2

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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0052273

DATE: December 16 , 2003

MEMORANDUM

SUBJECT: **PENOXSULAM** - 1st Report of the Hazard Identification Assessment Review Committee.

FROM: Edwin Budd, Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Karen Whitby, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: William Cutchin, Risk Assessor
Science Information Management Branch
Health Effects Division (7509C)

PC Code: 119031

On December 2, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for penoxsulam with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to penoxsulam was evaluated as required by the Food Quality Protection Act (FQPA) of 1996 in accordance with the 2002 OPP 10X Guidance Document. The conclusions drawn at this meeting are presented in this report.

RC
01/04

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Bill Dykstra, Pamela Hurley, Paula Deschamp, John Liccione, Susan Makris, PV Shah, Karen Whitby, Jessica Kidwell (Executive Secretary)

Member(s) in absentia: Elizabeth Mendez, Jess Rowland, Brenda Tarplee

Also in attendance were: Jeffrey Herndon, Charles Stafford

Data evaluation prepared by: Edwin Budd, Registration Action Branch 2

Data Evaluation / Report Presentation

Edwin Budd
Toxicologist

INTRODUCTION

Penoxsulam, also known as XDE-638, is a new active ingredient systemic post-emergence herbicide chemical. 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.

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.

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.

On December 2, 2003 , the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for penoxsulam with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to penoxsulam was evaluated as required by the Food Quality Protection Act (FQPA) of 1996 in accordance with the 2002 OPP 10X Guidance Document.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

With respect to FQPA hazard considerations, the HIARC concluded that the toxicology database for penoxsulam is complete.

The available toxicology data base for penoxsulam includes the following acceptable studies:

Developmental toxicity study, rats	OPPTS 870.3700, MRID 45830917
Developmental toxicity study, rabbits	OPPTS 870.3700, MRID 45830918
2-Generation reproduction study, rats	OPPTS 870.3800, MRID 45830920
Acute neurotoxicity study, rats	OPPTS 870.6200, MRID 45830902
Chronic neurotoxicity study, rats	OPPTS 870.6200, MRID 45830912, 45830901

2. Evidence of Neurotoxicity

The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to penoxsulam.

No evidence of neurotoxicity was observed in the acute or chronic neurotoxicity studies in rats or in any of the subchronic or chronic feeding studies in rats, mice or dogs.

Executive Summary: In an acute neurotoxicity study (MRID 45830902), four groups (10/sex/group) of fasted, 7 week old, Charles River Fischer 344 rats were given a single oral dose of XDE-638 (97.5% a.i., Lot # ND05167938) in 0.5% aqueous methylcellulose at doses of 0, 500, 1000, or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment [functional observational battery (FOB) and motor activity testing] was performed in 10 animals/sex/group before treatment and at Day 1, 8, and 15. At Day 16, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, males and females in the control and high dose groups were subjected to histopathological evaluation of selected central and peripheral nervous system tissues.

There were no treatment-related effects on mortality, clinical signs, body weight, ophthalmaloscopic findings, or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no treatment-related effects.

Postive control studies were provided. An FOB profiency report demonstrated the ability of the technician observer to detect major neurotoxic endpoints. Motor activity positive control data demonstrated the ability to detect both increases (amphetamine) and decreases (chlorpromazine) in motor activity. Neuropathology positive control data, validated with trimethyltin and acrylamide, demonstrated the ability to detect central and peripheral nervous system histopathologic changes.

Based on the results of this acute neurotoxicity study, the neurotoxic NOAEL for XDE-638 in male and female rats is 2000 mg/kg (limit dose). The LOAEL was not identified (>2000 mg/kg).

This neurotoxicity study is classified as **Acceptable/Guideline** and **does** satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

Executive Summary - In a chronic neurotoxicity study (MRID 45830912), penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 97.7% a.i.) was administered to 10 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for one year. This study was incorporated in a combined chronic toxicity/carcinogenicity study (MRID 45830901). Neurobehavioral assessment (including functional observational battery (FOB), grip performance, landing foot splay, rectal temperature, and motor activity testing) was performed on 10 animals/sex/group pretreatment and at months 1, 3, 6, 9 and 12. At 12 months, five animals/sex from the control and 250 mg/kg/day group were euthanized and perfused *in situ* followed by gross examination and histopathological examination of selected tissues from the central and peripheral nervous systems. The remaining rats were sacrificed and examined according to standard procedures used in the combined chronic toxicity/carcinogenicity study.

There was no treatment-related effect on mortality or ophthalmoloscopic examination. Although statistically significant decreases in body weights and body weight gains in males and females dosed at 250 mg/kg/day were not observed in the 10 rats/sex/dose assigned to the neurotoxicity study, statistically significant decreases in body weights and body weight gains were observed for the 65 rats/sex/dose assigned to the larger more comprehensive study. In the larger study, body weights were statistically significantly decreased in both males and females at 250 mg/kg/day beginning on day 8 and continued throughout the first year of the study (decreased 2-4% in both sexes). At 250 mg/kg/day, body weight gains were decreased during days 1-8 (11% and 17% in males and females, respectively) and days 1-92 (6% and 5% in males and females, respectively). Based on the above findings, the high dose was considered sufficient to test the chronic neurotoxicity of the chemical. An additional treatment-related effect was an increased incidence of urine perineal soiling in males and females at 250 mg/kg/day and females at 50 mg/kg/day observed during the FOB testing; this was not considered to be a toxicologically significant adverse effect.

There was no toxicologically significant evidence of neurotoxicity observed in this study. There was no treatment-related effect on FOB findings, grip performance, landing foot splay, rectal temperature, motor activity or neuropathology. A FOB profiency report and positive control data for motor activity and neuropathology examinations were submitted. These studies produced the expected results and demonstrated the laboratory's proficiency in conducting FOB testing, motor activity testing and neuropathology examinations.

The LOAEL for neurotoxicity for males and females was not established (> 250 mg/kg/day, HDT). The neurotoxicity NOAEL for males and females was 250 mg/kg/day.

This chronic neurotoxicity study is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a chronic neurotoxicity study in rats (870.6200; OECD 424).

3. Developmental Toxicity Study Conclusions

Executive Summary: In a developmental toxicity study (MRID 45830917) XDE-638 (Penoxsulam; 97.5% a.i., lot #ND05167938, TSN101773) was administered to 25 time-mated female CD rats/dose by gavage in 0.5% aqueous METHOCEL™ at dose levels of 0, 100, 500, or 1000 mg/kg bw/day on gestation days (GD) 6 through 20, inclusive. On GD 21, surviving females were sacrificed and necropsied. All fetuses were weighed, sexed, and examined for external alterations. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination.

Dose selection was based on the results from a range-finding developmental toxicity study with Penoxsulam in rats (MRID 45830916), in which administration to groups of 8 time-mated females by gavage at dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day on GD 6-20 resulted in decreased body weight gain by high-dose dams during GD 15-18 (79% of controls), with no treatment-related effects on postimplantation loss, live litter size, or resorptions per dam.

In the main study, there were no treatment-related effects on survival, clinical signs, or absolute body weights. Maternal toxicity was evident at 1000 mg/kg bw/day as decreased body weight gain (84% of control) and food consumption (91% of control) during GD 18-21 and increased absolute and relative (to body) kidney weights (118% and 121%, respectively; $p<0.05$). **The maternal toxicity LOAEL for Penoxsulam in CD rats is 1000 mg/kg bw/day, based on decreased body weight gain and food consumption and increased absolute and relative kidney weights. The maternal toxicity NOAEL is 500 mg/kg bw/day.**

There were no treatment-related increases in fetal deaths/resorptions, and there was no evidence of altered growth or an effect on developmental variations. Malformations were observed in 0, 2, 2 and 3 fetuses and in 0/24, 2/24, 1/25, and 2/22 litters from the control, low-, mid-, and high-dose groups, respectively. Incidences of individual variations were similar in the treated and control groups, and there were no significant increases in fetal or litter incidences of any individual structural abnormalities for any treated group. An apparently rare external malformation (cutis laxis) was observed in 2 fetuses in single litters at both the 500 and 1000 mg/kg/day dose levels. However, based on a weight-of-the-evidence consideration of all the available information/data, it is concluded that the cutis laxis observed in this study most likely has a genetic etiology. There is insufficient information to conclude that it is a treatment-related effect due to the test material. **Therefore, the developmental toxicity LOAEL for penoxsulam in CD rats is not identified (>1000 mg/kg day), and the developmental toxicity NOAEL is 1000 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study [OPPTS 870.3700a; OECD 414] in the rat.

Executive Summary: In a developmental toxicity study (MRID 45830918), XDE-638 (97.5% a.i., Lot # ND05167938, TSN101773) was administered to 25 mated New Zealand white rabbits/dose daily by gavage (7 days per week) in 0.5% aqueous METHOCEL™ at dose levels of 0, 5, 25, or 75 mg/kg bw/day on gestation days (GD) 7 through 27, inclusive. Dose selection was based on the results from a range-finding prenatal developmental toxicity study with XDE-638 in New Zealand white rabbits (MRID 45830919). In the main study, on GD 28, all surviving does were killed and necropsied. All fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations, and heads from approximately one-half the fetuses per litter were examined by serial sections.

One high-dose doe died on GD 27 after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity beginning on GD 22. One high-dose female aborted on GD 23 after exhibiting severely reduced food consumption beginning on GD 12 with decreased to absent defecation and/or black feces beginning on GD 15. This abortion was considered to not be treatment-related. An increased number of high-dose animals exhibited gastrointestinal tract effects including decreased or absent feces or mucoid, soft, or abnormally colored feces (5, 5, 2, and 12 females from the control, low-, mid-, and high-dose groups, respectively). High-dose females had decreased body weight gains during GD 13-24 and decreased mean daily food consumption during GD 19-25 (74% and 81-90% of controls, respectively), although cumulative body weight gain during dosing was unaffected due to increased body weight gain during GD 24-28 (252%). There were no treatment-related effects on absolute body weights, corrected (for gravid uterus) body weights and body weight gains, or liver and kidney weights. Although of small magnitude, the maternal effects observed in this study were considered to be treatment-related. This conclusion was supported by the occurrence of the same treatment-related effects in the dams in a range-finding study. **The maternal toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on death, clinical signs, and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 25 mg/kg bw/day.**

A single dead fetus was noted in the high-dose group. There were no total litter resorptions. High-dose females had very slight increases in mean postimplantation loss (10.8±17.4% vs.5.6±9.0% for controls) and percentage of resorbed implantations (12.1% vs. 5.6%) due to small increases in the mean numbers of resorptions per dam and late resorptions per dam (1.1±1.9 vs. 0.5±0.8 and 0.7±1.3 vs. 0.2±0.5, respectively). Due to the small magnitude of these increases and the large standard deviations and the lack of similar findings in the range-finding study, these increases were not considered to be treatment-related. There were no treatment-related effects on fetal body weights or sex ratios. Malformations were observed in a total of 3/24, 3/22, 4/24, and 2/21 litters from the control, low-, mid-, and high-dose groups, respectively, with no treatment-related increases in the fetal or litter incidences of any individual malformation or variation and no evidence of altered ossification. **The developmental toxicity LOAEL for XDE-638 in New Zealand white rabbits is not identified (>75 mg/kg/day) and the developmental toxicity NOAEL is 75 mg/kg bw/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/ Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b; OECD 414) in the rabbit.

4. Reproductive Toxicity Study Conclusions

Executive Summary: In a two-generation reproduction toxicity study (MRID 45830920), XDE-638 (97.7% a.i., lot #B-765-44, TSN102058) was administered to 30 male and 30 female Crl:CD (SD) IGS BR rats/dose at dietary concentrations that provided 0, 30, 100, or 300 mg/kg/day. One litter was produced in each generation. F_0 and F_1 parental animals were administered test or control diet for 10 weeks prior to mating, throughout mating, gestation, and lactation and until sacrifice. Doses were selected on the basis of a range-finding study in non-mated CD rats (MRID 45830907).

Intercurrent deaths of several F_0 and F_1 animals were considered incidental to treatment. No treatment-related clinical signs of toxicity were observed in any animal during the study. No treatment-related effects on body weights, body weight gains, or food consumption values were observed in males or females of the F_0 generation during the premating interval. Absolute body weights of the high-dose F_1 males were significantly ($p \leq 0.05$; 88-94% of controls) less than those of the controls throughout the study. High-dose F_1 females had significantly lower ($p \leq 0.05$; 93% of controls) body weight than the controls only for the first week of premating. Body weight gains by the high-dose F_1 animals were similar to the controls. Reduced body weights of the high-dose F_1 parental animals during premating were considered a continuation of preweaning effects. Food consumption by the high-dose F_1 males was significantly less ($p \leq 0.05$; 92-93% of controls) than that of the control group for the first two weeks of premating.

Body weights of the high-dose F_0 and F_1 dams were significantly lower ($p \leq 0.05$; 87-94% of controls) than that of controls from GD 21 through lactation day 14. The most pronounced effect on body weight gains during gestation was for days 14-21 when the high-dose F_0 and F_1 dams had weight gains 79% and 82%, respectively, of the control group levels. Weight changes by the high-dose dams during the first week of lactation consisted of marked weight loss during days 1-4 and a lower weight gain than the controls for days 4-7. Recovery was noted in the high-dose dams after lactation day 7. During gestation, food consumption was similar between the treated and control groups of both generations. Food consumption by the high-dose F_0 dams was significantly less ($p \leq 0.05$; 76-88% of controls) than that of the controls on lactation days 1-11. Food consumption by the high-dose F_1 dams was significantly ($p \leq 0.05$; 70-72% of controls) less than that of the controls on lactation days 1-7. Compensation was noted in the high-dose F_0 and F_1 dams with food consumption reaching 115% and 110%, respectively, of controls (both $p \leq 0.05$) during lactation days 17-19.

At necropsy, mid- and high-dose males of both generations had increased absolute and/or relative liver weights due to slight hepatocellular hypertrophy that was not considered to be adverse. High-dose females of both generations had significantly increased ($p \leq 0.05$; 109-115% of control) absolute and relative kidney weights. Microscopic lesions of the kidney of high-dose F_0 and F_1 females included epithelial hyperplasia, inflammation, and crystal formation in the pelvis and tubular degeneration. The incidences (severity) of kidney lesions in control and high-dose females were 1-2/30 (1.00) and 25-26/30 (1.58-2.04), respectively, for hyperplasia, 0/30 and 7-

8/30 (1.25-2.14), respectively, for inflammation, and 3/30 (1.00) and 20-21/30(1.62-1.85), respectively, for degeneration. In addition, crystals were observed in 0, 0, 2, and 16 F_0 females and in 2, 1, 7, and 11 F_1 females in the control, low-, mid-, and high-dose groups, respectively. **Therefore, the parental systemic toxicity LOAEL for female rats is 100 mg/kg/day based on kidney lesions (crystals) and for male rats is 300 mg/kg/day based on reduced absolute body weights of the F_1 males. The parental systemic toxicity NOAEL for female rats is 30 mg/kg/day and for male rats is 100 mg/kg/day.**

No differences in mating or fertility indices, precoital interval, or gestation length were seen between the treated and control groups of either generation. Estrous cyclicity, follicle counts, and sperm parameters were not affected by treatment. For litters of both generations, no treatment-related effects were observed on live birth and viability indices, mean litter sizes, post-implantation losses, numbers of stillborn pups, and sex ratios. No treatment-related clinical signs of toxicity were observed in the pups during lactation and gross necropsy was unremarkable. At birth, body weight of the high-dose pups was slightly (n.s.) lower than that of the control group. High-dose male and female pups from both generations had significantly lower ($p \leq 0.05$) body weights on lactation days 4-21 compared with the controls. Lower body weights of the high-dose pups were a result of weight gains 76-80% of the control group levels from lactations days 1-7. Weight gains by the high-dose pups were slightly lower than the controls from lactation days 7-14 and comparable to control levels from lactation days 14-21.

Preputial separation, an indicator of sexual maturation, was significantly ($p \leq 0.05$) delayed in mid- and high-dose F_1 males. The mean age at which preputial separation was attained for the control, low-, mid-, and high-dose groups was 43.6, 44.0, 45.5, and 46.0 days, respectively. In addition, at the mid-dose, 1 animal did not separate and at the high-dose, 3 animals did not separate whereas all animals at the control and low-doses did separate. The delay in preputial separation at the mid- and high-dose was considered to be a treatment-related effect. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment. **The reproductive/offspring toxicity LOAEL is 100 mg/kg/day based on delay in preputial separation in F_1 males. The reproductive/offspring toxicity NOAEL is 30 mg/kg/day.**

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in rats.

5. <u>Additional Information from Literature Sources</u>

No additional information is available from the literature.

6. Pre- and/or Post-natal Toxicity

The HIARC concluded that there is not a concern for pre- and/or postnatal toxicity resulting from exposure to penoxsulam.

A. Determination of Susceptibility

There was no quantitative or qualitative evidence of susceptibility in rats or rabbits following *in utero* exposures. No developmental toxicity was seen at the highest dose tested in either species. Following pre/post-natal exposure in the two-generation study, offspring toxicity was seen at the same dose that induced parental toxicity and was not more severe than maternal toxicity.

B. Degree of Concern Analysis and Residual Uncertainties:

There are no concerns or residual uncertainties for pre/post-natal toxicity following exposure to penoxsulam.

C. Special FQPA Safety Factor(s):

Based upon the above data, **no Special FQPA Safety Factor is needed (i.e. 1X) since there are no residual uncertainties for pre- and/or post-natal toxicity.**

The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary, food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is not a concern for developmental neurotoxicity resulting from exposure to penoxsulam.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:

None.

B. Evidence that do not support a need for a Developmental Neurotoxicity study:

There was no evidence of neurotoxicity or neuropathology in the acute or chronic neurotoxicity studies in rats. In addition, there was no evidence of neurotoxicity in any of the following studies: subchronic or chronic toxicity studies in rats, mice or dogs; developmental toxicity studies in rats or rabbits; or a 2-generation reproduction study in rats.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - ALL POPULATIONS

Study Selected: None

Guideline No.: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing aRfD: Not applicable

Uncertainty Factor (UF): Not applicable

Comments about Study/Endpoint: In the developmental toxicity study in rabbits, one high-dose doe died on GD 27 after exhibiting clinical signs of toxicity beginning on GD 22. Since the test material was administered each day from GD 7 through GD 27, this doe died only after 21 doses. It is unlikely that this death was caused by a single dose of the test material. There were no other treatment-related effects observed in any of the available toxicity studies on penoxsulam that could be considered to have resulted from a single dose of the test material.

2. Chronic Reference Dose (cRfD) - ALL POPULATIONS

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: In a chronic toxicity study (MRID 45830914), XDE-638 (97.7%; Lot No. B-765-44) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equivalent to 0, 5.3, 14.7, or 46.2 mg/kg/day, respectively, for males and 0, 4.4, 14.0, or 44.8 mg/kg/day, respectively, for females) for one year.

There were no toxicologically significant compound-related effects on mortality, clinical signs, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, organ weights, or gross pathology. There appeared to be marginal inhibition of body weight gain and food consumption in males, but not females, receiving 0.15% XDE-638. The only effect of toxicological significance was the occurrence of very slight, multifocal hyperplasia of the pelvic epithelium in both kidneys of one male in the 0.15% group. Similar lesions were seen in male and female dogs in 4- and 13-week dietary studies with XDE-638. Exacerbation of the lesions observed in these shorter-term studies was not observed in the one-year study. The incidence of

kidney lesions seen in the 13-week study was actually greater (2/4 males and 2/4 females) than in the one-year study (1/4 males and 0/4 females) at the same dietary level (0.15%) of XDE-638. In addition, crystals were seen in the renal pelvis and collecting ducts of both genders in the 13-week study, but not in the one-year study.

The LOAEL is 46.2 mg/kg/day for males based on slight multifocal hyperplasia in the renal epithelium; a LOAEL was not established for females (>44.8 mg/kg/day). The NOAEL for males is 14.7 mg/kg/day; the NOAEL for females is 44.8 mg/kg/day.

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog.

Dose and Endpoint for Establishing cRfD: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney of males at the LOAEL of 46.2 mg/kg/day.

Uncertainty Factor (UF): 100, based on 10X for interspecies extrapolation and 10X for intraspecies variation.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is based on an oral study, which is the route of interest for a dietary risk estimate. Although the multifocal hyperplasia of the pelvic epithelium of the kidney observed at the LOAEL of 46.2 mg/kg/day in the selected study was described as very slight and occurred in only one male dog, this effect was nevertheless considered to be of sufficient concern to be the basis for determining the chronic RfD for penoxsulam. The reason for this was that a higher incidence of the same histopathological lesion in the kidneys of both male and female dogs was observed in the 13-week feeding study in dogs (MRID 45830909) at almost identical dose levels. The LOAEL in the 13-week study was 49.4 mg/kg/day (males) and 57.1 mg/kg/day (females) and the NOAEL was 17.8 mg/kg/day (males) and 19.9 mg/kg/day (females). In addition, crystals were seen in the renal pelvis and collecting ducts of both genders in the 13-week study, but not in the one-year study. The reason for the greater response in the kidneys of dogs in the 13-week study as compared to that in the 1-year study is not clear, but the overall findings clearly support the interpretation of the multifocal hyperplasia of the pelvic epithelium of the kidney observed in one dog at the LOAEL of 46.2 mg/kg/day in the 1-year study as being a toxicologically significant finding. In addition, similar treatment-related histopathological findings were observed in the kidneys in a 4-week range-finding study in dogs (MRID 45830908) and in many other subchronic and chronic feeding studies in rats. It would seem that penoxsulam (and/or its metabolites) has a limited solubility in urine and tends to form crystals/calculi in the kidney and urinary bladder. These crystals/calculi apparently irritate the tissues in these organs, and following repeated administrations of penoxsulam, lead to hyperplasia, inflammation and/or other secondary effects in the kidney and urinary bladder.

$$\textbf{Chronic RfD} = \frac{\text{14.7 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.147 mg/kg/day}$$

3. Incidental Oral Exposure: Short-Term (1 - 30 days)

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: In a 90-day oral toxicity study (MRID 45830909), XDE-638 (97.5%; Lot No. ND05167938, TSN101773) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equal to 0, 5.9, 17.8, and 49.4 mg/kg bw/day, respectively, in males and 0, 5.7, 19.9 and 57.1 mg/kg bw/day, respectively, in females) for 13 weeks.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, or gross pathology. Increased relative liver/body weight ratios in males and females receiving 0.15% XDE-638 was considered a treatment-related effect, however, this effect did not have correlative changes in clinical pathology or histopathology. Treatment-related histopathologic changes in kidneys of 0.15% males and females consisted of very slight, multifocal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts.

The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/day, based on histopathologic changes in the kidneys. The NOAEL was 17.8 and 19.9 mg/kg/day for males and females, respectively.

This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409).

Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: This endpoint is based on an oral study, which is the route of interest for an oral risk estimate. This endpoint is also appropriate for the population of concern (infants and children). For this exposure scenario, a 13-week (90-day) study was selected to establish the toxicological endpoint for short-term (1-30 days) exposures. This selection is justified by the observation that the kidney lesions (including histopathologicic changes) observed in the 4-week, 13-week and 1-year feeding studies in dogs did not occur at lower dose levels or increase in severity as the duration of the study increased. In other words, exacerbation of the kidney lesions observed in the shorter-term studies did not occur in the longer-term studies. Therefore, results in both the 4-week and 1-year studies support this selection. In addition, this selection (NOAEL of 17.8 mg/kg/day based on kidney lesions at the LOAEL of 49.4 mg/kg/day) is also protective of the maternal effects observed in the developmental toxicity

study in rabbits (NOAEL of 25 mg/kg/day based on death, clinical signs, decreased body weight gain and decreased food consumption at the LOAEL of 75 mg/kg/day).

4. Incidental Oral Exposure: Intermediate-Term (1 - 6 months)

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See Incidental Oral Exposure: Short-Term (1 - 30 days)

Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: This endpoint is based on an oral study, which is the route of interest for an oral risk estimate. This endpoint is also appropriate for the duration of exposure (1- 6 months) and the population of concern (infants and children).

5. Dermal Absorption

Dermal Absorption Factor: 50% (upper bound estimate)

A dermal absorption study is not available. The percent dermal absorption was estimated by comparing the LOAEL for male and female rats from a 4-week dermal study (MRID 45830910) to the LOAEL for male and female rats from a 4-week feeding study (MRID 45830903).

The LOAEL for male and female rats from the 4-week dermal study was >1000 mg/kg/day, based on the lack of any treatment-related effects at 1000 mg/kg/day (the highest dose tested, limit dose).

The LOAEL for male rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, and decreased RBC parameters. The NOAEL for male rats was 100 mg/kg/day. The LOAEL for female rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, decreased RBC parameters, increased kidney weights, and histopathological changes in the kidney. The NOAEL for female rats was 100 mg/kg/day.

$$\text{LOAEL from 4-week feeding study} = \frac{500 \text{ mg/kg/day}}{\text{LOAEL from 4-week dermal study} = >1000 \text{ mg/kg/day}} \times 100 = 50\% \text{ (upper bound estimate)}$$

4-Week Dermal Study

Executive Summary: In a 4-week dermal toxicity study (MRID 45830910), technical grade penoxsulam (97.5% a.i., Lot# ND05167938, TSN101773) was applied to the shaved skin of 10 Fisher 344 rats/sex/dose at dose levels of 0, 100, 500, 1000 mg/kg bw/day, 6 hours/day for 7 days/week during a 28-day period (main study). Additional groups of 10 rats/sex were similarly administered 0 or 1000 mg/kg and held for 2 weeks following the treatment period to assess recovery from any treatment-related effects (recovery group).

There were no deaths reported during the study. There were no treatment-related effects on clinical observations, dermal observations, body weight, body weight gain, food consumption, urinalysis parameters, hematology, clinical chemistry, organ weights, or gross or histopathology during the 4-week dosing phase. The recovery group animals showed no treatment related effects in body weight, food consumption, or gross pathology (the only parameters assessed).

Based on the results of this study, the systemic and dermal NOAEL for XDE-638 in male and female rats is the limit dose of 1000 mg/kg/day, and the systemic and dermal LOAEL is not identified (>1000 mg/kg/day).

This 28-day dermal toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rats.

4-Week Feeding Study

Executive Summary: In a 4-week feeding study (MRID 45830903), XR-638 (penoxsulam) (99%, lot number 597-CO49-17C, TSN101644) 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. Animal care, diet preparation, and gross necropsy were as described in the main study (MRID 45830906). Tissues from animals receiving the control and 1000 mg/kg/day diets, as well as the liver, kidneys, and relevant gross lesions from the remaining dose groups, were processed as in the main study and examined microscopically.

All animals survived until scheduled sacrifice. Perineal urine soiling, observed in one 500 mg/kg/day male, four 500 mg/kg/day females and three 1000 mg/kg/day females, was not considered to be a toxicologically significant adverse effect. Ophthalmology was unremarkable. Body weights of both sexes receiving 1000 mg/kg/day were lower than those of controls throughout the study, and at day 29 were about 10% (males) and 6% (females) below those of controls. Body weight gains at day 29 were 25% (males and females) lower than those of controls. At 500 mg/kg/day, body weights of both sexes were also lower than those of controls throughout the study, and at day 29 were about 8% (males) and 4% (females) below those of controls. Body weight gains at day 29 were 20% (males and females) lower than those of controls. At 1000 and 500 mg/kg/day, overall food consumption by both sexes was about 5-11% lower than that of controls. Slight, statistically significant decreases in red blood cell parameters (<10% at 1000 mg/kg/day) were present in males and females from all dose levels but were more pronounced at 1000 and 500 mg/kg/day. There were no toxicologically significant changes in

clinical chemistry or urinalyses. Kidney weight was increased by about 10% in the 1000 and 500 mg/kg/day females. Slight multifocal hyperplasia of the renal pelvic epithelium, very slight subacute to chronic inflammation of the renal pelvic epithelium, and crystals in the urinary space of the renal pelvis were found in females of the 500 and 1000 mg/kg/day groups. One 500 mg/kg/day male had a few crystals in the urinary space of the renal pelvis of one kidney.

The LOAEL is 500 mg/kg/day based on 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 NOAEL is 100 mg/kg/day.

This 4-week oral 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.

6. Dermal Exposure: Short-Term (1 - 30 days) Exposure

Study Selected: None

Guideline No.: N/A

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: Quantification of dermal risk assessment is not required for this exposure scenario due to the lack of dermal, systemic, neuro, or developmental toxicity concerns. No dermal or systemic toxicity was seen at the limit dose in the dermal study. In the 4-week oral study, systemic toxicity was seen at a relatively high dose (500 mg/kg/day; one-half of the limit dose).

7. Dermal Exposure: Intermediate-Term (1 - 6 Months) Exposure

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See 3. Incidental Oral Exposure: Short-Term (1 - 30 days)

Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathological changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: An oral dose/endpoint was selected due to the concerns for the renal lesions seen after exposure for 90 days. The dermal study was determined to be not appropriate due to its shorter duration (i.e., 28 days). The endpoint selected for this exposure scenario is based on an oral study and therefore a 50% dermal absorption factor (upper bound estimate) should be used for route-to-route extrapolation for this risk assessment.

8. Dermal Exposure: Long-Term (> 6 Months) Exposure

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See Chronic Reference Dose (cRfD)

Dose and Endpoint for Risk Assessment: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney in males at the LOAEL of 46.2 mg/kg/day.

Comments about Study/Endpoint: The endpoint selected for this exposure scenario is based on an oral study and therefore a 50% dermal absorption factor (upper bound estimate) should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (> 6 months). See additional comments at 2. Chronic Reference Dose (cRfD).

9. Inhalation Exposure: Short-Term (1 - 30 days)

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See Incidental Oral Exposure: Short-Term (1 - 30 days)

Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: There is no acceptable inhalation study of any duration available on technical grade penoxsulam. Absorption via the inhalation route is assumed to be equivalent to oral absorption. This endpoint has been determined to be appropriate for the

duration of exposure (1 - 30 days). See additional comments at Incidental Oral Exposure: Short-Term (1 - 30 days).

10. Inhalation Exposure: Intermediate-Term (1 - 6 Months) Exposure

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See Incidental Oral Exposure: Short-Term (1 - 30 days)

Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathological changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: There is no acceptable inhalation study of any duration available on penoxsulam. Absorption via the inhalation route is assumed to be equivalent to oral absorption. This endpoint is appropriate for the duration of exposure (1 - 6 months). See additional comments at Incidental Oral Exposure: Short-Term (1 - 30 days).

11. Inhalation Exposure: Long-Term (> 6 Months) Exposure

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See Chronic Reference Dose (cRfD)

Dose and Endpoint for Risk Assessment: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney in males at the LOAEL of 46.2 mg/kg/day.

Comments about Study/Endpoint: The endpoint selected for this long-term inhalation risk assessment is based on an oral study. Absorption via the inhalation route is assumed to be equivalent to oral absorption. This endpoint is appropriate for the duration of exposure (> 6 months). See additional comments at Chronic Reference Dose (cRfD).

12. Margins of Exposure

The target Margins of Exposure (MOEs) for occupational and residential exposure risk assessments are as follows:

Summary of Target Margins of Exposure (MOEs) for Risk Assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	N/A	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal	N/A	100	100
Inhalation	100	100	100

N/A = Not Applicable

For Occupational Exposure: The MOEs are based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

For Residential Exposure: The MOEs are based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

13. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows:

Common toxicological effects (histopathologic changes in the kidneys in the same 90-day feeding study in dogs) were selected for assessment of short-term exposures by oral and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure duration should include oral and inhalation exposures appropriate to the populations of concern. Short-term dermal exposure need not be aggregated because no toxicological endpoint was selected.

Common toxicological effects (histopathologic changes in the kidneys in the same 90-day feeding study in dogs) were selected for assessment of intermediate-term oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure duration should include oral, dermal and inhalation exposures appropriate to the populations of concern.

Common toxicological effects (multifocal hyperplasia of the pelvic epithelium of the kidney in the same 1-year chronic feeding study in dogs) were selected for assessment of long-term oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure duration should include oral, dermal and inhalation exposures appropriate to the populations of concern.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Guideline No: § 870.4300

MRID No.: 45830901

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 45830901, 45830913) penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 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 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.

In the main study groups, there was a statistically significant increase in the incidence (24%, 60%, 58% and 60% at 0, 5, 50 and 250 mg/kg/day, respectively) and the severity of malignant Large Granular Lymphocyte (LGL) leukemia in all groups of treated male rats. There was no dose response with all treated groups having an approximately 2.5-fold increase over control animals. The histopathology slides were reviewed by an external Pathology Working Group (PWG) to establish consensus diagnoses which were presented in the study report. The incidence in all groups of treated males exceeded the conducting laboratory's historical control

mean (28.5%) and range (16-40%) for 8 studies, but did not exceed the National Toxicology Program (NTP) historical control mean (50.5%) and range (32-74%). **The study demonstrated that XDE-638 may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats.** The dosages in the study were adequate in males and marginally adequate in females to assess the carcinogenicity of the chemical based primarily on decreased body weight and body weight gain and the effects on the urinary system.

This combined chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

Discussion of Tumor Data: This study presented evidence that penoxsulam (XDE-638) may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats. **This results from this study along with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.**

Adequacy of the Dose Levels Tested: The dosages in this study were considered adequate in males and marginally adequate in females to assess the carcinogenicity of the test material based primarily on decreased body weight and body weight gain and the effects on the urinary system.

2. Carcinogenicity Study in Mice

Guideline No: § 870.4200b

MRID No.: 45372009, 45372030

Executive Summary: In a carcinogenicity study (MRID 45830915), XDE-638 (97.7% a.i., lot # B-765-44, TSN 102058) 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).

XDE-638 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. **However, in males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose.** In females, 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 conclusion 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.

This study is classified as **Unacceptable/Guideline** and **does not satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice because the highest dose tested in the male mice was inadequate for carcinogenicity testing.

Discussion of Tumor Data: At the doses tested, there were no treatment-related increases in tumor incidence when compared to controls in either male or female mice.

Adequacy of the Dose Levels Tested: In males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose. In females, 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 conclusion 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.

3. Classification of Carcinogenic Potential

To be determined. The results from the carcinogenicity studes in rats and mice together with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.

IV. MUTAGENICITY

Technical grade penoxsulam did not demonstrate any mutagenic potential in a battery of 4 mutagenicity studies. The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to penoxsulam.

Results were negative without and with 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. In an *in vitro* chromosomal aberration study in primary rat lymphocytes, penoxsulam was negative when tested without and with rat S-9 activation. In an *in vivo* micronucleus study in mice using bone marrow cells, the results were negative.

In addition, GF-443, a formulated product containing 21.9% penoxsulam, did not demonstrate any mutagenic potential in 2 mutagenicity studies. Results were negative without and with rat S-9 activation in a reverse gene mutation study using *Salmonella typhimurium/Escherichia coli* and in an *in vivo* micronucleus study in mice using bone marrow cells.

V. HAZARD CHARACTERIZATION

Technical grade penoxsulam (XDE-638), an off-white powder of 97.5% purity, exhibited minimal acute toxicity in the available studies. The acute oral LD_{50} in male and female rats was >5000 mg/kg (Toxicity Category IV) and the acute dermal LD_{50} in male and female rabbits was >5000 mg/kg (Toxicity Category IV). In a primary eye and skin irritation studies in rabbits, it produced only minimal irritation (Toxicity Category IV) and in a dermal sensitization study in guinea pigs (maximization method), it was negative for dermal sensitization. An acute inhalation toxicity study in rats was classified as unacceptable/guideline due to a technical error during the study.

In subchronic and chronic feeding studies in rats and dogs, the most sensitive target organ was the urothelium of the urinary system. Due to limited solubility in urine, penoxsulam (and/or its metabolites) formed crystals/calculi, which were regularly observed in the pelvis of the kidney and the lumen of the urinary bladder. These crystals/calculi apparently irritated the urothelium in these organs and following repeated dosing lead to numerous secondary effects which resulted in significant damage to the urinary system. In various studies, these secondary effects were manifested as altered clinical chemistry parameters (increased blood urea nitrogen), altered urinalyses parameters (increased urine volume,

decreased urine specific gravity), increased absolute and relative kidney weights, gross pathological findings in the kidneys (calculi and roughened surface), , and a variety of histopathological findings in the kidney and urinary bladder, particularly hyperplasia, inflammation and mineralization in the pelvic epithelium of the kidney and hyperplasia in the mucosa of the urinary bladder. Renal tubular degeneration was also sometimes observed. Although a treatment-related increased severity of chronic progressive glomerulonephropathy was observed in male rats, kidney damage observed in shorter-term studies was generally not exacerbated in longer-term studies. At similar and/or somewhat higher dose levels, mildly decreased body weight/body weight gain, often accompanied by decreased food consumption, were often observed in feeding studies in rats and dogs. In addition, in male rats, slightly decreased erythrocyte parameters (erythrocyte count, hemoglobin and hematocrit) were occasionally observed.

In subchronic and chronic feeding studies in mice, no effects of toxicological significance were observed in the 4-week, 13-week or 18-month feeding studies. In these studies, the only treatment-related effects observed at the dose levels tested were increased liver weights, increased hepatocellular hypertrophy, and related observations indicating stimulation of the liver microsomal enzyme system. These effects were considered to be an adaptive response to administration of the test material and not toxicologically significant adverse effects.

In a developmental toxicity study in rats, decreased body weight gain, decreased food consumption and increased kidney weights were observed in the dams. No developmental toxicity was observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this study. In a developmental toxicity study in rabbits, decreased body weight gain, decreased food consumption and clinical signs of toxicity (decreased/absent feces, or mucoid, soft, or abnormally colored feces) were observed in dams at the highest dose tested. One high dose doe died late in the study after exhibiting signs of clinical toxicity for several days. No developmental toxicity was observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this study. In a 2-generation reproduction study in rats, microscopic lesions in the kidney were observed in the parental females at the mid and high dose levels. Preputial separation, an indicator of sexual maturation, was significantly ($p \leq 0.05$) delayed in mid and high dose F_1 males. The mean age at which preputial separation was attained for the control, low, mid, and high dose groups was 43.6, 44.0, 45.5, and 46.0 days, respectively. In addition, at the mid dose, 1 animal did not separate and at the high dose, 3 animals did not separate whereas all animals at the control and low doses did separate. The delay in preputial separation at the mid and high doses was considered to be a treatment-related effect. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment. There was no increased quantitative or qualitative susceptibility of fetuses or offspring, as compared to adults, in this study.

No treatment-related neurotoxicity was observed in acute or chronic neurotoxicity studies in rats, or in any of the other available studies on penoxsulam. No systemic or dermal toxicity was noted in a 28-day dermal toxicity study in rats.

In a carcinogenicity study in rats, male and female rats were given penoxsulam in the diet for two years at dose levels of 0, 5, 50 or 250 mg/kg/day. In this study, there was a statistically significant increased incidence of malignant large granular lymphocyte (LGL) leukemia in each of the male treatment groups. The incidence was 24%, 60%, 58% and 60% in the control, low, mid and high dose level groups respectively. There was no dose response with all treated male groups having an approximately 2.5 fold increase over control animals. The incidence in the male treatment groups exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%), but fell within the National Toxicology Program (NTP) historical control data base of mean (50.5%) and range (32-74 %). There was also an increased severity (Stage 3) of LGL leukemia in all the treated male groups compared to the control group. There was no increase in incidence or severity of LGL leukemia for the treated female rats in this study. The dose levels in this study were considered to be adequate in male rats and marginally adequate in female rats to assess the carcinogenicity of penoxsulam. In a carcinogenicity study in mice, penoxsulam was administered in the diet for 18-months at dose levels up to 375 mg/kg/day in male mice and up to 750 mg/kg/day in female mice. An increased incidence of treatment-related tumors of any kind was not observed in the male or female mice. However, in males, the highest dose tested (375 mg/kg/day) was considered to be inadequate for carcinogenicity testing because no toxicologically significant adverse effects were observed at this dose (or in subchronic studies at doses up to 1000 mg/kg/day). In females, 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. Like males, no toxicologically significant adverse effects were observed in females at this dose (or in subchronic studies at doses up to 1000 mg/kg/day). The results from the carcinogenicity studies in rats and mice together with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.

Technical grade penoxsulam did not demonstrate any mutagenic potential in a battery of four mutagenicity studies. There is not a concern for mutagenicity resulting from exposure to penoxsulam.

In a metabolism study in rats, ^{14}C-penoxsulam was rapidly and nearly completely absorbed at the low dose of 5.0 mg/kg, but at the high dose of 250 mg/kg, there was evidence that absorption was largely incomplete (i.e. absorption was saturated). Both gender and dose affected the excretion pattern. At the low dose, the major route of excretion of radioactivity was via the feces in males and via the urine in females. At the high dose, radioactivity was predominantly excreted via the feces in both sexes. A significant enterohepatic circulation was observed, particularly in males. Most (>90%) of the administered dose was excreted within 36-48 hours. There was negligible radioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although numerous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the administered dose. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.

VI. DATA GAPS / REQUIREMENTS

There is no acceptable inhalation study of any duration available on technical grade penoxsulam. The HIARC recommends that a 28-day inhalation study in rats be required to be submitted to the Agency within a reasonable period of time.

The 18-month carcinogenicity study in mice (NRID 45372009, 45372030) was classified as **Unacceptable/Guideline** and **does not satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice because the highest dose tested in the male mice was inadequate for carcinogenicity testing. Therefore, there is a data gap for this requirement.

VII. ACUTE TOXICITY

Acute Toxicity of Penoxsulam (PC Code 119031)

Six acute studies conducted on **Penoxsulam (XDE-638) Technical** (EPA File Symbol 62719-UOO); Lot No. NDO5167938; purity = 97.5%; off-white powder. All studies were classified as Acceptable/Guideline, except for the acute inhalation study which was classified as Unacceptable/guideline.

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral Rats	45830812	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal Rabbits	45830815	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1300	Acute Inhalation Rats **UNACCEPTABLE**/ guideline	45830818	------	------
870.2400	Primary Eye Irritation Rabbits	45830820	Minimal irritation	IV
870.2500	Primary Skin Irritation Rabbits	45830823	Minimal irritation	IV
870.2600	Dermal Sensitization Guinea Pigs (Maximization)	45830826	Negative for dermal sensitization	N/A

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicological Doses and Endpoints for Penoxsulam (PC Code 119031)

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	None UF = N/A	Not applicable	No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on penoxsulam.
Chronic Dietary (all populations)	NOAEL= 14.7 mg/kg/day UF = 100 **Chronic RfD = 0.147 mg/kg/day**	FQPA SF = 1X **cPAD** = chronic RfD / FQPA SF **= 0.147 mg/kg/day**	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.
Incidental Oral Short-Term (1 - 30 days)	NOAEL = 17.8 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL = 17.8 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Dermal Short-Term (1 - 30 days)	None	Not applicable	No dermal, systemic, neuro or developmental toxicity concerns.
Dermal Intermediate-Term (1 - 6 months)	Oral study NOAEL= 17.8 mg/kg/day (dermal absorption rate = 50%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Dermal Long-Term (> 6 months)	Oral study NOAEL= 14.7 mg/kg/day (dermal absorption rate = 50%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation Short-Term (1 - 30 days)	Oral study NOAEL= 17.8 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Inhalation Intermediate-Term (1 - 6 months)	Oral study NOAEL= 17.8 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Inhalation Long-Term (> 6 months)	Oral study NOAEL= 14.7 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.
Cancer (oral, dermal, inhalation)	**The results from the carcinogenicity studies in rats and mice together with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.**		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, N/A = Not Applicable.

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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