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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 9/29/2004

SUBJECT: PP#3F6542 -- **Human Health Risk Assessment for Penoxsulam.** Proposal for Tolerance of Residues in/on Rice.

DP Barcode:	D307079	Decision No.:	305735
Chemical#:	119031	Class:	Herbicide
Trade Name:	GF-443 SC SF	EPA Reg#:	62719-LNN
	GF-947 Granule		62719-LNG
	GF-947 Granule		62719-LNR
40 CFR:	NA	Chem Class:	sulfonamide

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OCT 12 2004

1.0 EXECUTIVE SUMMARY

General Background

Dow AgroSciences LLC has proposed, in PP#3F6542, the establishment of permanent tolerances for residues of the he bicide penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] in/on rice commodities. Penoxsulam i s a member of the triazolopyrimidine sulfonamide pesticide class. Its mode of action in susc ptible weeds is by inhibition of acetolactate synthase (ALS), an enzyme required for the biosynt esis of certain amino acids necessary for plant growth. Penoxsulam is intended for the c ntrol of *Echinochloa* grasses, broadleaf weeds, and sedge weeds in both water-injected (tr nsplanted paddy) and postemergence (direct-seeded) rice. This is the first proposed agricultural se for penoxsulam. At this time, no residential uses have been proposed for penoxsulam.

Registrations have been equested for technical grade penoxsulam, which contains 97.5% active ingredient, and for GF-88 , a liquid manufacturing use concentrate containing 50% active ingredient. Penoxsulam is prop sed to be used in the U.S. in a liquid formulation GF-443 SC SF (containing 21.7% active ing edient) and in 2 granular formulations GF-947 SF and GF-947 CA (both containing 0.24% acti e ingredient) for the selective control of various weeds in dry-seeded and water-seeded rice in he southern United States and California. Permanent tolerances have been requested for residue of penoxsulam (expressed as parent only) in/on rice grain, straw, hulls, bran, and polished r ce (PP 3F06542).

A single postemergence pplication of penoxsulam is to be made to rice from the one-leaf growth stage (7-12 days after se ding) to 60 days prior to rice harvest. The application is to be made by aerial or ground equipr ent once per growing season at a maximum rate of 0.045 lb ai/A. Penoxsulam is to be form lated as a granular (for water-seeded rice) or suspension concentrate (for direct-seeded ri e) formulation.

Hazard Assessment

In subchronic and chroni feeding studies in rats and dogs, the most sensitive target organ was the urothelium of the urinar system. Due to limited solubility in urine, penoxsulam (and/or its metabolites) formed crystals/ alculi, which were regularly observed in the pelvis of the kidney and the lumen of the urinary bla der. These crystals/calculi apparently irritated the urothelium in these organs and following repe ted dosing lead to numerous secondary effects which resulted in significant damage to the urinar system. In various studies, these secondary effects were manifested as altered clinical ch mistry parameters (increased blood urea nitrogen), altered urinalyses parameters (increased urine volume, decreased urine specific gravity), increased absolute and relative kidney wei hts, gross pathological findings in the kidneys (calculi and roughened surface), and a variet of histopathological findings in the kidney and urinary bladder, particularly hyperplasia, inflamm ation and mineralization in the pelvic epithelium of the kidney and hyperplasia in the mucosa o 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 (also referred to as mononuclear cell leukemia (MNCL)) 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 ar mals. The incidence in the male treatment groups exceeded the conducting laboratory's historic l control mean (28.5%) and range (16-40%), but fell within the National Toxicology Program (l TP) historical control data base of mean (50.5%) and range (32-74 %). There was also an incre sed 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 ats in this study. The dose levels in this study were considered to be adequate in male rats and ma ginally adequate in female rats to assess the carcinogenicity of penoxsulam. In a carcinogenicit y study in mice, penoxsulam was administered in the diet for 18-months at dose levels up to 375 ng/kg/day in male mice and up to 750 mg/kg/day in female mice. An increased incidence o 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 a this dose (or in subchronic studies at doses up to 1000 mg/kg/day). In females, the hig est 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 toxi ologically significant adverse effects were observed in females at this dose (or in subchronic stu dies at doses up to 1000 mg/kg/day). The Cancer Assessment Review Committee (CARC) det rmined that although dosing in the males was not considered to be adequate, an additional mous carcinogenicity study was <u>not</u> required because a repeat of the male mouse cancer study would have no impact on the regulation of penoxsulam. Penoxsulam was classified as "Suggestive E dence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" and, the efore, quantification of human cancer risk is not required.

Technical grade penoxsu am did not demonstrate any mutagenic potential in a battery of four mutagenicity studies. Ther 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 ng/kg, but at the high dose of 250 mg/kg, there was evidence that absorption was largely inco nplete (i.e. absorption was saturated). Both gender and dose affected the excretion pattern. A t the low dose, the major route of excretion of radioactivity was via the feces in males and via th urine in females. At the high dose, radioactivity was predominantly excreted via the f ces 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 r dioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although n merous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the admi istered dose. Parent compound and a 2-hydroxyphenyl derivative were the major comp unds in urine and feces.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

The Hazard Identificatio Assessment Review Committee (HIARC) concluded that the toxicology database for penoxsu lam is complete for FQPA purposes. HIARC concluded that a database uncertainty factor is nc needed for penoxsulam (i.e., removed or 1x). The HIARC concluded that there is not a co cern 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. The HIARC determined that no Special FQPA Safety Factor is needed (i.e. 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity. The risk assessment team concurred with this finding. Using the 1x FQPA Special Safety Factor will not result in underestimated exposure and risks.

On December 2, 2003, the HIARC selected endpoints for acute and chronic dietary exposure, short- and intermediate-term incidental oral exposure and short-, intermediate- and long-term dermal and inhalation exposure. There were no 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, therefore no acute endpoint was established for penoxsulam. The chronic dietary endpoint is based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (chronic PAD = 0.147 mg/kg/day). The incidental oral exposure short- (1-30 days) and intermediate- (1-6 months) term endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL= 17.8 mg/kg/day, MOE = 100). The dermal absorption factor was estimated to be 50% as an upper bound estimate for all dermal exposure scenarios. The absence of dermal, systemic, neuro or developmental toxicity concerns resulted in there being no selection of a dermal short-term (1-30 days) endpoint. The dermal intermediate-term (1-6 mo) endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL= 17.8 mg/kg/day, MOE = 100). The dermal long-term (>6 mo) endpoint based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (NOAEL= 14.7 mg/kg/day, MOE = 100). The inhalation exposure short- (1-30 days) and intermediate- (1-6 months) term endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL= 17.8 mg/kg/day, MOE = 100). The inhalation long-term (>6 mo) endpoint is based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (NOAEL= 14.7 mg/kg/day, MOE = 100).

Exposure Scenario	NOAEL	Dose or Target MOE*	Study/Effect
Acute dietary (all populations)	None	None	No toxicological endpoint attributable to a single exposure was identified in the available toxicology studies on penoxsulam.
Chronic dietary	14.7 mg/kg/day	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 (all durations)	17.8 mg/kg/day	Residential 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) Absorption: 50%	None	Not applicable	No dermal, systemic, neuro or developmental toxicity concerns.
Dermal Intermediate-term (1-6 mo) Absorption: 50%	17.8 mg/kg/day	Residential MOE = 100 Occupational 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) Absorption: 50%	14.7 mg/kg/day	Residential MOE = 100 Occupational 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.
Inhalation Short-Term (1 - 30 days) Absorption: 100%	17.8 mg/kg/day	Residential MOE = 100 Occupational 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) Absorption: 100%	17.8 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	
Inhalation Long-Term (> 6 months) Absorption: 100%	14.7 mg/kg/day	Residential MOE = 100 Occupational 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.

* MOE = margin of exposure

Dietary Exposure Estimates

Residue Chemistry

Based on the submitted r ce metabolism study, penoxsulam primarily degrades to its 5-OH metabolite (5-OH XDE-638) and at least two minor unknown metabolites in rice matrices; little translocation of penoxsular residues or its metabolites into the grain was observed. The available goat and poultry metab olism data indicate that penoxsulam is primarily excreted and not significantly metabolized in (ither goats or poultry. Because no significant differences were observed between the two labels the sulfonanilide bridge in penoxsulam does not appear to be cleaved as a result of goat metab olism. Based on data from the confined rotational crop study, no quantifiable residues of penoxsu am or 5-OH XDE-638 are expected to be present in the raw agricultural commodities of sma l grains, leafy vegetables, and root crops planted 90 days following treatment with penoxs ulam. HED's Metabolism Assessment Review Committee (MARC) determined that for the tolerance expression and risk assessment the residue of concern for penoxsulam in rice, livestock and rotational crops is parent only.

Adequate field trial data re available for rice; although the field trial data reflect exaggerated application rates, a ditional data will not be required unless the petitioner wishes to lower the recommended toleran es. Residues were generally below the method limit of quantitation (LOQ; 0.01 ppm) i rice grain samples ranging from less than the Limit of Detection (LOD; 0.002 ppm) to 0.013 ppm . Residues on rice straw ranged from <LOD to 0.484 ppm. In the submitted rice processing st dy, residues of penoxsulam were <LOD in/on rice grain, hulls, bran, and polished rice processe from rice treated at 4x the proposed rate. The treatment rate for the processing study is abov the apparent where phytotoxic effects were observed in other studies. No further processing s udies are required; penoxsulam residues greater than the grain tolerance are not expected on ri e processed commodities. The submitted storage stability study will be considered "interim" dat until the full, final report is submitted. Storage stability data for future uses will require the r ceipt and acceptance of the final rice report as well as any data

required for the additional use. Penoxsulam has very low potential to bioconcentrate in edible tissues of crayfish. The available data for crayfish indicate that tolerances for penoxsulam residues in crayfish are not required to support this petition.

HED concludes that the proposed use of penoxsulam on rice results in a 40 CFR §180.6(a)(3) situation for ruminant and poultry commodities; i.e., there is no reasonable expectation of finite residues in ruminant and poultry commodities. The available analytical methodology (LC/MS/MS method) is considered to be adequate for tolerance enforcement provided some revisions are made (see Section 8.2). The available rotational crop data indicate that tolerances for rotational crop commodities are not required. There are currently no U.S. or international Codex tolerances established for penoxsulam.

Dietary Exposure Analysis

The HIARC did not identify a treatment-related effect in any of the available toxicity studies on penoxsulam that could be considered to have resulted from a single dose of the test material. An acute dietary exposure assessment is not required.

The chronic dietary analysis for penoxsulam was conducted with Lifeline™ Model (Version 2.0) using the tolerance levels and 100 % crop treated (CT) for the requested use on rice. This conservative (Tier 1) analysis indicates that chronic risk from the dietary exposure to penoxsulam from the requested use did not exceed HED's level of concern for the U.S. population or any population subgroup. All exposures were determined to be <1% cPAD for the U.S. population and all sub populations of interest.

Penoxsulam is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." A human cancer dietary risk assessment is not required.

Drinking Water Exposure Estimates

Environmental fate studies indicated that penoxsulam is expected to be mobile in the environment. Penoxsulam is not expected to be persistent in environmental water/sediment systems typical of the rice paddies where penoxsulam is being proposed for use. The major routes of dissipation for penoxsulam in the environment are aqueous photolysis, anaerobic metabolism, and soil photolysis. The degradates which are to be included in the risk assessment are BSTCA, 2-amino TCA, 5-OH-XDE-638, SFA, sulfonamide, and 5,8-diOH. EFED determined Tier 1 Estimated Drinking Water Concentrations (EDWCs) for ground and surface water. Applying the method outlined in the current EFED interim policy, the estimated environmental concentrations (EECs) and EDWCs resulting from the use of pesticides on rice crops produced an upper bound screening estimation of 45 ppb (ug/L) in paddy waters. The EECs calculated in accordance with the EFED interim policy should be used for both acute and chronic EECs, as well as for both aquatic ecological risk assessments and for EDWCs in human health risk assessments. Modeling ground water concentrations using the standard Tier 1 model, SCI-GROW, estimated combined residue EDWCs of 5.86 ppb (ug/L).

Aggregate Exposure Scenarios and Risk Conclusions

Acute Aggregate Risk (Food + Water)

The HIARC did not identify a treatment-related effect 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. An acute risk assessment is not required.

Short- and Intermediate- Term Aggregate Risk (Residential + Food + Water)

There are no established or proposed residential uses for penoxsulam; therefore, no short- or intermediate-term risk assessment is required.

Chronic Aggregate Risk (Food + Water + Residential)

The chronic aggregate risk assessment will take into account only food and drinking water since there are no residential uses of penoxsulam. The Tier 1 chronic dietary exposure estimates are below HED's level of concern for the general U.S. population and all population subgroups with all exposure estimates below 1% cPAD, as reported by Lifeline. The calculated chronic DWLOCs for chronic exposure to penoxsulam in drinking water range from 1500 to 5100 µg/L. EECs generated by EFED (surface water: 45 ug/L and groundwater: 5.86 ug/L) are less than HED's calculated chronic DWLOCs. Therefore, the chronic aggregate risk associated with the proposed use of penoxsulam does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Cancer

Penoxsulam is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." A human cancer risk assessment is not required.

Occupational Exposure Estimates

Occupational Handler Exposure

All estimated MOE's are > 100 (HED's level of concern) except for intermediate-term exposures to mixer/loaders not using gloves with liquid, open-pour loading in support of aerial operations. Loaders using liquid open-pour in support of aerial operations (and who may experience intermediate-term exposures) should wear protective gloves. Generally speaking, HED advises the use of protective gloves for mixer/loaders.

Postapplication Exposure

The HED HIARC did not identify a short-term (1 - 30 days) dermal toxicological endpoint. HED expects post-application inhalation exposure to be negligible. Therefore, post-application exposures of agricultural workers were not quantified. There is a 12 hour restricted entry

interval. Based on the category IV acute toxicity of penoxsulam, this REI is consistent with the Worker Protection Standard.

Recommendations:

Regulatory Recommendations and Deficiencies

HED concludes that there is a reasonable certainty that no harm will result to the U.S. Population including infants and children from acute, short- and intermediate- term, and chronic aggregate exposure to penoxsulam residues. Contingent on the submission of a revised Section F and revised tolerance enforcement method (see Section 8.2), HED has no objection to the establishment of permanent tolerances for the residues of penoxsulam, expressed as parent, in or on the following:

Rice, Grain . . . . . 0.02 ppm
Rice, Straw . . . . . 0.50 ppm

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Penoxsulam herbicide [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] is member of the sulfonamide pesticides. Sulfonamide pesticides control plant growth through the inhibition of animo acid synthesis.

Table 1. Penoxsulam Nomenclature.

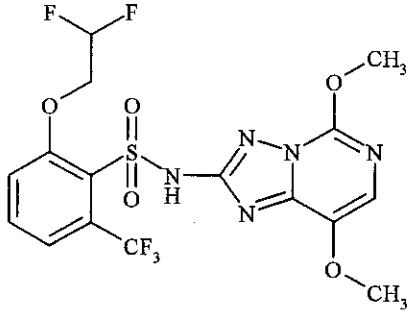
Chemical structure	
Common name	Penoxsulam
Company experimental name	XDE-638
IUPAC name	6-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide
CAS name	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide
CAS #	219714-96-2
End-use formulations (EUP)	GF-443 SC SF (File Symbol 62719-LNN) GF-947 Granule SF (File Symbol 62719-LNG) GF-947 Granule CA (File Symbol 62719-LNR)

Table 2. Physicochemical Properties of Penoxsulam.		
Parameter	Value	
Melting point/range	Not available	
pH	Not available	
Density	Not available	
Water solubility	pH	Solubility (mg/L)
	(unbuffered)	4.91
	5	5.66
	7	408
	9	1460
Solvent solubility	Solvent	Solubility (g/L)
	DMSO	78.4
	NMP	40.3
	DMF	39.8
	acetone	20.3
	acetonitrile	15.3
	ethyl acetate	3.23
	methanol	1.48
	octanol	0.035
	xylene	0.017
	heptane	<1 µg/mL
Vapor pressure	7.16×10^{-16} mm Hg at 25 C	
Dissociation constant, pK_a	5.1	
Octanol/water partition coefficient, $Log(K_{OW})$	pH	$Log(K_{OW})$
	(unbuffered)	-0.354
	5	1.137
	7	-0.602
	9	-1.418

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Table 3. Acute Toxicity Profile Penoxsulam (XDE-638) Technical				
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	45830818	LD 50 > 2 mg/L	IV
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

Table 4. Toxicology Study Summary

STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
2-YR FEEDING/CARCINOGENIC, RAT (2002) MRID 45830901, 45830913 M: 0, 5, 50, 250 m/k/d F: 0, 5, 50, 250 m/k/d Chronic toxicity-Acceptable/Guideline Carcinogenicity---Acceptable/Guideline	M: 50 F: 50 <u>Carcinogenicity</u>	M: 250 In M based on ↓BW/BWG, ↓RBC parameters, ↑BUN, ↑urine vol, ↓urine S.G., ↑kidney wt, ↑crystals/calculi in kidney and urinary bladder, hyperplasia of kidney pelvis epithelium and urinary bladder mucosa, ↑severity of chronic glomerulonephropathy. F: 250 In F based on ↓BW/BWG, ↑urine vol, ↑crystals/calculi in urinary bladder, hyperplasia of kidney pelvis epithelium and urinary bladder mucosa. M: <u>Possibly treatment-related ↑ incidence of Large Granular Lymphocyte (LGL) leukemia at 5, 50 & 250 m/k/d. Also ↑ severity at 250 m/k/d.</u> Dosing was adequate. F: Negative for carcinogenicity, but dosing was only marginally adequate.

Table 4. Toxicology Study S ımmary

STUDY TYPE - DOSE l EVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
18-MN CARCINOGENIC, MOUSE (2002) MRID 45830915 M: 0, 10, 100, 375 m/k/d F: 0, 10, 100, 750 m/k/d Carcinogenicity—**UNACCEPTABL** / Guideline	M: 375 (HDT) F: 750 (750) <u>Carcino-genicity</u>	M: Not determined >375 (HDT) F: Not determined >750 (HDT) M: Negative for carcinogenicity at the doses tested. **<u>Dosing inadequate</u>**. F: Negative for carcinogenicity at the doses tested. Dosing adequate (750 mg/kg/day is sufficiently close to limit dose of 1000 mg/kg/day).
1-YR FEEDING, DOG (2002) MRID 45830914 0, 0.015, 0.045, 0.15 % in diet M:0, 5.3, 14.7, 46.2 m/k/d F:0, 4.4, 14.0, 44.8 m/k/d Acceptable/Guideline	M: 14.7 F: 44.8 (HDT)	M: 46.2 In M based on slight multifocal hyperplasia in the kidney epithelium. F: Not determined >44.8 (HDT)
2-GEN REPRODUCTION, CD RAT (<u>Sprague-Dawley derived</u>) (2002) MRID 45830920 M: 0, 30, 100, 300 m/k/d F: 0, 30, 100, 300 m/k/d Acceptable/Guideline DER also includes results for a 13-we :k range-finding study in CD rats (MRID 45830907).	<u>Parental</u> M: 100 F: 30 <u>Repro/ offspring</u> 30	<u>Parental</u> M: 300 Based on ↓BW of F_1 males. F: 100 Based on kidney lesions. <u>Repro/offspring</u> 100 Based on delayed preputial separation.

Table 4. Toxicology Study Summary

STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
DEVELOPMENTAL TOX, CD RAT (Sprague-Dawley derived) (2000) MRID 45830917 F: 0, 100, 500, 1000 m/k/d On GD 6-20 Acceptable/Guideline DER also includes results for a range-finding study in CD rats (MRID 45830916).	Mat Tox: 500 Dev Tox: 1000 (HDT)	Mat Tox: 1000 Based on ↓BWG, ↓food consumption, ↑kidney weights Dev Tox: Not identified >1000 (HDT)
DEVELOPMENTAL TOX, RABBIT (2001) MRID 45830918 F: 0, 5, 25, 75 m/k/d On GD 7-27 Acceptable/Guideline DER also includes results for a range-finding study in rabbits (MRID 45830919).	Mat Tox: 25 Dev Tox: 75	Mat Tox: 75 Based on death, clinical signs, ↓BWG, ↓food consumption. Dev Tox: Not identified >75 (HDT)
13-WEEK FEEDING, RAT (2000) MRID 45830906 M: 0, 5, 50, 250, 500 m/k/d F: 0, 5, 50, 250, 500 m/k/d With a 4-week recovery phase (0 and 500 m/k/d) Acceptable/Guideline DER also includes results for a 4-week range-finding study in rats (MRID 45830903).	M: 50 F: 250	M: 250 In M based on ↓BW/BWG, ↓food consumption, ↓RBC parameters. F: 500 In F based on ↑mineralization and hyperplasia of the kidney pelvic epithelium.

Table 4. Toxicology Study S ımmary

STUDY TYPE - DOSE I EVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
13-WEEK FEEDING, DOG (20(3) MRID 45830909 0, 0.015, 0.045, 0.15 % in diet M: 0, 5.9, 17.8, 49.4 m/k/d F: 0, 5.7, 19.9, 57.1 m/k/d Acceptable/Guideline DER also includes results for a 4-wee : range-finding study in dogs (MRID 45830908).	M: 17.8 F: 19.9	M: 49.4 In M based on histopathologic changes in kidney. F: 57.1 In F based on histopathologic changes in kidney.
13-WEEK FEEDING, MOUSE (2)01) MRID 45830905 M: 0, 10.2, 102, 511, 1027 m/k/d F: 0, 10.4, 104, 524, 1029 m/k/d Acceptable/Guideline DER also includes results for a 4-wee : range-finding study in mice (MRID 45830904).	M: 1027 (HDT) F: 1029 (HDT)	M: Not determined >1027 (HDT) F: Not determined >1029 (HDT)
4-WEEK RANGE-FINDING, RAT (998) MRID 45830903 M: 0, 10, 100, 500, 1000 m/k/d F: 0, 10, 100, 500, 1000 m/k/d Acceptable/Non-Guideline (as a rang -finding study) Review is in DER for 90-day rat feedi ıg study.	M: 100 F: 100	M: 500 In M based on ↓BW/BWG,↓food consumption, ↓RBC parameters. F: 500 In F based on ↓BW/BWG,↓food consumption, ↓RBC parameters, ↑Kidney weights, ↑crystals in kidney pelvis, ↑hyperplasia and inflammation of kidney pelvic epithelium.
4-WEEK RANGE-FINDING, DOG (1998) MRID 45830908 0, 0.09, 0.45, 0.9 % in diet M: 0, 29, 133, 192 m/k/d F: 0, 32, 163, 196 m/k/d Acceptable/Non-Guideline (as a rang -finding study) Review is in DER for 90-day dog fee ing study.	M: 29 F: <32 (LDT)	M: 133 In M based on ↑liver weights; ↑ALT, ALK, AST; histo-pathologic changes in liver and kidneys. F: 32 In F based on histopathologic changes in kidneys. At 163 m/k/d, treatment-related effects very similar to those in males.

Table 4. Toxicology Study Summary

STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
4-WEEK RANGE-FINDING, MICE (1998) MRID 45830904 M: 0, 10.5, 103, 530, 1018 m/k/d F: 0, 10.8, 110, 545, 1069 m/k/d Acceptable/Non-Guideline (as a range-finding study) Review is in DER for 90-day mouse feeding study.	M: 1018 (HDT) F: 1069 (HDT)	M: Not determined >1018 (HDT) F: Not determined >1069 (HDT)
ACUTE NEUROTOXICITY, RAT (2000) MRID 45830902 M: 0, 500, 1000, 2000 mg/kg F: 0, 500, 1000, 2000 mg/kg Acceptable/Guideline	M: 2000 (HDT) F: 2000 (HDT)	M: Not determined >2000 (HDT) F: Not determined >2000 (HDT)
CHRONIC NEUROTOXICITY, RAT (2002) MRID 45830912, 45830901 M: 0, 5, 50, 250 m/k/d F: 0, 5, 50, 250 m/k/d Acceptable/Guideline	M: 250 (HDT) F: 250 (HDT)	M: Not determined >250 (HDT) F: Not determined >250 (HDT)
28-DAY DERMAL TOXICITY, RAT (2000) MRID 45830910 M: 0, 100, 500, 1000 m/k/d F: 0, 100, 500, 1000 m/k/d With a 2-week recovery phase (0 and 1000 m/k/d) Acceptable/Guideline	Systemic: M: 1000 F: 1000 Dermal: M: 1000 F: 1000	Systemic: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) Dermal: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT)

Table 4. Toxicology Study S ımmary

STUDY TYPE - DOSE I EVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
28-DAY DERMAL TOXICITY, RA' (2002) MRID 45830911 **TEST MATERIAL: GF-443 (form ılated product containing 21.9% penoxsulam)** M: 0, 100, 500, 1000 m/k/d F: 0, 100, 500, 1000 m/k/d Dose levels are in mg/kg/day of GF-4 3, and not in mg/kg/day of penoxsulam. Acceptable/Guideline	Systemic: M: 1000 F: 1000 Dermal: M: 500 F: 1000	Systemic: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) Dermal: M: 1000 Based on very slight hyperplasia at test site F: Not determined >1000 (HDT)
GENERAL METABOLISM, RAT (002) MRID 45830927 5.0 mg/kg (Single low oral dose) 250 mg/kg (Single high oral dose) Also 14 daily oral doses of 5.0 mg/kg lay followed by 5.0 mg/kg orally on day 15. Biliary elimination was examined in a ldditional rats following a single oral dose of 5.0 mg kg. Acceptable/Guideline	At the low dose of 5.0 mg/kg, penoxsulam was rapidly and nearly completely [81-88% of administered dose (AD)]absorbed, 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 AD 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 AD. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.	
MUTA-REVERSE GENE MUTATI)N (1999) (*S. typhimurium /E. coli*) MRID 45830921 Acceptable/Guideline	Negative without and with rat S-9 activation.	

Table 4. Toxicology Study Summary

STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
MUTA-REVERSE GENE MUTATION (2002) (*S. typhimurium /E. coli*) MRID 45830922 **TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)** Acceptable/Guideline	Negative without and with rat S-9 activation.	
MUTA-FORWARD GENE MUTATION (1999) (CHO Cells/HGPRT locus) MRID 45830923 Acceptable/Guideline	Negative without and with rat S-9 activation.	
MUTA-*in vitro* MAMMALIAN CYTOGENETICS (Chromosomal aberrations in primary rat lymphocytes) (1999) MRID 45830924 Acceptable/Guideline	Negative without and with rat S-9 activation.	
MUTA-*in vivo* MICRONUCLEUS,MICE (1999) (Bone marrow cells) MRID 45830925 Acceptable/Guideline	Negative at oral doses (once per day on two consecutive days) of up to 2000 mg/kg.	
MUTA-*in vivo* MICRONUCLEUS,MICE (2002) (Bone marrow cells) MRID 45830926 **TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)** Acceptable/Guideline	Negative at oral doses (once per day on two consecutive days) of up to 2000 mg/kg.	

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). Based on an acute inhalation toxicity study in rats,

inhalation toxicity is also Catego y 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 meth(d), it was negative for dermal sensitization.

In subchronic and chroni : feeding studies in rats and dogs, the most sensitive target organ was the urothelium of the urinar system. Due to limited solubility in urine, penoxsulam (and/or its metabolites) formed crystals/(alculi, which were regularly observed in the pelvis of the kidney and the lumen of the urinary bla(der. These crystals/calculi apparently irritated the urothelium in these organs and following repe: ted dosing lead to numerous secondary effects which resulted in significant damage to the urinar system. In various studies, these secondary effects were manifested as altered clinical che nistry parameters (increased blood urea nitrogen), altered urinalyses parameters (increased urine volume, decreased urine specific gravity), increased absolute and relative kidney wei hts, gross pathological findings in the kidneys (calculi and roughened surface), and a variet of histopathological findings in the kidney and urinary bladder, particularly hyperplasia, inflamm ıtion and mineralization in the pelvic epithelium of the kidney and hyperplasia in the mucosa o the urinary bladder. Renal tubular degeneration was also sometimes observed. Although treatment-related increased severity of chronic progressive glomerulonephropathy was obse ved in male rats, kidney damage observed in shorter-term studies was generally not exacer ated in longer-term studies. At similar and/or somewhat higher dose levels, mildly decreased bo y weight/body weight gain, often accompanied by decreased food consumption, were often o served in feeding studies in rats and dogs. In addition, in male rats, slightly decreased erythroc te parameters (erythrocyte count, hemoglobin and hematocrit) were occasionally observed.

In subchronic and chroni : feeding studies in mice, no effects of toxicological significance were observed in the 4-week, 1 -week or 18-month feeding studies. In these studies, the only treatment-related effects observ d at the dose levels tested were increased liver weights, increased hepatocellular hypertr phy, and related observations indicating stimulation of the liver microsomal enzyme system. Th se effects were considered to be an adaptive response to administration of the test materi l and not toxicologically significant adverse effects.

In a developmental toxic ty study in rats, decreased body weight gain, decreased food consumption and increased kidn y weights were observed in the dams. No developmental toxicity was observed. There w s no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, ir this study. In a developmental toxicity study in rabbits, decreased body weight gain, dec eased food consumption and clinical signs of toxicity (decreased/absent feces, or muc id, soft, or abnormally colored feces) were observed in dams at the highest dose tested. One hig a dose doe died late in the study after exhibiting signs of clinical toxicity for several days. No de elopmental toxicity was observed. There was no increased quantitative or qualitative susce tibility of fetuses, as compared to dams, in this study. In a 2-generation reproduction study ir rats, microscopic lesions in the kidney were observed in the parental females at the mid and l igh 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 a ttained for the control, low, mid, and high dose groups was 43.6, 44.0, 45.5, and 46.0 days, respe tively. 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 LGL leukemia (also known as mononuclear cell leukemia or MCNL) 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). Penoxsulam was classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" and, therefore, quantification of human cancer risk is not required.

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 f ces 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 r dioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although nu merous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the admi istered dose. Parent compound and a 2-hydroxyphenyl derivative were the major compc unds in urine and feces.

3.2 FQPA Considerations

On December 2, 2003, th e HED HIARC evaluated the potential for increased susceptibility of infants and child en from exposure to penoxsulam as required by the Food Quality Protection Act (FQPA) c f 1996 in accordance with the 2002 OPP 10X Guidance Document (HIARC Report, TXI . No. 0052273, 12/16/03, E. Budd). The HIARC concluded that the toxicology database for penc xsulam is complete for FQPA purposes. The HIARC concluded that there is not a concern for ne urotoxicity 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 stu dies in rats, mice or dogs. The HIARC determined that no Special FQPA Safety Factor is n eded (i.e. 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity. The S pecial FQPA Safety Factor recommended by the HIARC assumes that the exposure datab ses (dietary, food, drinking water, and residential) are complete and that the risk assessment for c ach potential exposure scenario includes all metabolites and/or degradates of concern and does ot underestimate the potential risk for infants and children.

In an acute neurotoxicity study, rats were given a single oral dose of penoxsulam and observed for 14 days. There we e no treatment-related effects on mortality, clinical signs, body weight, ophthalmaloscopic findi gs, or gross and histologic pathology or neuropathology. Functional observational battery (FOB) and motor activity testing revealed no treatment-related effects. In a chronic neurotoxici y study, penoxsulam was administered to rats in the diet for one year. Neurobehavioral assessme it (FOB, grip performance, landing foot splay, rectal temperature, and motor activity esting) was performed at prescribed intervals. There was no treatment-related effect on FOB findings, grip performance, landing foot splay, rectal temperature, motor activity or n uropathology. There was no treatment-related effect on mortality or ophthalmoloscopic xamination. There was no toxicologically significant evidence of neurotoxicity observed in this study.

In a developmental toxic ty study, penoxsulam was administered to time-mated female rats daily by gavage. Results inc icated decreased body weight gain by high-dose dams, with no treatment-related effects on post mplantation loss, live litter size, or resorptions per dam. There were no treatment-related effect on survival, clinical signs, or absolute body weights. Maternal toxicity was evident at as decrea ed body weight gain and food consumption and increased absolute and relative (to body) k dney weights. There were no treatment-related increases in fetal deaths/resorptions, and there wa s no evidence of altered growth or an effect on developmental variations. Malformations were observed in the treated and control groups, and there were no significant increases in fetal or li ter incidences of any individual structural abnormalities for any treated group. An apparently ra e external malformation (cutis laxis) was observed in 2 fetuses

in single litters. 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.

In a developmental toxicity study, penoxsulam was administered to rabbits daily by gavage. One high-dose doe died after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity. One high-dose female aborted after exhibiting severely reduced food consumption with decreased to absent defecation and/or black feces 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. High-dose females at times had decreased body weight gains and decreased mean daily food consumption, although cumulative body weight gain during dosing was unaffected due to increased body weight gain later in the study. 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. 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 and percentage of resorbed implantations due to small increases in the mean numbers of resorptions per dam and late resorptions per dam. 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 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.

In a two-generation reproduction toxicity study, penoxsulam was administered to male and female rats. 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. 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 less than those of the controls throughout the study. High-dose F_1 females had significantly lower 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 than that of the control group for the first two weeks of premating. 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 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. There wei e incidences of kidney lesions, hyperplasia, inflammation, and degeneration in control and high dose females. In addition, crystals were observed in the control, low-, mid-, and high-dose group . No differences in mating or fertility indices, precoital interval, or gestation length were seen be ween 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 tre atment-related effects were observed on live birth and viability indices, mean litter sizes, post-in plantation losses, numbers of stillborn pups, and sex ratios. No treatment-related clinical signs o toxicity were observed in the pups during lactation and gross necropsy was unremarkable. At birth, body weight of the high-dose pups was slightly lower than that of the control group. High- lose male and female pups from both generations had significantly lower body weights during lactation compared with the controls. Preputial separation, an indicator of sexua maturation, was significantly delayed in mid- and high-dose F_1 males. In addition, at the mid-d se, 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-d ose was considered to be a treatment-related effect. No other endpoints of reproductive toxici y or offspring growth and survival were affected by treatment.

Based upon the above da a, the HIARC concluded that no Special FQPA Safety Factor is needed (i.e. 1x) since there are n residual uncertainties for pre- and/or post-natal toxicity. The penoxsulam risk assessment tear evaluated the quality of the hazard and exposure data; and, based on these data, recommend d that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

- There was no toxicologi ally significant evidence observed of neurotoxicity in either the acute or chronic neuroto icity study.
- No definitive quantitativ or qualitative susceptibility was observed in either of the developmental rat or rab it studies
- Significant dose-related e ffects in the two-generation reproduction study were limited to the delay in preputial sep ration. No other endpoints of reproductive toxicity or offspring growth and survival wer affected by treatment.
- The *chronic* dietary food exposure assessment utilizes proposed tolerance level residues and 100% CT informatic n for all commodities. By using these conservative assessments, actual and chronic expos ures/risks will not be underestimated.
- The dietary drinking wat r assessment (Tier 1 estimates) utilizes values generated by model and associated mc deling parameters which are designed to provide conservative, health protective, high-e d estimates of water concentrations.

3.3 Dose-Response Assessment

Discussion of Toxicological Endpoints:

3.3.1. Acute Dietary Endpoints

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.

3.3.2. Chronic Dietary Endpoints

In a chronic toxicity study, penoxsulam was administered to male and female dogs in the diet 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. The only effect of toxicological significance was the occurrence of very slight, multifocal hyperplasia of the pelvic epithelium in both kidneys of one male. Similar lesions were seen in male and female dogs in 4- and 13-week dietary studies. 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 than in the one-year study at the same dietary level. 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. The 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, was chosen for chronic dietary risk assessment. The Uncertainty Factor (UF) is 100, based on 10x for interspecies extrapolation and 10x for intraspecies variation. The Chronic RfD is 0.147 mg/kg/day (14.7 mg/kg/day (NOAEL)/100 (UF)). This RfD is protective of the effects observed in the 2-generation reproductive study (NOAEL = 30 mg/kg/day).

3.3.3. Incidental Oral Exposure - Short-Term (1 - 30 days) and Intermediate-Term (1 - 6 months)

In a 90-day oral toxicity study penoxsulam was administered to male and female dogs in the diet 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 was considered a treatment-related effect; however, this effect did not have correlative changes in

clinical pathology or histopathol gy. Treatment-related histopathologic changes in kidneys of males and females consisted of v ry slight, multifocal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting du cts. The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/da , based on histopathologic changes in the kidneys. The NOAEL was 17.8 and 19.9 mg/kg/day fo males and females, respectively. The NOAEL of 17.8 mg/kg/day, based on histopathol gic changes in the kidneys at the LOAEL of 49.4 mg/kg/day, was chosen to assess incidental c ral exposure.

3.3.4. Dermal Absorption Facto (50% - upper bound estimate)

A dermal absorption stuc y is not available. The percent dermal absorption was estimated by comparing the LOAEL for m le and female rats from a 4-week dermal study to the LOAEL for male and female rats from a -week feeding study. The LOAEL for male and female rats from the 4-week dermal study w is >1000 mg/kg/day, based on the lack of any treatment-related effects at 1000 mg/kg/day (the h ghest dose tested, limit dose). The LOAEL for male rats from the 4-week feeding study was 5( ) mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food con umption, and decreased RBC parameters. The NOAEL for male rats was 100 mg/kg/day. T ie LOAEL for female rats from the 4-week feeding study was 500 mg/kg/day, based on decrea ed body weight, decreased body weight gain, decreased food consumption, decreased RBC pa ameters, increased kidney weights, and histopathological changes in the kidney. The NO EL for female rats was 100 mg/kg/day.

LOAEL from 4-week fe ding study = 500 mg/kg/day x 100 = 50% (upper
LOAEL from 4-week de rmal study = >1000 mg/kg/day bound estimate)

3.3.5. Dermal Exposure - Short Term (1 - 30 days) Exposure

Quantification of dermal isk is not required for this exposure scenario due to the lack of dermal, systemic, neuro, or deve opmental toxicity concerns. No dermal or systemic toxicity was seen at the limit dose in the dern al study. In the 4-week oral study, systemic toxicity was seen at a relatively high dose (500 mg/k /day; one-half of the limit dose).

3.3.6. Dermal Exposure - Interr iediate-Term (1 - 6 Months) Exposure

See Incidental Oral Expo sure: Short-Term (1 - 30 days). The NOAEL of 17.8 mg/kg/day is based on histopathologic chan ges in the kidneys at the LOAEL of 49.4 mg/kg/day.

3.3.7. Dermal Exposure - Long Term (> 6 Months) Exposure

See Chronic Reference I ose (cRfD). The NOAEL of 14.7 mg/kg/day is based on multifocal hyperplasia of the pel ic epithelium of the kidney in males at the LOAEL of 46.2 mg/kg/day.

3.3.8. Inhalation Exposure - Short-Term (1 - 30 days)

See Incidental Oral Exposure: Short-Term (1 - 30 days). The NOAEL of 17.8 mg/kg/day is based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

3.3.9. Inhalation Exposure - Intermediate-Term (1 - 6 Months) Exposure

See Incidental Oral Exposure: Short-Term (1 - 30 days). The NOAEL of 17.8 mg/kg/day is based on histopathological changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

3.3.10. Inhalation Exposure - Long-Term (> 6 Months) Exposure

See Chronic Reference Dose (cRfD). The NOAEL of 14.7 mg/kg/day is based on multifocal hyperplasia of the pelvic epithelium of the kidney in males at the LOAEL of 46.2 mg/kg/day.

3.3.11. Margins of Exposure

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

Table 5. 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).

3.3.12. Recommendation for A; gregate Exposure Risk Assessments

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

Common toxicological e fects (histopathologic changes in the kidneys in the same 90-day feeding study in dogs) were sele :ted for assessment of short-term exposures by oral and inhalation (oral equivalent) route s. The aggregate risk assessment for this exposure duration should include oral and inhalatio ı exposures appropriate to the populations of concern. Short-term dermal exposure need not l e aggregated because no toxicological endpoint was selected.

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

Common toxicological e fects (multifocal hyperplasia of the pelvic epithelium of the kidney in the same 1-year chron : feeding study in dogs) were selected for assessment of long-term oral, dermal (oral equivaler t) and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure dur ation should include oral, dermal and inhalation exposures appropriate to the populations o concern.

3.3.13. Combined Chronic Toxi ity/Carcinogenicity Study

3.3.13.a. Rats

In a combined chronic tc xicity/carcinogenicity study, penoxsulam was administered to rats in the diet for two years. Ar additional set of rats were treated at the same dosages and necropsied after one year of trea :ment. Another set of rats were treated at the same dosages and examined for neurological effect ; as part of a chronic (one-year) neurotoxicity study. There was no treatment-related increase in nortality. An increase in perineal urine soiling, particularly in females, while treatment-related was not considered to be a toxicologically significant adverse effect. Statistically significant d creases in body weight and body weight gain in males and females although of relatively sn all magnitude, were considered to be toxicologically significant. Slight but statistically significant decreases in RBC parameters (RBC counts, HGB and HCT) in males were also considered to b toxicologically significant. There were no ophthalmoscopic effects due to treatment. Blood urea nitrogen (BUN) was significantly increased at 18 and 24 months in males. Urine volume vas increased in males and females throughout the study. Specific gravity was decreased i ı treated males with statistical significance achieved at 12, 18 and 24 months The urinary syst :m effects were not considered toxicologically significant in males or females at the lowest d ıses 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 males and females as compared to male and female control rats. Some female rats also had perineal soiling. Male rats at had increased absolute and relative kidney weights 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; enlarged spleen (with probable lymphoid tumor) in all treated males; and urinary bladder calculi in males and females. Terminal body weight was significantly decreased in males. There was a statistically significant increase (in the absolute and relative kidney weights of males. Microscopic examination of the kidney showed an increase in the severity of CPGN at all dose levels in males; the increase in severity was not dose related and therefore was considered an incidental finding. The incidence of crystals in the renal pelvis was significantly increased in males. The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats 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; 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: 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 and the severity of malignant LGL leukemia (or mononuclear cell leukemia (MNCL)) 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 and range for 8 studies, but did not exceed the National Toxicology Program (NTP) historical control mean and range. **The study demonstrated that XDE-638 may produce an increase in the incidence and severity of LGL/MNC 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.

3.3.13.b. Mice

In a carcinogenicity stuc y penoxsulam was administered to groups of mice in the diet for 18 months. There were no treat nent-related effects on mortality, clinical signs, body weight, body weight gain, food consum tion, ophthalmologic examinations, hematology, or gross pathology. Treatment-related el ects were limited to the liver. Absolute and relative liver weights were increased by in ma es. Absolute and relative liver weights were marginally increased in females. Microscop ically, changes in the liver included hepatocellular hypertrophy in males and in females. The he atocellular hypertrophy in males and females was associated with increased eosinophilic stain ng properties, and along with the increased liver weights was considered to be an adaptive cha ge resulting from induction of the liver microsomal enzyme system by the test material. Thi change was not considered to be an adverse effect.

The affected hepatocytes in male mice were said to contain clear cytoplasmic vacuoles, but there was no quantitative de cription 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 ad lition, very slight to slight dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in males. Because of the severity of this lesion (very slight/slight) and its ow frequency, it also is not considered to be of toxicological significance.

The NOAEL for the mal and female mice in this study is considered to be the highest dose tested viz. 375 mg/kg/day or males and 750 mg/kg/day for females. A LOAEL was not observed in this study for the m le or female mice (>375 mg/kg/day for males and >750 mg/kg/day for females). XDE-6 38 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 mal s or females. **However, in males, the highest dose tested (375 mg/kg/day) was inadequate fo carcinogenicity testing because no adverse effect was observed at this dose.** In fema es, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity tes ing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional su port for this conclusion 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 or in females. All treatment-related effects observed in the 90-day subchro ic study were essentially the same liver effects as in the 18-month carcinogenicity study anc were considered to be adaptive rather than adverse effects. This study is classified as **Unaccepta le/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.

3.3.13.c. Classification f Carcinogenic Potential

The Cancer Assessment Review Committee met on February 18, 2004 to evaluate the carcinogenic potential of Penox ulam. The weight-of-the-evidence for this classification is as follows:

i) Evidence of carcinogenicity (LGL/MNC leukemia or LGLL/MNCL) was seen in one sex (males) of one species (rat).

ii) There was an increased incidence of LGLL/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 LGLL/MNCL is recognized as a common neoplasm in Fischer rats, the mechanism of producing this leukemia is not completely understood. Therefore, the significance of LGLL/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 LGLL/MNCL.

Note: **Although dosing in the male mice was not considered to be adequate, the CARC concluded that an additional mouse carcinogenicity study was <u>not</u> 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.

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 quantification of human cancer risk is not recommended.

3.3.14. 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.

Table 6. Summary of Toxico ogical Doses and Endpoints for Penoxsulam			
Exposure Scenario	Dose Use l in Risk Assess nent, 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.: 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.: 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 NO \EL= 17.8 mg/kg/d: y (dermal absor tion 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 NO \EL= 14.7 mg/kg/da (dermal absor tion 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.
Inhalation Short-Term (1 - 30 days)	Oral study NO \EL= 17.8 mg/kg/d: y (inhalation absorption rat: = 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.

Table 6. Summary of Toxicological Doses and Endpoints for Penoxsulam			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
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)	"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"		

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.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, penoxsulam may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMEN T

4.1 Summary of Registered Us :s

Dow AgroSciences LLC has proposed, in PP#3F6542, the establishment of permanent tolerances for residues of the her)icide penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c])yrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] in/on rice commodities. Penoxsulam i a member of the triazolopyrimidine sulfonamide pesticide class. Its mode of action in susc)ptible weeds is by inhibition of acetolactate synthase (ALS), an enzyme required for the biosynth esis of certain amino acids necessary for plant growth. Penoxsulam is intended for the c)ntrol of *Echinochloa* grasses, broadleaf weeds, and sedge weeds in both water-injected (tra nsplanted paddy) and postemergence (direct-seeded) rice. This is the first petition for the use of)enoxsulam. No residential uses are requested at present.

Table 7. Summary of Penoxs lam End-Use Products

Trade Name	File Symbol No.	ai (% o formulati n)	Formulation Type	Target Crops	Target Pests	Label Version
GF-947 Granule SF	62719-LNG	0.24%	G	Water-seeded rice	Grass, broadleaf and sedge weeds (selective control)	Draft, dated 11/18/02
GF-947 Granule CA	62719-LNR	0.24%	G	Water-seeded rice		Draft, dated 11/18/02
GF-443 SC SF	62719-LNN	21.7% 2 lb ai/g l	suspension concentrate	Water- and dry-seeded rice		Draft, dated 11/18/02

Table 8. Summary of Directi ns for Use of Penoxsulam

Trade Name	Applic. Timing, Type, and Equip.	A pplic. Rate (ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Rice						
GF-947 Granule SF	Postemergence (1-leaf stage up to 60 days prior to harvest) Broadcast Ground or aerial equipment	.031-.044	1	0.044	60	Restricted to use in AR, FL, LA, MS, MO, TN, and TX. Apply to shallow flooded water-seeded rice; field water depth at application (and for 10 days following application) should be 2-4 inches.
GF-947 Granule CA	Postemergence (1- to 3-leaf stage) Broadcast Ground or aerial equipment	.036-.044	1	0.044	60	Restricted to use in CA. Apply to shallow flooded water-seeded rice; field water depth at application (and for 10 days following application) should be 2-4 inches.

Table 8. Summary of Directions for Use of Penoxsulam

Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
GF-443 SC SF	Postemergence (1-leaf stage up to 60 days prior to harvest) Broadcast Ground or aerial equipment	0.027-0.044	1	0.044 (first and ratoon crops combined)	60	Restricted to use in AR, FL, LA, MS, MO, TN, and TX. For water-seeded rice, fields must be partially drained prior to application. For dry-seeded rice, use is recommended as a preflood application. Postflood applications to dry-seeded rice may be made to partially drained fields (1-2 inches water depth). Re-flooding of fields should begin 24-48 hours after application. Application must be made with an agriculturally approved crop oil concentrate (1 qt/A) in a minimum of 10 GPA (ground and aerial equipment). Use of organosilicone surfactants is prohibited. May be applied as a tank mix with compatible materials with postemergence uses on rice.

The proposed general use directions (for all end-use product labels) specify a restricted entry interval (REI) of 12 hours and include the following restrictions: 1) treated land may not be rotated to crops other than rice for 3 months following application; 2) fishing or commercial growing of fish, shellfish, or crustaceans, other than crayfish, may not be conducted in treated areas during the year of treatment; 3) application may not be made where runoff or irrigation water may flow directly onto agricultural land other than rice fields; and 4) application may not be made through any type of irrigation system.

The proposed use directions are adequate to allow an assessment of whether the submitted residue data reflect the maximum residues likely to occur in rice.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile (PP#3F6542, D288152, W. Cutchin, 8/9/04)

4.2.1.a. Nature of the Residue

Based on the penoxsulam rice plant metabolism study, HED's Metabolism Assessment Review Committee (MARC) concluded that, for the currently proposed uses, the nature of the residue has been adequately delineated and that parent only is the residue of concern to be used in risk assessment and the tolerance expression for rice (TXR No. 0052740, W. Cutchin, 7/19/04). Metabolism studies conducted on rice with both [triazolopyrimidine-2-^{14}C] and [phenyl-U-^{14}C] labeled penoxsulam indicated that parent and 5-OH XDE-638 are major residues (>10% TRR). However, 5-OH XDE-638 is only found as a major metabolite in minor feed items (rice shoots

34% and rice straw 30%) at lev ls <0.1 ppm, and is considered to be no more toxic than the parent based on the structural sir ilarities between parent and 5-OH XDE-638. Also, based on the livestock metabolism study, r o animal tolerances are needed [180.6 (a)(3)] even if the metabolite were to be included a a residue of concern. Field trials indicated that parent was found in adequate amounts in ric straw and therefore parent can serve as a good indicator of misuse. Any future uses of penc sulam, including those on cereal grains, will require additional nature of the residue data. As ar alternative to metabolism data on other cereal crops, the registrant may submit crop field rial data which include residue data for the metabolite 5-OH XDE-638 as well as parent.

Based on the penoxsulan ruminant metabolism study, HED's MARC concluded that, for the currently proposed uses, the ature of the residue has been adequately delineated and that parent only is the residue of con ern to be used in risk assessment and the tolerance expression for ruminants. The available goa t and poultry metabolism data indicate that penoxsulam is primarily excreted and not signif cantly metabolized in either goats or poultry. The metabolism study of penoxsulam in lactating goat indicated that parent is the major residue. There are no specific toxicity concerns for all netabolites. No poultry tolerance is needed at this point and no decision was made on the residu of concern in poultry.

Based on the penoxsulan confined rotational crop studies, HED's MARC concluded that, for the currently proposed uses, he nature of the residue has been adequately delineated and that parent only is the residue of con ern to be used in risk assessment and the tolerance expression for rotational crops. Confined r tational studies conducted on potatoes with both [triazolopyrimidine-2-^{14}C] and [p henyl-U-^{14}C] labeled penoxsulam indicated that BSTCA and 5-OH XDE-638 are major residue (>10% TRR) in potato foliage. However, only 5-OH XDE-638 is found at >0.01 ppm in potato oliage (at 2x application rate). Considering the fact that the absolute value of 5-OH XDE-63 is less than 0.01 ppm after the correction (to 1x), MARC concluded that parent only is the residue of concern to be included in risk assessment and tolerance expression.

Table 9. Summary of MARC Decisions for Penoxsulam		
Meeting Date: 19-May-2 04		
	Residues of Concern	
Matrix	For Risk Asses ment	For Tolerance Expression
Plants	Parent only	Parent only
Ruminant	Parent only	Parent only
Rotational crops	Parent only	Parent only
Water	parent, BSTCA , 2-amino TCA, 5-OH-XDE-638, SFA , sulfonamide, 5,8-diOH	N/A

4.2.1.b. Residue Method

Residue data on rice commodities were obtained using an LC/MS/MS method, designated GRM 01.25. The registrant has proposed the method for enforcement purposes for residues of penoxsulam in/on rice commodities. Samples of rice matrices are homogenized/extracted with acetonitrile/water, shaken for 60 minutes, and centrifuged. An aliquot of the supernatant is diluted with water and cleaned up on a mixed-mode polymeric-anion exchange solid phase extraction (SPE) plate. Residues are eluted with ACN:formic acid, evaporated to dryness, and redissolved in mobile phase. Residues are quantitated by LC/MS/MS using a C8 column, a gradient mobile phase of ACN/methanol/ acetic acid and water/acetic acid and electrospray ionization in the positive ion mode. Residues are quantified using external standards. The validated limit of quantitation (LOQ) and calculated limit of detection (LOD) for penoxsulam were 0.01 and 0.002 ppm, respectively, in/on rice forage, straw, grain, hulls, bran, and polished rice. Adequate method recoveries were obtained for rice commodities at the LOQ (0.01 ppm) and up to 100x the LOQ.

A successful independent laboratory validation (ILV) of the LC/MS/MS method has been completed with rice grain and straw. However, some changes/clarifications were recommended to the method. Although extraction efficiency data were submitted, penoxsulam residues in the samples examined were too low to allow determination of the ability of the residue analytical method to extract aged residues. However, because the extraction procedures of the method are very similar to those used in the metabolism study, no additional extraction efficiency data will be required. The LC/MS/MS method was submitted to ACB/BEAD for method validation. ACB concluded that the method is adequate for enforcement purposes without the need for an Agency laboratory validation provided some revisions are made in the procedure (C. Stafford, 9/17/04, D303172). See Section 8.2 for the necessary revisions.

4.2.1.c. Multiresidue Methods

The multiresidue method data indicate that penoxsulam is not adequately recovered using any of the multiresidue methods. These data have been forwarded to FDA for further evaluation.

4.2.1.d. Storage Stability

The interim storage stability data indicate that residues of penoxsulam are stable under frozen storage conditions in rice grain, straw, immature forage, bran, hulls, and polished rice for up to 7 months. The petitioner stated that the full study will include storage intervals of up to 24 months for rice commodities. Although the interim data support the storage intervals of samples from the crop field trial and processing studies, the interim study did not include a signed QA statement. Therefore, the study will be considered "interim" data until the full, final report is submitted. Storage stability data for future uses will require the receipt and acceptance of the final rice report as well as any data required for the additional use.

4.2.1.e. Water, Fish, anc Irrigated Crops

Penoxsulam has very low potent al to bioconcentrate in edible tissues of crayfish. Following exposure to 494 ppb penoxsulan in water (>10x the 45 ppb screening level recommended by EFED for the use in rice, L. Sha aman, 7/8/04), total radioactive residues in crayfish tail muscle were 14.4 ppb (0.014 ppm). Afi r 6 hours of depuration, [^{14}C]residues decreased to <2% of the exposure levels and by day 2 we e below the limit of detection. After 5 days of depuration, total [^{14}C]residues were not detected n the crayfish tissue. The available data for crayfish indicate *that tolerances for penoxsulam r sidues in crayfish are not required to support this petition.*

4.2.1.f. Crop Field Trial

The registrant has submi ed 16 field trials for penoxsulam in/on rice forage, straw, and grain following treatment with e her a suspension concentrate or granular (G) formulation. The number and location of field tria s are adequate with respect to geographic representation of residue data for rice. In separat plots at each field trial, a single application of the 2 lb/gal suspension concentrate or 0.11% G formulation was made to rice plants at 0.090 lb ai/A (2x the maximum proposed seasonal rat). Application of the suspension concentrate formulation was made to rice at the 30-32 Biolog sche Bundesanstalt, Bundessortenamt and CHemical (BBCH) growth stage to target a 60-day PHI; the suspension concentrate formulation was applied as a foliar broadcast spray in water w ith crop oil concentrate. Application of the G formulation was made to rice ~40 days after seed ng, when the permanent flood was established (21-23 BBCH); the G formulation was applied d ectly (broadcast) to flooded rice. Samples of mature rice grain and straw were collected from b th plots at each trial site. Residues of penoxsulam were less than the method LOQ (<0.01 pp n) to 0.013 ppm in/on rice grain samples and <0.01-0.484 ppm in/on rice straw samples harvest d 47-97 days following a single application of the suspension concentrate formulation at 0.088-0.093 lb ai/A. Residues of penoxsulam were less than the method LOQ (<0.01 ppm) in/on rice grain and straw samples harvested 64-101 days following a single application of the G formu lation at 0.09 lb ai/A.

Although the use pattern of the crop field trials did not exactly reflect the proposed use pattern (field trials were conduc ed at 2x; samples from the trials with the G formulation were collected at post-treatment inter als longer than the proposed 60-day PHI), no additional crop field trial data will be required at this time because the trials were conducted at an exaggerated rate, low residues were found in rice grain, and residue transfer to animals is expected to be minimal. The petitioner should note that if lower tolerances for rice grain and straw are desired, additional crop field trial data w ich accurately reflect the proposed use pattern would be required.

Table 10. Summary of Residues from the Crop Field Trials with Penoxsulam.							
Crop Matrix	Total Application Rate (lb ai/A); Formulation	PHI (days)	Residues (ppm)				
			Min.	Max.	HAFT	Mean	Std. Dev.
Rice (proposed use = 0.044 lb ai/A total application rate, 60-day PHI)							
Rice, grain	0.088-0.093; suspension concentrate	47-97	ND	0.013	0.013	0.006	0.002
	0.09; G	64-101	ND	ND	<0.01	0.005	0
Rice, straw	0.088-0.093; suspension concentrate	47-97	ND	0.484	0.463	0.066	0.116
	0.09; G	64-101	ND	0.008	<0.01	0.005	0.001

4.2.1.g. Processed Food/Feed

In rice processing studies mature rice grain was harvested following a single broadcast application at 4x the proposed maximum seasonal rate (~0.2 lb ai/A). The suspension concentrate formulation was applied as a broadcast foliar spray to rice at the 32 BBCH growth stage, using water containing a crop oil concentrate. The G formulation was applied directly to flooded rice, 40 days after seeding, when the permanent flood was established. Residues of penoxsulam were nondetectable (<0.002 ppm) in/on rice grain treated with either formulation and residues were nondetectable in hulls, bran, and polished rice processed from treated rice grain. Processing factors could not be determined because the residue levels were nondetectable in both the RAC and processed commodities. The maximum theoretical concentration factor for rice is 8x (OPPTS 860.1520, Table 1), based on concentration factors of 5x for hulls and 7.7x for bran (OPPTS 860.1520, Table 3). The submitted processing study data are adequate to satisfy data requirements. Tolerances are not required for the processed commodities of rice. Although the petitioner did not address the issue of conducting field trials on rice at higher rates, to potentially generate samples containing detectable or quantifiable residues, it was noted in the rice metabolism study that phytotoxic effects were observed in plants treated at the equivalent of 0.13 lb ai/A.

4.2.1.h. Meat, Milk, Poultry, and Eggs

The petitioner did not submit any livestock feeding studies with this petition. The maximum residues of penoxsulam observed in any matrix in the goat metabolism study were 0.047 ppm in kidney from the goat dosed with [PH-^{14}C]penoxsulam. Based on a 220x dosing level for that goat, the expected residues of penoxsulam at a 10x dosing level are 0.002 ppm, which is less than the (plant) method LOQ of 0.01 ppm. The maximum residues of penoxsulam observed in any matrix in the poultry metabolism study were 0.017 ppm in liver from the hens dosed with [TP-^{14}C]penoxsulam. Based on a 1800x dosing level for those hens, the expected residues of penoxsulam at a 10x dosing level are 0.00009 ppm, which is less than the (plant) method LOQ of 0.01 ppm. HED concludes that the proposed use of penoxsulam on rice results in a 40 CFR §180.6(a)(3) situation for ruminant and poultry commodities; i.e., there is no reasonable expectation of finite residues in ruminant and poultry commodities. Therefore, no

ruminant or poultry feeding stud ' need be submitted to support the subject petition. We note that if additional uses of penoxsulam with livestock feed items are proposed in the future, feeding studies may be required.

4.2.2 Acute Dietary

The HIARC did not iden ify a treatment-related effect in any of the available toxicity studies on penoxsulam that coul be considered to have resulted from a single dose of the test material. An acute dietary expo ure assessment is not required.

4.2.3 Chronic Dietary

The chronic dietary analy sis for penoxsulam was conducted using the Lifeline™ Model Version 2.0, which uses food co sumption data from the United States Department of Agriculture's Continuing Survey of Food Intakes by Individuals (CFSII) from 1994-1996 and 1998. The assessment was base on tolerance level residues and 100 %CT for the requested use on rice. This conservative (Tier I) analysis indicates that chronic risk from the dietary exposure to penoxsulam from the requeste d use did not exceed HED's level of concern for the U.S. population or any population sul group. All exposures were determined to be <1% cPAD for the U.S. population and all sub popu lations of interest.

Table 11. Sum nary of Dietary Exposure for Penoxsulam

Population S bgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Popul tion	0.000005	<1
All Infants (< 1 yea old)	0.000014	<1
Children 1-2 years ld	0.000010	<1
Children 3-5 years ld	0.000008	<1
Children 6-12 years old	0.000006	<1
Youth 13-19 years ld	0.000005	<1
Adults 20-49 years old	0.000004	<1
Adults 50+ years ol l	0.000004	<1
Females 13-49 yea s old	0.000005	<1

4.2.4 Cancer Dietary

Penoxsulam is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." The quantification of human cancer risk is not required.

4.3 Water Exposure/Risk Pathway (D298489, L. Shanaman, 7/8/04)

Environmental fate studies indicated that penoxsulam is expected to be mobile in the environment. Penoxsulam is not expected to be persistent in environmental water/sediment systems typical of the rice paddies where penoxsulam is being proposed for use. The major routes of dissipation for penoxsulam in the environment are aqueous photolysis, with half-lives between 1 and 14 days; anaerobic metabolism, with half-lives between 5 and 11 days; and soil photolysis, with half-lives between 19 and 109 days. The degradates which are to be included in the risk assessment are BSTCA, 2-amino TCA, 5-OH-XDE-638, SFA, sulfonamide, and 5,8-diOH.

EFED determined Tier 1 EDWCs for ground and surface water for the postemergence herbicide, penoxsulam, when used on rice crops. Applying the method outlined in the current EFED interim policy for calculating both the Tier I EECs and EDWCs resulting from the use of pesticides on rice crops produced an upper bound screening estimation, using the lowest K_d value (0.13) for a non-sand soil, of 45 ppb (ug/L) in paddy waters. The estimated EEC calculated in accordance with the EFED interim policy should be used for both acute and chronic EECs, as well as for both aquatic ecological risk assessments and for EDWCs in human health risk assessments. Modeling ground water concentrations using the standard Tier 1 model, SCI-GROW, estimated combined residue EDWCs of 5.86 ppb (ug/L). Ground water concentrations were estimated for parent-only EEC of 0.67 ppb (ug/L). However, EFED does not regard ground water contamination from a pesticide applied to rice to be a significant route of dissipation.

Table 12. Estimated Tier 1 Concentrations of Combined Penoxsulam Residues in Drinking Water.

Chemical	Surface Water (ug/L)	Groundwater (ug/L)
	Acute and Chronic	Acute and Chronic
Penoxsulam Residues	45	5.86

4.4 Residential Exposure/Risk Pathway

There are currently no es ablished or proposed residential uses for penoxsulam; therefore, no residential exposure assessme nt is required.

5.0 AGGREGATE RISK ASS ESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Risk

The HIARC did not iden ify a treatment-related effect observed in any of the available toxicity studies on penoxsulam t hat could be considered to have resulted from a single dose of the test material. An acute risk a ssessment is not required.

5.2 Short- and Intermediate-T erm Risk

There are no established or proposed residential uses for penoxsulam; therefore, no short- or intermediate-term risk assessr ient is required.

5.3 Chronic Risk

5.3.1 Chronic Aggregate Risk Assessment

The chronic aggregate ri k assessment takes into account average exposures estimates from dietary consumption of per oxsulam (food and drinking water) and residential uses. Since there are no residential uses of p noxsulam, the chronic aggregate risk assessment will take into account only food and drinking water. The Tier 1 chronic dietary food exposure estimates are below HED's level of concern fc r the general U.S. population and all population subgroups with all exposure estimates below 1% cPAD, as reported by Lifeline.

For considering exposur to residues of penoxsulam in drinking water, HED has calculated Drinking Water Leve s of Comparison (DWLOCs). These values are the maximum concentration of a chemical that can occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled EECs provided by the EFED. D WLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed HED's level of concern. The calculated chronic DWLOCs for chronic exposure o penoxsulam in drinking water range from 1500 to 5100 µg/L. EECs generated by EFED (surfa ce water: 45 ug/L and groundwater: 5.86 ug/L) are less than HED's calculated chronic DWL OCs. Therefore, the chronic aggregate risk associated with the proposed use of penoxsulam do s not exceed HED's level of concern for the general U.S. population or any population sul groups.

Table 13 Chronic DWLOC Calculations for Penoxsulam.

Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day[a]	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (µg/L)[b]
General U.S. Population	0.147	0.000005	0.146995	5.86	45	5100
All Infants (< 1 year old)	0.147	0.000014	0.146986	5.86	45	1500
Children 1-2 years old	0.147	0.000010	0.146990	5.86	45	1500
Children 3-5 years old	0.147	0.000008	0.146992	5.86	45	1500
Children 6-12 years old	0.147	0.000006	0.146994	5.86	45	1500
Youth 13-19 years old	0.147	0.000005	0.146995	5.86	45	5100
Adults 20-49 years old	0.147	0.000004	0.146996	5.86	45	5100
Females 13-49 years old	0.147	0.000005	0.146995	5.86	45	4400
Adults 50+ years old	0.147	0.000004	0.146996	5.86	45	5100

[a] Maximum water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - food exposure (mg/kg/day)]
[b] DWLOC(µg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)] ÷ [water consumption (L) x 10^{-3} mg/µg]. Consumption = 1 L/day for populations <13 years old and 2 L/day for populations ≥ 13 years old. Default body weights = 70 kg for males ≥ 13 years old and general U.S. population, 60 kg for females ≥ 13 years old, and 10 kg for all others. Values are rounded to 2 significant figures.

5.4 Cancer Risk

Penoxsulam is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential." A human cancer risk assessment is not required.

6.0 Cumulative Risk

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether penoxsulam has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to penoxsulam and any other substances and penoxsulam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that penoxsulam has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 Occupational Exposure ( )301888, M. Dow, 5/4/04)

Dow has requested regis ration of three products, one liquid formulation and two granular formulations, for selective poste iergence weed control in rice. The proposed labels for the liquid and SF granular formulati n indicates that they may be used in Arkansas, Florida, Louisiana, Mississippi, Missouri, Tennessee and Texas. The proposed label for the CA granular formulation indicates that it may only be used in California.

The liquid formulation is known as GF-443 SC SF (EPA File Symbol 62719 - LNN) and is a 21.7 % (2.0 lb active ingredi nt per gallon) liquid. It may be applied one time per year by aerial or ground equipment at a naximum rate of 0.044 lb a.i./A. It may not be applied through any type of irrigation equipment. It may be applied to water seeded rice or dry seeded rice. The application is to be made betwee n the 1 leaf stage of crop growth and 60 days before harvest. The label states: "Use of an agri ulturally approved crop oil concentrate at a rate of 1 quart per acre must be used for all applica ions of GF-443 SC SF." Depending upon cropping practices, the label includes specific water nanagement directions relative to an application of penoxsulam.

The second product is G -947 Granule SF (EPA File Symbol 62719 - LNG) for selective weed control in water-seeded ric e. It is a 0.24 % granular formulation. The proposed product is designated for use at a rate of 18 .5 lb (0.044 lb a.i.) per acre. It may be applied one time per year in ground or aerial equipment. T he application should occur between the 1 leaf stage of rice growth and 60 days prior to har est. For optimum performance, fields should be flooded to a depth of 2 to 4 inches prior to ap plication and water maintained at 2 to 4 inches in depth for 10 days following application.

The third proposed prod ct is GF-947 Granule CA and is intended to be used for selective weed control in water-s eeded rice. The product is a 0.24 % granule and may be applied by air or ground equipment to w ter seeded rice. Penoxsulam should be applied to rice and susceptible weeds from the 1 to leaf stage of growth at a rate of 18.5 lb (0.044 lb a.i.) per acre. This usually occurs 7 - 12 days fter seeding. After application, water should be maintained at 2 - 4 inches of depth. It may not b e applied within 60 days of harvest. It may not be applied through any type of irrigation sy tem.

All three products sugge t a 12 hour restricted entry interval (REI). All proposed labels indicate pesticide handlers must wear long sleeved shirt, long pants and shoes plus socks.

7.1 Occupational Handler

Based upon the propose new use pattern, HED believes the most highly exposed occupational pesticide handlers a re: 1) mixer/loader using open pour loading of granules; 2) mixer/loader using open pour lic uid; 3) applicator using open cab ground boom equipment; and 4) applicator using open cab gra ular broadcast equipment. Aerial applicators (pilots) are not assessed since many data availab e to HED indicate pilots are exposed to a much lesser extent than are applicators using open (ab ground equipment.

HED expects occupational pesticide handler exposure will typically be short-term (1 - 30 days). One application per year is permitted. Since this is a new chemistry and use, it is not likely that even commercial applicators will experience intermediate-term (1 - 6 months) exposures applying this compound to rice.

7.1.1 Handler Exposure and Risk Estimates

Data Sources and Assumptions

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" (that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves) as well as "baseline" plus the use of protective gloves or other Personal Protective Equipment (PPE) as might be necessary. The proposed product labels involved in this assessment direct applicators and other handlers to wear long-sleeved shirt, long pants and shoes and socks.

Although HED does not expect handlers to experience intermediate-term exposures, risks are estimated for short-term inhalation exposures and for intermediate-term combined risks (i.e., dermal plus inhalation exposures).

Table 14. Estimated Handle	Exposure and Risk from the Use of Penoxsulam on Rice				
Unit Exposure[1] mg a.i./lb handled	**Appli . Rate**	**Units Treated[3] Per Day**	**Average Daily Dose[4] mg a.i./kg bw/day**	**NOAEL[5] mg a.i./kg bw/day**	**Short-term Inhalation MOE Intermediate-term Combined MOE[6]**
Mixer/Loader · Granular - Open Pour Supporting Aerial Operations					
Inhal. 0.0017 HC Dermal: No Glove 0.0084 LC With Glove 0.0069 MC	0.044 b a.i./A	1200 A	Inhal 0.00128 Dermal: No Glove 0.003168 W Glove 0.0026	17.8	Short term inhalation 13,906 Intermed. Term No Glove 4001 W Glove 4587
Mixer/Loade · - Liquid - Open Pour Supporting Aerial Operations					
Inhal. 0.0012 HC Dermal: No Glove 2.9 HC With Glove 0.023 HC	0.044 › a.i./A	1200 A	Inhal 0.000905 Dermal: No Glove 1.09 W Glove 0.00867	17.8	Short term inhalation 19,668 Intermed. Term **No Glove 16** W Glove 1859
Applicator - Open Cab - Ground-boom					
Inhal 0.00074 HC Dermal: No Glove 0.014 HC With Glove 0.014 MC	0.044 b a.i./A	200 A	Inhal 0.000093 Dermal: No Glove 0.00088 W Glove 0.00088	17.8	Short term inhalation 191,397 Intermed. Term No Glove 18,293 W Glove 18,293
Applicator - Open Cab - Granule Broadcast					
Inhal 0.0012 LC Dermal: No Glove 0.0099 LC With Glove 0.0069 LC	0.044 b a.i./A	200 A	Inhal 0.000151 Dermal: No Glove 0.000622 W Glove 0.000434	17.8	Short term inhalation 117,880 Intermed. Term No Glove 23,027 W Glove 30,427

1. Unit Exposures are taken from "PHED SURR GATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. D ermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of acti e ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from proposed labels.
3. Units Treated are taken from "Standard Value for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000.
4. Average Daily Dose = Unit Exposure * Applic Rate * Units Treated * % absorption (50 % dermal absorption; 100 % inhalation absorption) ÷ Body Weight (70 kg).
5. No Observed Adverse Effect Level (NOAEL) short-term inhalation NOAEL = 17.8 mg a.i./kg bw/day; intermediate-term (1 - 60 months)

dermal and inhalation NOAEL from 13 week dog feeding study NOAEL 17.8 mg a.i./kg bw/day.
6. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. For intermediate-term risk, dermal exposure and inhalation exposure are summed then divided into the NOAEL.

Exposure and Risk Estimates

A MOE of 100 is adequate to protect occupational pesticide handlers. All estimated MOE's are > 100 except for intermediate-term exposures to mixer/loaders not using gloves with liquid, open-pour loading in support of aerial operations (at either 1200 acres per day or 350 acres per day). Loaders using liquid open-pour in support of aerial operations (and who may experience intermediate-term exposures) should wear protective gloves. Generally speaking, HED advises the use of protective gloves for mixer/loaders. Otherwise, the proposed uses do not exceed HED's level of concern.

7.2 Postapplication Exposure and Risk Estimates

The HED HIARC did not identify a short-term (1 - 30 days) dermal toxicological endpoint. HED expects post-application inhalation exposure to be negligible. Therefore, post-application exposures of agricultural workers were not quantified.

7.3 Restricted Entry Interval

Penoxsulam is classified in acute toxicity category IV for acute dermal toxicity, primary eye irritation, primary skin irritation and it is not a dermal sensitizer. Therefore, the interim Worker Protection Standard (WPS) REI of 12 hours is adequate to protect agricultural workers from post-application exposures to penoxsulam.

8.0 DATA NEEDS

8.1 Toxicology

There is no acceptable inhalation study of any duration available on technical grade penoxsulam. The HIARC recommended that a 28-day inhalation study in rats be required to be submitted to the Agency within a reasonable period of time. However, based on the low volatility and low inhalation toxicity (Category IV) of penoxsulam and large inhalation margins of exposure (MOEs>1000) for the proposed uses in this risk assessment, penoxsulam qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses [HED Standard Operating Procedure (SOP) 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02]. **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

8.2 Residue Chemistry

OPPTS 860.1340 Residue Analy ical Methods

1. The submitted LC/MS/M S method is adequate for tolerance enforcement purposes for plant commodities witho t the need for an Agency laboratory validation, provided the following revisions are in corporated. In step 9.3.9 of the method, there is an instruction to "Dilute" with no ident fication of what should be diluted or what solvent should be used; presumably the wo d "Dilute" is a typo and should be deleted. The independent laboratory validation rep rt noted a discrepancy in Section 10.2.2 regarding the calculation of the concen ration of XDE-638 which needs to be addressed. Finally, ACB/BEAD has recomm ended that the petitioner add information to the method which documents either one ad itional ion transition, or a different chromatographic column/mobile-phase co ibination as a confirmatory option to reduce the possibility of false positive residues. T hese modifications will have to be made to the method prior to its acceptance as a tolera ice enforcement method.

860.1380 Storage Stability

2. The final report of the or going storage stability study must be submitted in support of any future food uses. Storag stability data for future uses will require the receipt and acceptance of the final ri e report as well as any data required for the additional use.

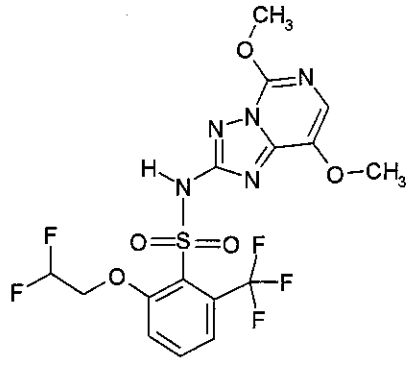
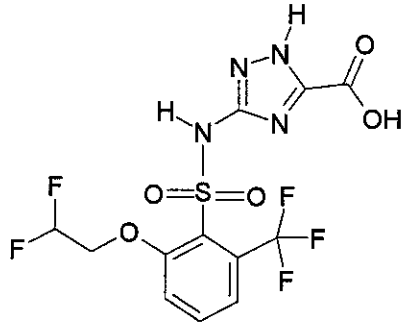
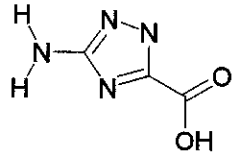
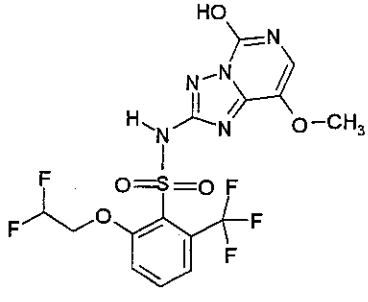
860.1550 Proposed Tolerances

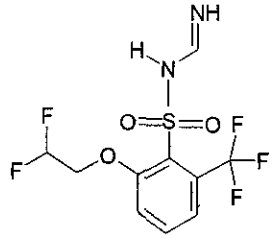
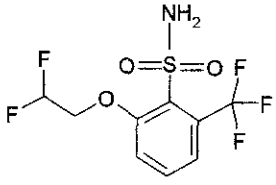
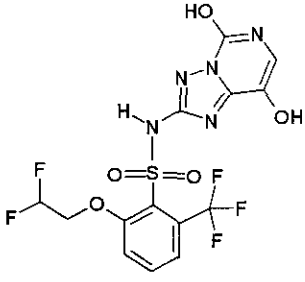
3. The available crop field t ial data for rice grain do not support the proposed tolerance of 0.01 ppm; a tolerance of 0.02 ppm should be proposed for rice grain. The rice processing data indicate that toleran es for rice processed commodities are not needed. In addition, the proposed tolerances hould be revised to reflect the correct commodity definitions as specified. A revised Sec ion F is required.

Attachment: 1. Penoxsulam a id Metabolite Structures

References:
1. HED HIARC Report, TXR No. 0052273, 12/16/03
2. HED Residue Chemistry, PP#3F6542, D288152, W. Cutchin, 9/28/04
3. HED MARC, TXR No. 0052740, W. Cutchin, 7/19/04
4. HED Dietary Exposure, D305545, W. Cutchin, 8/2/2004
5. EFED Water, D298489, L. Shanaman, 7/8/04
6. HED ORE, D 01888, M. Dow, 5/4/04

cc with Attachment: RAB2 reac ng file, PP#3F6542,W. Cutchin

Attachment 1. Penoxsulam and Metabolite Structures.	
Name	**Structure**
Penoxsulam **CAS. No.:** 219714-96-2 **CAS Name:** 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy [1,2,4]triazolo [1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide **IUPAC Name:** 3-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluorotoluene-2-sulfonamide **Synonyms:** XDE-638	
BSTCA **CAS Name:** 3-[[[2-(2,2-difluoroethoxy)-6-(trifluoromethyl)phenyl]-sulfonyl]amino]-1H-1,2,4-triazole-5-carboxylic acid **IUPAC Name:** 3-[6-(2,2-Difluoroethoxy)-α,α,α-(trifluoro-o-toluenesulfonamido]-s-triazole-5-carboxylic acid **Synonyms:**	
2-amino TCA **CAS name:** 2-amino-1,2,4-triazole carboxylic acid **Synonyms:** Polars	
5-OH-XDE-638 **CAS name:** 2-(2,2-difluoroethoxy)-N-(5,6-dihydro-8-methoxy-5-oxo[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide **IUPAC name:** 6-(2,2-Difluoroethoxy)-N-(5,6-dihydro-8-methoxy-5-oxo-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide	

Attachment 1. Penoxsulam and Me tabolite Structures.	
Name	**Structure**
SFA **CAS name:** 2-(2,2-difluoroethoxy)-N -(iminomethyl)-6-(trifluoromethyl)-benzenesulfonamide **IUPAC name:** 2-(2,2-difluoroethoxy) -N-[(E)iminomethyl-6-	
sulfonamide **CAS name:** 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-benzenesulfonamide **IUPAC name:** 2-(2,2-difluoroethoxy -6-(trifluoromethyl)-benzenesulfonamide	
5,8-diOH **CAS name:**2-(2,2-Difluoroethoxy)-6-trifluoromethyl-N-(5,8-dihydroxy-[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)benzenesulfonamide	

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R102878

Chemical:	**Penoxsulam**
PC Code:	**119031**
HED File Code	**12000 Exposure Reviews**
Memo Date:	**09/29/2004**
File ID:	**DPD307079**
Accession Number:	***412-05-2000***

HED Records Reference Center
10/21/2004