biological relevance for human cancer risk remains uncertain and cannot be discounted.

- No treatment-related tumors were seen in female Fischer 344 rats.

- The high dose (250 mg/kg/day) in the chronic toxicity/carcinogenicity study was **adequate** in male and female rats to assess the carcinogenicity of penoxsulam based primarily on decreased body weight/body weight gain and the effects on the urinary system. In males at 250 mg/kg/day, the findings in the urinary system included chronic progressive glomerulonephropathy (CPGN), crystals in the renal pelvis, increased incidence and severity of hyperplasia of the renal pelvic epithelium. In the urinary bladder, a significant increase in the incidence and/or severity of the following was observed in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only). A metabolism study suggests that saturation of absorption occurred at a dose level of 250 mg/kg/day. A higher dose may have produced more precipitation of the test material and exacerbated the irritative urinary tract effects.

*Mouse*

- Penoxsulam administered to male CD-1 mice at up to 375 mg/kg/day and to female CD-1 mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females.



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- In male mice, the highest dose tested (375 mg/kg/day) was **inadequate** for carcinogenicity testing because no adverse effect was observed at this dose. In female mice, the highest dose tested (750 mg/kg/day) was considered **adequate** for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this determination was provided in the 90-day subchronic oral study in mice. In this study treatment-related toxicologically significant adverse effects were not observed at the highest dose tested in males (1027 mg/kg/day) or in females (1029 mg/kg/day). All treatment-related effects observed in the 90-day subchronic study were essentially the same liver effects as in the 18-month carcinogenicity study and were considered to be adaptive rather than adverse effects.

**2. Mutagenicity**

- There is no concern for mutagenicity of penoxsulam.

**3. Structure Activity Relationship**

Penoxsulam is a member of the triazolopyrimidine sulfonamide chemistry family, which includes chloransulam-methyl, diclosulam, and flumetsulam. These pesticides were negative for MNCL.

**4. Mode of Action**

No mode of action data were available for penoxsulam.

## VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Proposed Guidelines for Carcinogen Risk Assessment (July 1999), the Committee classified Penoxsulam as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." The weight-of-the-evidence for this classification is as follows:

i) Evidence of carcinogenicity (MNCL) was seen in one sex (males) of one species (rat).

ii) There was an increased incidence of MNCL at all dose levels with all incidences exceeding the laboratory historical control, however, the dose-response was flat over a wide range of doses.

iii) Although MNCL is recognized as a common neoplasm in Fischer rats, the mechanism of producing MNCL is not completely understood. Therefore, the significance of MNCL and its

biological relevance for human cancer risk remains uncertain and cannot be discounted.

iv) There is no mutagenicity concern for penoxsulam.

v) SAR data are negative for MNCL.

## VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The quantification of human cancer risk is not recommended.

Note: **Although dosing in the males was not considered to be adequate, the CARC concluded that an additional mouse carcinogenicity study was not required.** This was based on the following:1) no treatment-related effects were seen up to the limit dose of a 1000 mg/kg/day in a subchronic mouse study; 2) no hyperplasia was seen in the mouse carcinogenicity study at 350 mg/kg/day in males and 750 mg/kg/day in females; 3) no structural alerts were seen with the SAR data; 4) rat data indicate saturation of absorption at 250 mg/kg/day; and 5) no mutagenic activity. Based on these data, the CARC determined that a repeat of the male mouse cancer study would have no impact on the regulation of penoxsulam.

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