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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

**OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361**

DATE: 6/18/07

SUBJECT: Penoxsulam. Human Health Risk Assessment for Proposed Uses on Fish and Shellfish. PC Code: 119031, Petition No: 5F7012, DP Num: 325461.

Regulatory Action: Registration Action
Risk Assessment Type: Single Chemical Aggregate

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The ARIA Team of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that ARIA evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed and registered uses of the pesticide penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] as a result of the proposed aquatic and turf uses. A summary of the findings and an assessment of human risk resulting from the registered and proposed tolerances for penoxsulam is provided in this document. The risk assessment and the dietary risk assessment by W. Cutchin (ARIA), the residue chemistry data review by D. Soderberg (Reregistration Branch 3; RRB3), the occupational/residential exposure assessment by M. Collantes (RAB2), and the drinking water assessment by L. Shanaman (Environmental Fate and Effects Division; EFED).

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1.0 Executive Summary

Penoxsulam (XDE-638) is a sulfonamide herbicide currently registered on rice for the selective control of grasses, broadleaf, and sedge weeds. The use on rice represents the only registered food/feed use of penoxsulam. Dow AgroSciences LLC has now submitted a Section 3 registration application for the end-use product GF-443 SC as an aquatic herbicide.

Concurrently, the petitioner has requested an exemption from the requirement of a tolerance on fish and shellfish when penoxsulam is applied in aquatic areas. In addition, the use of products containing penoxsulam is proposed for turf, including residential turf.

Hazard Assessment

Technical grade penoxsulam (XDE-638) exhibited minimal acute toxicity in the available studies. The acute oral and the acute dermal LD₅₀ in male and female rats was >5000 mg/kg (Toxicity Category IV). Based on an acute inhalation toxicity study in rats, inhalation toxicity is also Category IV. In primary eye and skin irritation studies in rabbits, it produced only minimal irritation (Toxicity Category IV) and in a dermal sensitization study in guinea pigs (maximization method), it was negative for dermal sensitization.

In subchronic and chronic feeding studies in rats and dogs, the most sensitive target organ was the urothelium of the urinary system. 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 feeding 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 F₁ 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.

Penoxsulam was classified by the HED CARC as Suggestive in 2004. The classification was based on an increase in large granular lymphocyte leukemia (also called mononuclear cell leukemia (MNCL)). There were increases at all dose levels in the male Fischer 344 rats, which exceeded the laboratory historical control data. There is considerable controversy about the significance and relevance of the tumors for humans; however, they cannot be discounted in the overall weight of the evidence. There is some cancer concern but the data are judged not sufficient for a stronger conclusion or a quantitative cancer risk assessment; 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, ¹⁴C-penoxsulam was rapidly and nearly completely absorbed at the low dose, but at the high dose, there was evidence that absorption was largely incomplete (i.e. absorption was saturated). Both gender and dose affected the excretion pattern. At the low dose, the major route of excretion of radioactivity was via the feces in males and via the urine in females. At the high dose, radioactivity was predominantly excreted via the feces in both sexes. A significant enterohepatic circulation was observed, particularly in males. Most (>90%) of the administered dose was excreted within 36-48 hours. There was negligible radioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although numerous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the administered dose. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.

Previously selected doses and endpoints for risk assessments have been used for the current action. The toxicology database for penoxsulam is complete for Food Quality Protection Act (FQPA) purposes. A database uncertainty factor is not needed for penoxsulam. There is not a concern for neurotoxicity resulting from exposure to penoxsulam. No evidence of neurotoxicity was observed in the acute or chronic neurotoxicity studies in rats or in any of the subchronic or chronic feeding studies in rats, mice or dogs. The FQPA Safety Factor (FQPA SF) has been removed (i.e. reduced to 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity.

Risk assessments were conducted for the following specific exposure scenarios listed below. The cPAD was calculated by dividing the chronic point of departure (POD), in this case the NOAEL, by 100 (10X for interspecies extrapolation, 10X for intraspecies variation). Since the FQPA SF has been reduced to 1X, the cPAD is not further adjusted.

<u>Exposure Scenario</u>	<u>Dose</u>	<u>Endpoint</u>	<u>Study/Effect</u>
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	NOAEL=14.7 mg/kg/day	cPAD=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)	NOAEL=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%	NOAEL=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%	NOAEL=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%	NOAEL=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%	NOAEL=17.8 mg/kg/day	Residential MOE = 100 Occupational MOE = 100	
Inhalation Long-Term (> 6 months) Absorption: 100%	NOAEL=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

Exposure Assessment

Penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolopyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] is a sulfonamide herbicide currently registered on rice for the selective control of grasses, broadleaf, and sedge weeds. Dow AgroSciences LLC has now submitted a Section 3 registration application for the use as an aquatic herbicide and a use on turf. Concurrently, the petitioner has requested an exemption from the requirement of a

tolerance on fish and shellfish when penoxsulam is applied in aquatic areas. The proposed use is as an aquatic herbicide in the water of lakes, ponds, canals, and reservoirs. Typical application rates of penoxsulam will be 10-20 ppb in an initial application with additional 'bump' applications of 5-10 ppb to keep the water concentration at 5-10 ppb for 45-90 days. There is a season maximum of all applications of 150 ppb. Although typical multiple application rates are proposed at 5-20 ppb, a single in-water application is allowed at up to the maximum rate of 150 ppb.

The nature of the residue in rice is adequately understood. The nature of the residue in rotational crops is also adequately understood. The nature of the residue in animals is adequately understood. The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and is not significantly metabolized in either goats or poultry. HED has determined that for the tolerance expression and risk assessment, the residue of concern for penoxsulam in plants, rotational crops, and livestock (including poultry), following the rice use, is parent only.

The available analytical methodology, designated Method GRM 01.25, a liquid chromatography with tandem mass spectroscopy-mass spectroscopy detection method (LC/MS/MS), is considered to be adequate for the rice tolerance enforcement. The method that was used to collect data in the analysis of freshwater clam and catfish samples from the field accumulation study is a modification of LC/MS/MS, Method GRM 05.08. Adequate method validation data, including data from an independent laboratory, were submitted for Method GRM 05.08 applied to bovine matrices and fish tissues. The limit of quantitation (LOQ) is 0.01 ppm, and the calculated limit of detection (LOD) was 0.003 ppm in tested bovine matrices and in fish tissue. Method GRM 05.08 is similar to Method GRM 01.25, using a reasonably similar extraction; therefore, including the ILV that was submitted, Method GRM 05.08 should also be appropriate for enforcement of tolerances for fish and shellfish. The FDA multiresidue protocol data show that penoxsulam is not adequately recovered using any of the protocol methods. The multiresidue data have been forwarded to FDA for further evaluation.

No supporting storage stability data were submitted to validate the storage conditions and intervals of samples taken from the magnitude of the residue study in freshwater clams and catfish. Looking at the study dates, however, the samples could not have been stored for more than 1.6 months prior to residue analysis. Because samples were stored for a relatively short interval and because the Agency has also previously noted in the rice petition that comparative analysis of goat milk and tissue extracts show that residue profiles are similar after 135 and 300 days of sample collection, no additional supporting storage stability data are required.

To support the current request, a study investigating the nature and potential for bioaccumulation of penoxsulam residues in bluegill sunfish was submitted. Bluegill sunfish were exposed for 28 consecutive days to the radiolabeled test substance at 1x and 10x the maximum annual proposed application rate. Following exposure of the fish in this study at 0.150 mg/L, total radioactive residues (TRR) were below the minimum quantifiable limit (MQL ; <0.007 ppm) in fish samples exposed to [phenyl-U-¹⁴C]penoxsulam, and ranged from <MQL to 11.4 ppb (0.0114 ppm) in fish samples exposed to [het-2-¹⁴C]penoxsulam.

Calculated bioconcentration factors (TRR in tissue/TRR in water) were ≤ 0.10 , indicating that there is little potential for the test substance or its metabolites to bioaccumulate.

A study investigating the magnitude and potential for bioaccumulation of penoxsulam residues in freshwater clams and catfish was also submitted. The test organisms were exposed for 28 consecutive days to penoxsulam under static aquatic conditions at concentrations of 0.150 mg ai/L and 1.50 mg ai/L (1x and 10x). The bioconcentration factors (concentration in tissue/concentration in water) in all samples were ≤ 0.15 indicating that penoxsulam has very low potential to bioconcentrate in edible tissues of freshwater clams and catfish. Because concurrent recoveries and raw data were not submitted with this study, HED has classified it as scientifically acceptable pending submission of this supporting data.

A previously reported study also showed the TRR residues in crayfish during 14 days of exposure to 494 ppb penoxsulam in water, followed by 7 days of depuration. Maximum TRR in crayfish tail muscle occurred on day 11 of the treatment and was 14.4 ppb. On that basis the registrant concluded that no tolerance associated with the rice use was needed for crayfish (or crustaceans). Since the 10x concentration in paddy water of 45 ppb (0.5 ppm) from the rice use is $\sim 3x$ the proposed annual 150 ppb (0.15 ppm) aquatic application rate, assuming linearity, at 1x the proposed maximum aquatic application rate the TRR in crayfish would thus be estimated at about $14.4 \text{ ppb}/3 = 4.8 \text{ ppb}$ (0.005 ppm) and, if the linear extrapolation held the other way, at 10x the crayfish TRR would be around 48 ppb (0.05 ppm).

HED has reviewed the available data, and finds that it does not support the petitioner's request for tolerance exemptions on shellfish and finfish, resulting from the proposed aquatic uses. Tolerances are required for residues in fish. The petitioner is required to propose tolerances on fish and shellfish in a revised Section F. Based on the available residue data for freshwater clams and catfish treated at 0.15 mg ai/L, HED tentatively recommends tolerances of 0.02 ppm for mollusc, and 0.01 ppm for both fish and for crustaceans after a direct aquatic use. Based upon the reviewed studies the tolerance expression should be penoxsulam, per se. In general, from the bluefish study, 5-hydroxypenoxsulam is present in penoxsulam residues at about 40% of the parent penoxsulam. Thus, residues of concern in fish (finfish, mollusc and crustacean) for risk assessment based upon these studies should be penoxsulam plus 5-hydroxy penoxsulam.

The HED ChemSAC agreed that some irrigation studies were needed to support direct use of penoxsulam on waterways because the treated water may be used on food crops. That information was conveyed to Dow. Dow responded with changes that they assert will preclude the need for irrigation studies. ChemSAC supported Dow's proposal to remove treatment of irrigation canals from the label. ChemSAC agreed that application of penoxsulam to lakes and ponds can be controlled through rigorous enforcement of Dow's proposed stewardship program.

Penoxsulam is expected to be very mobile in the environment with the degradation products of toxicological concern to be even more mobile than the parent compound. The Estimated Drinking Water Concentrations (EDWC) in a perennial surface water body were calculated

using the EPA Tier I FIRST (FQPA Index Reservoir Screening Tool) using the Environmental Fate and Effects Division (EFED) Index Reservoir environment. Based upon results of the Tier 1, surface model, FIRST, the upper bound peak and chronic EDWC values resulting from the use of penoxsulam on turf are 9.4 ppb and 0.92 ppb, respectively.

The SCI-GROW, Tier I EDWC value for penoxsulam evaluated at the maximum annual application to turf is 12.0 ppb. The SCI-GROW, Tier I EDWC value for penoxsulam evaluated at the maximum single application to exposed sediment after drawdown is 23.3 ppb. The maximum penoxsulam value for surface and ground water used in this assessment, 150 ppb, is directly from the maximum target concentration listed on the proposed labels. EFED expects that the actual concentration found in surface and ground water from these aquatic uses will be less than 150 ppb.

There are no acute endpoints established for any population subgroup for exposure to penoxsulam; therefore, no acute dietary exposure assessment was conducted. An unrefined (using tolerance-level residues and assuming 100 percent crop treated (%CT) for all registered and proposed commodities), chronic dietary exposure assessment was conducted for the general U.S. population and various population subgroups. Drinking water was incorporated directly in the dietary assessment using the penoxsulam concentration as an aquatic herbicide in the water of lakes, ponds, canals, and reservoirs at 150 ppb. This assessment concludes that the chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (2% of the cPAD) and all other population subgroups. The most highly exposed population subgroup is all infants (<1 year old), at 7% of the cPAD. Penoxsulam was determined to be "Suggestive of Carcinogenicity;" therefore, a cancer dietary exposure assessment was not conducted and the chronic PAD is expected to be protective of human health.

Residential

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. There is a potential for postapplication exposure from oral and dermal routes of exposure while swimming in aquatic and/or turf (lawns, golf courses, sports fields, and sod farms) sites treated with penoxsulam.

HED used the SWIMODEL from the Residential Standard Operating Procedures (SOPs) to assess dermal and oral exposure to recreational swimmers. Parameters used in calculating exposure and risk are based on information for competitive swimmers both adult and children (6 years) in swimming pools which includes an exposure duration of 5 hours. Therefore, HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk and therefore does not recommend that these MOEs be used when aggregating risk.

Residential exposure is considered to generally be short-term in duration; however, no short-term dermal endpoint was selected. Short-term exposure to adults during handling will include only an inhalation assessment. The only route of postapplication short-term exposure for turf to be aggregated for children is oral (hand-to-mouth, object-to-mouth, and ingestions of soil). The aggregate short-term MOE for adults and children was greater than the level of concern (Total MOE > 100) and therefore was not of concern to HED.

Since postapplication inhalation exposure is anticipated to be negligible and based on information which indicates that the amount of residues remaining on the turf after 30 days would be negligible, HED does not expect intermediate-term dermal exposure to result from application of penoxsulam to turf. No intermediate-term aggregate exposure assessment to turf is required.

Aggregate Exposure and Risk

In accordance with the FQPA, ARIA must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, ARIA considers both the route and duration of exposure.

An acute aggregate (food + drinking water) was not conducted because no acute endpoint was determined for penoxsulam.

Aggregate penoxsulam exposures can result from the aquatic and turf use scenarios. Since HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk and does not recommend that these MOEs be used when aggregating risk, the swimming exposure assessment will not be used in calculating the short- and intermediate-term aggregate risk and only the exposures resulting from the turf use will be considered.

The short-term aggregate risk assessment estimates include oral and inhalation exposures appropriate to the populations of concern. Short-term dermal exposure need not be aggregated because no toxicological endpoint was selected. For adults, short-term exposure to penoxsulam can occur as a result of the residential use on turf. Because oral exposure from the residential use as a handler is not expected in adults and no short-term dermal endpoint was selected, only the short-term residential exposure by inhalation is expected in adults. The worst-case MOE residential exposure estimate was aggregated with the chronic dietary (food + water) to provide a worst-case estimate of short-term aggregate risk for U.S. population. As the aggregate MOE is greater than 100, the short-term aggregate risk to adults does not exceed HED's level of concern.

For children/toddlers, short-term exposure to penoxsulam can occur as a result of the residential use on turf. Because postapplication inhalation exposure is anticipated to be negligible and no short-term dermal endpoint was selected, only the short-term residential exposure from oral exposure was included with food and drinking water in the short-term aggregate risk assessment for children/toddlers. The worst-case MOE residential exposure estimate for children was aggregated with the chronic dietary (food + water) to provide a worst-case estimate of short-term aggregate risk for all infants (<1 year old), the child population subgroup with the highest estimated chronic dietary food exposure. As the aggregate MOE is greater than 100, the short-term aggregate risks to children do not exceed HED's level of concern.

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of penoxsulam (food and drinking water) and residential uses. However, due to the existing and proposed use patterns, no chronic residential exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and

drinking water only. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (2% of the cPAD) and all population. The most highly exposed population subgroup is all infants (<1 year old), at 7% of the cPAD. 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.

Occupational Exposure and Risk

Since a short-term dermal point was not selected, the only route of short-term exposure to be addressed for handlers is inhalation. All turf and aquatic handler short-term exposure scenarios resulted in MOEs greater than 100 and therefore not of concern to HED.

Dermal and inhalation endpoints were selected for intermediate-term exposure. Since both endpoints were derived from the same study, toxicological effects were the same and therefore exposures could be combined to determine a total margin of exposure for intermediate-term scenarios. All intermediate-term aquatic handler scenarios resulted in Total MOEs greater than HED's level of concern (MOE > 100) when occupational handlers wore single layer of clothing plus gloves. Based on information provided in the proposed turf labels; handler exposure is anticipated to only be short-term in duration. Therefore, neither a dermal nor inhalation intermediate-term handler exposure assessment was performed for turf uses.

In regard to aquatic scenarios, postapplication exposure is expected to occur to only non-occupational individuals swimming in treated areas. Therefore an occupational postapplication exposure assessment is not required for the proposed use.

No short-term dermal exposure endpoint was selected. Although an intermediate-term dermal endpoint was selected, intermediate-term dermal postapplication exposure is expected to be negligible based on information on the proposed turf labels and chemical specific turf transfer residue studies. Therefore, a dermal postapplication exposure assessment for turf was not performed.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.ch.doe.gov/oeqa/guidance_justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, ARIA estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults

entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix D) have been determined to require a review of their ethical conduct, and have received that review.

Recommendation

ARIA has determined that the residue chemistry and hazard databases support the establishment of the permanent tolerances for the residues of penoxsulam, expressed as the parent, in/on the RACs listed below, provided the following data gaps are corrected:

- 1) The petitioner must submit a label restricting uses on moving waters (canals, rivers, etc), and include suitable directions to control the residues on non-moving waters (lakes, ponds, etc).
- 2) Acceptable review of concurrent recoveries and raw data recently submitted to support the catfish and clam study.
- 3) Additional confirmatory data/information must be submitted to upgrade the submitted sunfish study (MRID 46703506) to an acceptable status.
- 4) Submit a revised Section F for penoxsulam residues in fish and fish - shellfish, crustacean at 0.01 ppm and fish- shellfish, mollusc at 0.02 ppm.

Commodity	Tolerance (ppm)
fish - shellfish, mollusc	0.02
fish	0.01
fish - shellfish, crustacean	0.01

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

EPA granted a conditional registration to Dow AgroSciences for penoxsulam use on water- or dry-seeded rice on 9/27/04. The petitioner is currently requesting an exemption from the requirements of tolerances on fish and shellfish when penoxsulam is applied in aquatic areas such as lakes, reservoirs, ponds, and canals to control hydrilla, water hyacinth, egeria, and various other aquatic weeds.

Table 2.1. Summary of Directions for Use of Penoxsulam						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate	PHI (days)	Use Directions and Limitations
Lakes, Ponds, Canals, and Reservoirs						
Single In-Water Application	GF-443 SC [62719-XXX]	5-150 mg ai/L	1	150 mg ai/L	NA	Typical application rates of penoxsulam will be 10-20 ppb in an initial application with additional 'bump' applications of 5-10 ppb to keep the water concentration at 5-10 ppb for 45-90 days. The total concentration amount of all applications must not exceed 150 ppb per annual growth cycle.
Split or Multiple In-Water Applications		5-75 mg ai/L	Varies			
Turf						
	GF-443 SC SF [62719-LUA]	0.02-0.06 lb ai/A	1	0.06 lb ai/A	NA	
	GF-907 SC [62719-LUT]	0.02-0.06 lb ai/A	1	0.06 lb ai/A	NA	
	Penoxsulam GR [62719-LLN]	0.06 lb ai/A	1	0.06 lb ai/A	NA	
	Penoxsulam GR [62719-LUG]	0.06 lb ai/A	1	0.06 lb ai/A		
	Penoxsulam FERT [62719-LUO]	0.06 lb ai/A	1	0.06 lb ai/A	NA	Do not apply more than 150 lb of penoxsulam Fert 0.04% (0.06 lb ai) per acre per application or more than 225 lb of product (0.09 lb ai) per acre per growing season
	Penoxsulam FERT [62719-LUI]	0.06 lb ai/A	1	0.06 lb ai/A	NA	

2.2 Structure and Nomenclature

2.3 Physical and Chemical Properties

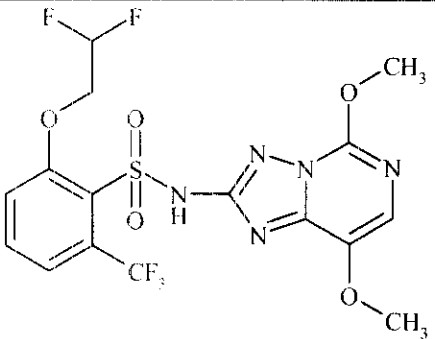
Table 2.3.a Penoxsulam Nomenclature.	
Compound	
Common name	Penoxsulam
Company experimental name	XDE-638
IUPAC name	26-(2,2-difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)- α,α,α -trifluoro-o-toluenesulfonamide
CAS name	32-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide
CAS registry number	4219714-96-2
End-use product (EP)	GF-443 SC (EPA Reg. No. 62719-XXX)

Table 2.3.b Physicochemical Properties of Penoxsulam.		
Parameter	Value	Reference
Melting point/range	Not available	
pH	5.2	MRID 45830707
Density	1.61 g/mL at 20 °C	MRID 45830707
Water solubility at 19 °C	Unbuffered 4.91 mg/L pH 5 5.66 mg/L pH 7 408 mg/L pH 9 1460 mg/L	MRID 45830720
Solvent solubility at 19 °C	Xylene 0.017 g/L 1-Octanol 0.035 g/L Methanol 1.48 g/L Ethyl acetate 3.23 g/L Acetonitrile 15.3 g/L Acetone 20.3 g/L Dimethylsulfoxide 78.4 g/L	MRID 45830720
Vapor pressure	57.16×10^{-16} mm Hg at 25 °C	MRID 45830720
Dissociation constant, pK _a	5.1 (ambient)	MRID 45830720
Octanol/water partition coefficient, Log(K _{OW})	Unbuffered 6-0.354 pH 5 71.137 pH 7 8-0.602 pH 9 9-1.418	MRID 45830720
UV/visible absorption spectrum	Not available	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

Technical grade penoxsulam (XDE-638), an off-white powder of 97.5% purity, exhibited minimal acute toxicity in the available studies. The acute oral LD₅₀ in male and female rats was >5000 mg/kg (Toxicity Category IV) and the acute dermal LD₅₀ 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 Category IV. In a primary eye and skin irritation studies in rabbits, it produced only minimal irritation (Toxicity Category IV) and in a dermal sensitization study in guinea pigs (maximization method), it was negative for dermal sensitization.

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

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

In a developmental toxicity study in rats, decreased body weight gain, decreased food consumption and increased kidney weights were observed in the dams. No developmental toxicity was observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this study. In a developmental toxicity study in rabbits, decreased body weight gain, decreased food consumption and clinical signs of toxicity (decreased/absent feces, or mucoid, soft, or abnormally colored feces) were observed in dams at the highest dose tested. One high dose doe died late in the study after exhibiting signs of clinical toxicity for several days. No developmental toxicity was observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this

study. In a 2-generation reproduction study in rats, microscopic lesions in the kidney were observed in the parental females at the mid and high dose levels. Preputial separation, an indicator of sexual maturation, was significantly ($p \leq 0.05$) delayed in mid and high dose F_1 males. The mean age at which preputial separation was attained for the control, low, mid, and high dose groups was 43.6, 44.0, 45.5, and 46.0 days, respectively. In addition, at the mid dose, 1 animal did not separate and at the high dose, 3 animals did not separate whereas all animals at the control and low doses did separate. The delay in preputial separation at the mid and high doses was considered to be a treatment-related effect. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment. There was no increased quantitative or qualitative susceptibility of fetuses or offspring, as compared to adults, in this study.

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

In a carcinogenicity study in rats, male and female rats were given penoxsulam in the diet for two years at dose levels of 0, 5, 50 or 250 mg/kg/day. In this study, there was a statistically significant increased incidence of malignant 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 feces in both sexes. A significant enterohepatic circulation was observed, particularly in males. Most (>90%) of the administered dose was excreted within 36-48 hours. There was negligible radioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although numerous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the administered dose. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.

3.1.1 Dose-response

3.1.1.1 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.

3.1.1.2 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 PAD is 0.147 mg/kg/day (14.7 mg/kg/day (NOAEL)/100 (UF)). This PAD is protective of the effects observed in the 2-generation reproductive study (NOAEL = 30 mg/kg/day).

3.1.1.3 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 histopathology. Treatment-related histopathologic changes in kidneys of males and females consisted of very slight, multifocal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts. The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/day, based on histopathologic changes in the kidneys. The NOAEL was 17.8 and 19.9 mg/kg/day for males and females, respectively. The NOAEL of 17.8 mg/kg/day, based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day, was chosen to assess incidental oral exposure.

3.1.1.4 Dermal Absorption Factor (50% - upper bound estimate)

A dermal absorption study is not available. The percent dermal absorption was estimated by comparing the LOAEL for male and female rats from a 4-week dermal study to the LOAEL for male and female rats from a 4-week feeding study. The LOAEL for male and female rats from the 4-week dermal study was >1000 mg/kg/day, based on the lack of any treatment-related effects at 1000 mg/kg/day (the highest dose tested, limit dose). The LOAEL for male rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, and decreased RBC parameters. The NOAEL for male rats was 100 mg/kg/day. The LOAEL for female rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, decreased RBC parameters, increased kidney weights, and histopathological changes in the kidney. The NOAEL for female rats was 100 mg/kg/day.

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

3.1.1.5 Dermal Exposure-Short-Term (1-30 days) Exposure

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

3.1.1.6 Dermal 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 histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

3.1.1.7 Dermal Exposure - Long-Term (> 6 Months)

See Chronic PAD. 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.

3.1.1.8 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.

3.1.1.9 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.

3.1.1.10 Inhalation Exposure - Long-Term (> 6 Months) Exposure

See Chronic PAD. 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.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

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

HED's MARC concluded that 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, ruminants, and rotated crops (TXR No. 0052740, W. Cutchin, 7/19/04). Metabolism studies conducted on rice with both [triazolopyrimidine-2-¹⁴C] and [phenyl-U-¹⁴C] 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 levels <0.1 ppm, and is considered to be no more toxic than the parent based on the structural similarities between parent and 5-OH XDE-638. Also, based on the livestock metabolism study, no animal tolerances are needed [180.6 (a)(3)] even if the metabolite were to be included as a residue of concern. The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and not significantly metabolized in either goats or poultry. The metabolism study of penoxsulam in lactating goat indicated that parent is the major residue. Confined rotational studies conducted on potatoes

with both [triazolopyrimidine-2-14C] and [phenyl-U-14C] labeled penoxsulam indicated that BSTCA and 5-OH XDE-638 are major residues (>10% TRR) in potato foliage. However, only 5-OH XDE-638 is found at >0.01 ppm in potato foliage (at 2x application rate).

3.3 FQPA Considerations

HED HIARC previously evaluated the potential for increased susceptibility of infants and children from exposure to penoxsulam as required by the Food Quality Protection Act (FQPA) of 1996 in accordance with the 2002 OPP 10X Guidance Document (HIARC Report, TXR No. 0052273, 12/16/03, E. Budd). No additional information has been submitted. The toxicology database for penoxsulam is complete for FQPA purposes. The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to penoxsulam. No evidence of neurotoxicity was observed in the acute or chronic neurotoxicity studies in rats or in any of the subchronic or chronic feeding studies in rats, mice or dogs. A developmental neurotoxicity study (DNT) is not required. The FQPA SF has been removed (i.e. reduced to 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity and there is no evidence of qualitative or quantitative susceptibility in developmental and reproductive studies. The FQPA SF assumes that the exposure databases (dietary, food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

The FQPA SF has been removed (i.e. reduced to 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity. The penoxsulam risk assessment team evaluated the quality of the hazard and exposure data; and, based on these data, recommended that the special FQPA SF be removed. The recommendation is based on the following:

- There was no toxicologically significant evidence observed of neurotoxicity in either the acute or chronic neurotoxicity study.
- No definitive quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies.
- Significant dose-related effects in the two-generation reproduction study were limited to the delay in preputial separation. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment, and offspring effects were observed in the presence of parental toxicity at similar doses.
- The chronic dietary food exposure assessment utilizes proposed tolerance level residues and 100% CT information for all commodities. By using these conservative assessments, chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

3.3.1 Adequacy of the Toxicity Database

With respect to FQPA hazard considerations, the toxicology database for penoxsulam is complete

The available toxicology database for penoxsulam includes the following acceptable studies:

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

3.3.2 Evidence of Neurotoxicity

There is not a concern for neurotoxicity resulting from exposure to penoxsulam.

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

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

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

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

Based on the results of this acute neurotoxicity study, the neurotoxic NOAEL for XDE-638 in male and female rats is 2000 mg/kg (limit dose). The LOAEL was not identified (>2000 mg/kg). This neurotoxicity study is classified as Acceptable/Guideline and does satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

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

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

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

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

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

3.3.3 Developmental Toxicity Studies

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

external alterations. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination.

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

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

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

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

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

One high-dose doe died on GD 27 after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity beginning on GD 22. One high-dose female aborted on GD 23 after

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

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

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

3.3.4 Reproductive Toxicity Study

Executive Summary: In a two-generation reproduction toxicity study (MRID 45830920), XDE-638 (97.7% ai, lot #B-765-44, TSN102058) was administered to 30 male and 30 female Crl:CD (SD) IGS BR rats/dose at dietary concentrations that provided 0, 30, 100, or 300 mg/kg/day. One litter was produced in each generation. F₀ and F₁ parental animals were administered test or control diet for 10 weeks prior to mating, throughout mating, gestation, and lactation and until sacrifice. Doses were selected on the basis of a range-finding study in non-mated CD rats (MRID 45830907).

Intercurrent deaths of several F₀ and F₁ 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 F₀ generation during the pre-mating interval. Absolute body weights of the high-dose F₁ males were significantly ($p \leq 0.05$; 88-94% of controls) less than those of the controls throughout the study. High-dose F₁ females had significantly lower ($p \leq 0.05$; 93% of controls) body weight than the controls only for the first week of pre-mating. Body weight gains by the high-dose F₁ animals were similar to the controls. Reduced body weights of the high-dose F₁ parental animals during pre-mating were considered a continuation of preweaning effects. Food consumption by the high-dose F₁ males was significantly less ($p \leq 0.05$; 92-93% of controls) than that of the control group for the first two weeks of pre-mating.

Body weights of the high-dose F₀ and F₁ dams were significantly lower ($p \leq 0.05$; 87-94% of controls) than that of controls from GD 21 through lactation day 14. The most pronounced effect on body weight gains during gestation was for days 14-21 when the high-dose F₀ and F₁ dams had weight gains 79% and 82%, respectively, of the control group levels. Weight changes by the high-dose dams during the first week of lactation consisted of marked weight loss during days 1-4 and a lower weight gain than the controls for days 4-7. Recovery was noted in the high-dose dams after lactation day 7. During gestation, food consumption was similar between the treated and control groups of both generations. Food consumption by the high-dose F₀ dams was significantly less ($p \leq 0.05$; 76-88% of controls) than that of the controls on lactation days 1-11. Food consumption by the high-dose F₁ dams was significantly ($p \leq 0.05$; 70-72% of controls) less than that of the controls on lactation days 1-7. Compensation was noted in the high-dose F₀ and F₁ dams with food consumption reaching 115% and 110%, respectively, of controls (both $p \leq 0.05$) during lactation days 17-19.

At necropsy, mid- and high-dose males of both generations had increased absolute and/or relative liver weights due to slight hepatocellular hypertrophy that was not considered to be adverse. High-dose females of both generations had significantly increased ($p \leq 0.05$; 109-115% of control) absolute and relative kidney weights. Microscopic lesions of the kidney of high-dose F₀ and F₁ females included epithelial hyperplasia, inflammation, and crystal formation in the pelvis and tubular degeneration. The incidences (severity) of kidney lesions in control and high-dose females were 1-2/30 (1.00) and 25-26/30 (1.58-2.04), respectively, for hyperplasia, 0/30 and 7-8/30 (1.25-2.14), respectively, for inflammation, and 3/30 (1.00) and 20-21/30 (1.62-1.85), respectively, for degeneration. In addition, crystals were observed in 0, 0, 2, and 16 F₀ females and in 2, 1, 7, and 11 F₁ females in the control, low-, mid-, and high-dose groups, respectively. Therefore, the parental systemic toxicity LOAEL for female rats is 100 mg/kg/day based on kidney lesions (crystals) and for male rats is 300 mg/kg/day based on reduced absolute body weights of the F₁ males. The parental systemic toxicity NOAEL for female rats is 30 mg/kg/day and for male rats is 100 mg/kg/day.

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

weights of the high-dose pups were a result of weight gains 76-80% of the control group levels from lactations days 1-7. Weight gains by the high-dose pups were slightly lower than the controls from lactation days 7-14 and comparable to control levels from lactation days 14-21.

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

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

3.3.5 Additional Information from Literature Sources

No additional information is available from the literature.

3.3.6 Pre-and/or Postnatal Toxicity

There is not a concern for pre- and/or postnatal toxicity resulting from exposure to penoxsulam.

3.3.6.1 Determination of Susceptibility

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

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

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

3.3.7 Recommendation for a Developmental Neurotoxicity Study

There is not a concern for developmental neurotoxicity resulting from exposure to penoxsulam.

3.4 FQPA Safety Factor for Infants and Children

Based upon the above data, the FQPA SF has been removed (i.e. reduced to 1X) since there are no residual uncertainties for pre- and/or post-natal toxicity.

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

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (RfD) – All Populations

Study Selected: None

Guideline No.: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing aPOD: Not applicable

Uncertainty Factor (UF): Not applicable

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

3.5.2 Chronic Reference Dose (RfD)

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

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

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

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

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

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

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

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

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

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

3.5.3 Incidental Oral Exposure (Short-Term)

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

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

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

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

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

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

Comments about Study/Endpoint: This endpoint is based on an oral study, which is the route of interest for an oral risk estimate. This endpoint is also appropriate for the population of concern (infants and children). For this exposure scenario, a 13-week (90-day) study was selected to establish the toxicological endpoint for short-term (1-30 days) exposures. This selection is justified by the observation that the kidney lesions (including histopathologic changes) observed in the 4-week, 13-week and 1-year feeding studies in dogs did not occur at lower dose levels or increase in severity as the duration of the study increased. In other words, exacerbation of the kidney lesions observed in the shorter-term studies did not occur in the longer-term studies. Therefore, results in both the 4-week and 1-year studies support this selection. In addition, this selection (NOAEL of 17.8 mg/kg/day based on kidney lesions at the LOAEL of 49.4 mg/kg/day) is also protective of the maternal effects observed in the developmental toxicity study in rabbits (NOAEL of 25 mg/kg/day based on death, clinical signs, decreased body weight gain and decreased food consumption at the LOAEL of 75 mg/kg/day).

3.5.4 Incidental Oral Exposure (Intermediate-Term)

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

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

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

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

3.5.5 Dermal Absorption

Dermal Absorption Factor: 50% (upper bound estimate)

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

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

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

LOAEL from 4-week feeding study	=	<u>500 mg/kg/day</u>	x	100	=	<u>50%</u> (upper
LOAEL from 4-week dermal study	=	>1000 mg/kg/day				bound estimate)

4-Week Dermal Study

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

There were no deaths reported during the study. There were no treatment-related effects on clinical observations, dermal observations, body weight, body weight gain, food consumption,

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

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

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

4-Week Feeding Study

Executive Summary: In a 4-week feeding study (MRID 45830903), XR-638 (penoxsulam) (99%, lot number 597-CO49-17C, TSN101644) was administered to 5 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day. Animal care, diet preparation, and gross necropsy were as described in the main study (MRID 45830906). Tissues from animals receiving the control and 1000 mg/kg/day diets, as well as the liver, kidneys, and relevant gross lesions from the remaining dose groups, were processed as in the main study and examined microscopically.

All animals survived until scheduled sacrifice. Perineal urine soiling, observed in one 500 mg/kg/day male, four 500 mg/kg/day females and three 1000 mg/kg/day females, was not considered to be a toxicologically significant adverse effect. Ophthalmology was unremarkable. Body weights of both sexes receiving 1000 mg/kg/day were lower than those of controls throughout the study, and at day 29 were about 10% (males) and 6% (females) below those of controls. Body weight gains at day 29 were 25% (males and females) lower than those of controls. At 500 mg/kg/day, body weights of both sexes were also lower than those of controls throughout the study, and at day 29 were about 8% (males) and 4% (females) below those of controls. Body weight gains at day 29 were 20% (males and females) lower than those of controls. At 1000 and 500 mg/kg/day, overall food consumption by both sexes was about 5-11% lower than that of controls. Slight, statistically significant decreases in red blood cell parameters (<10% at 1000 mg/kg/day) were present in males and females from all dose levels but were more pronounced at 1000 and 500 mg/kg/day. There were no toxicologically significant changes in clinical chemistry or urinalyses. Kidney weight was increased by about 10% in the 1000 and 500 mg/kg/day females. Slight multifocal hyperplasia of the renal pelvic epithelium, very slight subacute to chronic inflammation of the renal pelvic epithelium, and crystals in the urinary space of the renal pelvis were found in females of the 500 and 1000 mg/kg/day groups. One 500 mg/kg/day male had a few crystals in the urinary space of the renal pelvis of one kidney.

The LOAEL is 500 mg/kg/day based on decreased body weights (males and females), decreased body weight gains (males and females), decreased feed consumption (males and females), decreased RBC parameters (males and females), increased kidney weights (females), and histopathology in the kidneys of females (crystals in the pelvis and inflammation and hyperplasia of the pelvic epithelium). The NOAEL is 100 mg/kg/day.

This 4-week oral toxicity study in the rat is Acceptable/Non-Guideline as a range-finding study. It does not satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

3.5.6 Dermal Exposure

3.5.6.1 Dermal Exposure Short-Term

Study Selected: None

Guideline No.: N/A

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Risk Assessment: Not Applicable

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

3.5.6.2 Dermal Exposure Intermediate-Term

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

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

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

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

3.5.6.3 Dermal Exposure Long-Term

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See Chronic Reference Dose (RfD)

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

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

3.5.7 Inhalation Exposure

3.5.7.1 Inhalation Exposure Short-Term

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

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

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

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

3.5.7.2 Inhalation Exposure Intermediate-Term

Study Selected: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

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

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

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

3.5.7.3 Inhalation Exposure Long-Term

Study Selected: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See Chronic RfD

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

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

3.5.8 Level of Concern for Margin of Exposure

The target MOEs for occupational and residential exposure risk assessments are as follows:

Table 3.5.8 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).

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows (HIARC, TXR No. 0052273, E. Budd, 12/16/03):

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

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

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

3.5.10 Classification of Carcinogenic Potential

Penoxsulam was classified by the HED CARC as Suggestive in 2004. The classification was based on an increase in large granular lymphocyte leukemia (also called mononuclear cell leukemia (MNCL)). There were increases at all dose levels in the male Fischer 344 rats, which exceeded the laboratory historical control data. There is considerable controversy about the significance and relevance of the tumors for humans; however, they cannot be discounted in the overall weight of the evidence. There is some cancer concern but the data are judged not sufficient for a stronger conclusion or a quantitative cancer risk assessment.

3.5.11 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Penoxsulam			
Exposure Scenario	Point of Departure, UF	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.

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Penoxsulam			
Exposure Scenario	Point of Departure, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (all populations)	NOAEL = 14.7 mg/kg/day UF = 100 Chronic RfD = 0.147 mg/kg/day	FQPA SF = 1x cPAD = <u>Chronic RfD</u> FQPA SF = 0.147 mg/kg/day	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.
Incidental Oral Short-Term (1-30 days)	NOAEL = 17.8 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 17.8 mg/kg/day	Residential LOC for MOE = 100 Occupational = NA	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Dermal Short-Term (1-30 days)	None	Not applicable	No dermal, systemic, neuro or developmental toxicity concerns.
Dermal Intermediate-Term (1-6 months)	Oral study NOAEL = 17.8 mg/kg/day (dermal absorption rate = 50%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Dermal Long-Term (> 6 months)	Oral study NOAEL = 14.7 mg/kg/day (dermal absorption rate = 50%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.
Inhalation Short-Term (1-30 days)	Oral study NOAEL = 17.8 mg/kg/day (inhalation absorption rate = 100%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Inhalation Intermediate-Term (1-6 months)	Oral study NOAEL = 17.8 mg/kg/day (inhalation absorption rate = 100%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	13-Week Feeding Study in Dogs. LOAEL = 49.4 mg/kg/day based on histopathologic changes in kidneys.
Inhalation Long-Term (> 6 months)	Oral study NOAEL = 14.7 mg/kg/day (inhalation	Residential LOC for MOE = 100 Occupational LOC for	1-Year Chronic Feeding Study in Dogs. LOAEL = 46.2 mg/kg/day based on multifocal hyperplasia of the pelvic epithelium of the kidney.

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Penoxsulam			
Exposure Scenario	Point of Departure, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
	absorption rate = 100%	MOE = 100	
Cancer (oral, dermal, inhalation)	"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"		

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 Endocrine Disruption

EPA is required under the 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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis 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 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).

4.0 Public Health and Pesticide Epidemiology Data

There is no public health or epidemiology data for penoxsulam at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

An acceptable rice metabolism study was reviewed in the rice petition (PP#3F6542). Based on the submitted rice 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 penoxsulam residues or its metabolites into the grain was observed. Based upon this study the MARC determined that for the tolerance expression and risk assessment the residue of

concern for penoxsulam in/on rice is parent only. The response to the rice petition included a note that if uses on other crops are proposed, including uses on cereal grains, additional nature of the residue data will be needed. However, as an alternative to metabolism data on other cereal crops, the registrant might submit crop field trial data which include residue data for the metabolite 5-OH XDE-638 as well as parent.

5.1.2 Metabolism in Rotational Crops

HED review of an acceptable crop rotational crop study concluded that no quantifiable residues of penoxsulam or 5-OH XDE-638 are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops planted 90 days following treatment with penoxsulam at 0.045 or 0.090 lb ai/A (1x or 2x the rate for rice). The data also indicate that residues of the metabolite penoxsulam BSTCA could be present at ≥ 0.01 ppm in the foliage of root crops planted 90 days following treatment at 0.090 lb ai/A (2x). The MARC determined that penoxsulam BSTCA is not a residue of concern for penoxsulam in rotated crops.

It was noted that the submitted confined rotational crop study only included one plantback interval, 90 days. If in the future plantback intervals other than 90 days are proposed, an additional confined rotational crop study reflecting the proposed plantback interval would be required. Based on data from the confined rotational crop study, no quantifiable residues of penoxsulam, its 5-OH metabolite, or BSTCA are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops planted 90 days following treatment with penoxsulam at 1x the maximum seasonal rate. Therefore, field rotational crop studies are not required to support this petition.

5.1.3 Metabolism in Livestock

The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and not significantly metabolized in either 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 metabolism.

The MARC determined that for the tolerance expression and risk assessment, the residues of concern for penoxsulam in livestock (including poultry) is parent only.

5.1.4 Analytical Methodology

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. Residues are quantitated by LC/MS/MS using a C8 column and electrospray ionization in the positive ion mode. Residues are quantified using external standards. The validated LOQ and calculated LOD for penoxsulam were 0.01 and 0.002 ppm, respectively, in/on rice forage, straw, grain, hulls, bran, and polished rice. A successful independent laboratory validation (ILV) of the LC/MS/MS method has been completed with rice grain and straw. The LC/MS/MS method was submitted to ACB/BEAD for method validation and was found to be adequate for enforcement purposes without the

need for an Agency laboratory validation provided some revisions are made in the procedure (DP Num: 303172, C. Stafford, 9/17/04).

The method that was used to collect data in the analysis of freshwater clam and catfish samples from the field accumulation study is a modification of LC/MS/MS Method GRM 05.08. Adequate method validation data, including data from an independent laboratory, were submitted for Method GRM 05.08 applied to bovine matrices and fish tissues. The validated LOQ is 0.01 ppm, and the calculated LOD was 0.003 ppm in tested bovine matrices and in fish tissue. Method GRM 05.08 is similar to Method GRM 01.25, using a reasonably similar extraction; therefore, including the ILV that was submitted, Method GRM 05.08 should also be appropriate for enforcement of tolerances for fish and shellfish.

5.1.5 Environmental Degradation

Penoxsulam is stable to hydrolysis, and is expected to be somewhat persistent in non-aquatic environments. The major route of dissipation for penoxsulam in clear and shallow surface water under favorable light conditions is through direct aqueous photolysis ($t_{1/2} = 1.5-14$ days). Penoxsulam is slightly more persistent in aerobic aquatic ($t_{1/2} = 12-38$ days) and anaerobic environments ($t_{1/2} = 5-11$ days), and even more persistent in aerobic soil environments ($t_{1/2} = 34-118$ days). Penoxsulam is also very mobile ($K_d = 0.13-1.96$), and does have the potential to leach to ground water. The low vapor pressure and Henry's Law constant, limits the potential of penoxsulam to volatilization from soil and water.

Eleven major degradation products have been identified for penoxsulam (BSTCA, 2-amino-TCA, 5-OH-penoxsulam, SFA, sulfonamide, 5,8-di-OH-penoxsulam, BSA, 2-amino-TP, TPSA, BSTCA methyl, and 5-OH 2 amino TP). Data are not available to fully characterize these degradates and their respective degradation pathways. Six of these degradation products have been identified by HED as being of toxicological concern. These toxic residues are: BSTCA, 2-amino TCA, 5-OH-penoxsulam, SFA, sulfonamide, and 5,8-di OH.

5.1.6 Comparative Metabolic Profile

In a metabolism/disposition study, rats (four/sex/group) were given single or 15 multiple oral low doses or a single high dose of ^{14}C - XDE-638 (penoxsulam). Both a triazole ring label and phenyl ring label were utilized. An additional group of three male and three female rats were fitted with bile duct cannulae and biliary elimination monitored over 24 hours following an oral dose. The results of this study showed that ^{14}C - XDE-638 (penoxsulam) orally administered to male and female rats underwent fairly rapid but incomplete absorption which became dose-limited at or below a dose of 250 mg/kg. Although widely distributed among tissues, there was no evidence of sequestration or bioaccumulation. Excretion was primarily via the urine and feces, with unabsorbed test article accounting for much of the fecal radioactivity especially for the high-dose group. A large number of metabolites were detected in urine, feces, and bile. Minor qualitative, gender-related differences were observed. Most metabolites represented only a small portion (<1%) of the administered dose. Minor qualitative and quantitative differences in metabolite profiles observed for the phenyl and triazole labels provided information on biotransformation supportive of the proposed metabolism scheme.

An acceptable rice metabolism study was submitted and showed that penoxsulam primarily degrades to its 5-OH metabolite (5-OH XDE-638) and at least two minor unknown metabolites in rice matrices. HED review of an acceptable crop rotational crop study concluded that no quantifiable residues of penoxsulam or 5-OH XDE-638 are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops planted 90 days following treatment with penoxsulam. The data also indicate that residues of the metabolite penoxsulam BSTCA could be present at ≥ 0.01 ppm in the foliage of root crops planted 90 days following treatment, however the MARC determined that penoxsulam BSTCA is not a residue of concern for penoxsulam in rotated crops. The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and not significantly metabolized in either goats or poultry.

Penoxsulam is stable to hydrolysis, and is expected to be somewhat persistent in non-aquatic environments. Eleven major degradation products have been identified for penoxsulam. Six of these degradation products have been identified by HED as being of toxicological concern: BSTCA, 2-amino TCA, 5-OH-penoxsulam, SFA, sulfonamide, and 5,8-di OH.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

None of the penoxsulam metabolites or degradates have been identified as having a higher potential toxicity than the parent compound.

5.1.8 Pesticide Metabolites and Degradates of Concern

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent only	Parent only
	Rotational Crop	Parent only	Parent only
Livestock	Ruminant	Parent only	Parent only
	Poultry	No Decision	No Decision
	Fish and Shellfish	Parent plus 5-hydroxy penoxsulam	Parent only
Drinking Water		Parent, BSTCA, 2-amino TCA, 5-OH-XDE-638, SFA, sulfonamide, 5,8-diOH	N/A

5.1.9 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED; DP Num: 325468, L. Shanaman, 11/8/06) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Penoxsulam is expected to be very mobile in the environment. Environmental fate data submitted for the degradation products of toxicological concern indicate that they are even more mobile than the parent compound. However, EFED does not currently have a method for estimating a model input value for the mobility of combined toxic residues. Therefore, as a simplifying assumption, the lowest mobility values for one of the degradation products was used for this Tier 1 assessment.

The EDWCs (Estimated Drinking Water Concentrations) in a perennial surface water body were calculated using the EPA Tier I FIRST (FQPA Index Reservoir Screening Tool; version 1.1.0, December 12, 2005) using the EFED Index Reservoir environment. FIRST is used to simulate pesticide transport as a result of runoff and erosion from an agricultural field, and the environmental fate and transport of pesticides in surface water. All modeled metabolism input values were based upon total toxic residues. Values for the parent alone would be expected to be lower than these upper bound estimates. Based upon results of the Tier 1, surface model, FIRST, the upper bound (acute) peak EDWC value resulting from the use of penoxsulam on turf is 9.4 ppb. The upper bound, Tier 1 chronic EDWC value resulting from the use of penoxsulam on turf is 0.92 ppb. The upper bound peak and chronic EDWC value resulting from the subsurface injection of penoxsulam to control submerged aquatic vegetation is 150 ppb. This value was taken directly from the maximum target concentration listed on the proposed labels.

The average, peak EDWC value resulting from the use of penoxsulam on floating or emerged aquatic vegetation is 64 ppb per application, *per one foot water depth*. This concentration is not an EDWC, but is a factor that has been derived by direct calculation using the application rate per acre and the volume of water covering one acre at a depth of one foot. This value is inversely proportional to water depth. At deeper water depths, aquatic concentrations would be lower, at shallower water depths, aquatic concentrations would be higher. EFED does not expect concentrations resulting from spray application to floating or emergent weeds to exceed the target injection concentration 150 ppb. The water depth would need to be less than 6 inches to exceed the 150 ppb concentration value. Such a shallow water depth is not expected to be found in naturally occurring, perennial water bodies. In situations where such shallow water depths might be encountered, such as irrigation or drainage ditches, it is reasonable to expect that the most efficient application of penoxsulam would involve interrupting the water flow, "drawing down", and making the application directly to the exposed sediment. Based upon results of the Tier 1, surface model, FIRST, the upper bound, peak and chronic EDWC values resulting from the use of penoxsulam on exposed sediment after drawdown are 18.2 ppb and 1.8 ppb, respectively.

The SCI-GROW, Tier I EDWC value for penoxsulam evaluated at the maximum annual application to turf is 12.0 ppb. The SCI-GROW, Tier I EDWC value for penoxsulam evaluated at the maximum single application to exposed sediment after drawdown is 23.3 ppb. While SCI-GROW was developed for estimating ground water concentrations resulting from agricultural uses, EFED currently has no other method for estimating ground water EDWCs from exposed sediments, and these results are expected to be adequately conservative. In the absence of an approved method for calculating ground water concentrations resulting from use of penoxsulam on submerged, floating or emergent aquatic vegetation EFED can only assume that ground water concentration would not exceed the maximum estimated peak surface water

concentration of 150 ppb. EFED expects that the actual concentration found in ground water from these aquatic uses will be less than 150 ppb.

The maximum penoxsulam value for surface and ground water used in this assessment, 150 ppb, is directly from the maximum target concentration listed on the proposed labels. EFED expects that the actual concentration found in surface and ground water from these aquatic uses will be less than 150 ppb. For the purposes of this risk assessment, the drinking water concentration of 150 ppb from the aquatic uses will be used for both acute and chronic dietary (food + water) exposure.

5.1.10 Food Residue Profile

Penoxsulam (XDE-638) is a sulfonamide herbicide currently registered on rice for the selective control of grasses, broadleaf, and sedge weeds. The herbicide's mode of action at the cellular level involves the inhibition of acetolactate synthase (ALS). Dow AgroSciences LLC has now submitted a Section 3 registration application for the end-use product GF-443 SC as an aquatic herbicide (PP#5F7012). Concurrently, the petitioner has requested an exemption from the requirement of a tolerance on fish and shellfish when penoxsulam is applied in aquatic areas. Tolerances for residues of penoxsulam are listed in 40 CFR §180.605. Tolerances of 0.02 and 0.50 ppm have been established for rice grain and straw, respectively. The tolerance expression is in terms of the parent herbicide, penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide].

GF-443 SC is a suspension concentrate formulation containing 21.7% (2 lb ai/gal) penoxsulam that may be applied in-water, as a foliar application, or as an exposed sediment application for pre-emergence control of aquatic weeds. GF-443 SC is now proposed for use as an aquatic herbicide at a rate up to 150 ppb (penoxsulam) in the water of lakes, ponds, canals, and reservoirs. Typical application rates of penoxsulam will be 10-20 ppb in an initial application with additional 'bump' applications of 5-10 ppb to keep the water concentration at 5-10 ppb for 45-90 days. There is a season maximum of all applications of 150 ppb. Although typical multiple application rates are proposed at 5-20 ppb, a single in-water application is allowed at up to the maximum rate of 150 ppb.

The nature of the residue in rice is adequately understood. Based on the submitted rice metabolism study, penoxsulam primarily degrades to its 5-OH metabolite (5-OH XDE-638) and to at least two minor unknown metabolites in rice matrices. Little translocation of penoxsulam residues or its metabolites into the grain was observed. The nature of the residue in rotational crops is also adequately understood. The reviewed confined rotational crop study showed that no quantifiable residues of penoxsulam or 5-OH XDE-638 are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops. The nature of the residue in animals is adequately understood. The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and is not significantly metabolized in either goats or poultry. The HED MARC has previously determined that for the tolerance expression and risk assessment, the residue of concern for penoxsulam in plants, rotational crops, and livestock (including poultry), is parent only.

The available analytical methodology, Method GRM 01.25, a high performance liquid chromatography with tandem mass spectroscopy-mass spectroscopy detector (LC/MS/MS) is considered to be adequate for the rice tolerance enforcement. The method that was used to collect data in the analysis of freshwater clam and catfish samples from the field accumulation study is a modification of LC/MS/MS Method GRM 05.08. Adequate method validation data, including data from an independent laboratory, were submitted for Method GRM 05.08 applied to bovine matrices and fish tissues. The limit of quantitation (LOQ) is 0.01 ppm, and the calculated limit of detection (LOD) was 0.003 ppm in tested bovine matrices and in fish tissue. Method GRM 05.08 is similar to Method GRM 01.25, using a reasonably similar extraction; therefore, including the ILV that was submitted, Method GRM 05.08 should also be appropriate for enforcement of tolerances for fish and shellfish. The FDA multiresidue protocol data show that penoxsulam is not adequately recovered using any of the protocol methods. The multiresidue data have been forwarded to FDA for further evaluation.

No supporting storage stability data were submitted to validate the storage conditions and intervals of samples taken from the magnitude of the residue study in freshwater clams and catfish. The samples could not have been stored for more than 1.6 months prior to residue analysis. Because samples were stored for a relatively short interval and because the Agency has also previously noted in the rice petition that comparative analysis of goat milk and tissue extracts show that residue profiles are similar after 135 and 300 days of sample collection, no additional supporting storage stability data are required.

A study investigating the nature and potential for bioaccumulation of penoxsulam residues in bluegill sunfish was submitted. Bluegill sunfish were exposed for 28 consecutive days to the radiolabeled test substance. Calculated bioconcentration factors, total radioactive residues (TRR) in tissue/TRR in water, were ≤ 0.10 , indicating that there is little potential for the test substance or its metabolites to bioaccumulate. Selected edible bluegill fish tissues were subjected to residue characterization/identification. In Day 7 fish samples, penoxsulam, 5-hydroxy penoxsulam, penoxsulam sulfonamide, and penoxsulam-BSTCA were identified. In Day 28 fish samples, only penoxsulam and 5-hydroxy penoxsulam were identified. However, these total characterized residues were 174% of TRR in day 7 fish and 235% of TRR in day 28 fish. No explanation was provided for this discrepancy; thus, HED review cannot classify this study as scientifically acceptable until a clarification of this discrepancy and/or confirmatory data are submitted. While the discrepancy leaves uncertain the proportion of the TRR represented by penoxsulam, the conclusions below are expected to be valid within the range of that uncertainty.

A study investigating the magnitude and potential for bioaccumulation of penoxsulam residues in freshwater clams and catfish was also submitted. The test organisms were exposed for 28 consecutive days to penoxsulam. Residues ranged up to 0.02 ppm in clams and up to 0.004 ppm in fish at 1x application rate. The bioconcentration factors (concentration in tissue/concentration in water) in all samples were ≤ 0.15 indicating that penoxsulam has very low potential to bioconcentrate in edible tissues of freshwater clams and catfish. Because concurrent recoveries and raw data were not submitted with this study, HED has classified it as scientifically acceptable pending submission of this supporting data.

A previously reported study also showed the TRR residues in crayfish during 14 days of exposure to 494 ppb penoxsulam in water, followed by 7 days of depuration. Maximum TRR in crayfish tail muscle occurred on day 11 of the treatment and was 14.4 ppb. On that basis it was concluded that no tolerance associated with the rice use was needed for crayfish (or crustaceans). Since the 10x concentration in paddy water of 45 ppb (0.5 ppm) from the rice use is ~3x the proposed annual 150 ppb (0.15 ppm) aquatic application rate, assuming linearity, at 1x the proposed maximum aquatic application rate the TRR in crayfish would thus be estimated at about $14.4 \text{ ppb} / 3 = 4.8 \text{ ppb}$ (0.005 ppm) and, if the linear extrapolation held the other way, at 10x the crayfish TRR would be around 48 ppb (0.05 ppm).

HED has reviewed the available data, and finds that it does not support the petitioner's request for tolerance exemptions on shellfish and finfish, resulting from the proposed aquatic uses. The studies show real residues of penoxsulam at both the 10X rate and the 1X rate. At 1x the application rate (0.15 mg ai/L) the maximum penoxsulam residues in catfish were 4.16 ppb (0.004 ppm) and in clams were up to 18.3 ppb (0.018 ppm). In bluegills at 1X, the maximum TRR were 11.4 ppb (0.0114 ppm). If these results are multiplied by 34% of the TRR to estimate penoxsulam, per se, the estimated concentration of parent only becomes about 3.9 ppb (0.004 ppm). Based upon the crustacean study using rice treatment rates, and assuming linearity, TRR in crayfish in water treated at 0.15 mg ai/L are estimated to be at about 4.8 ppb (0.005 ppm). At 10X (1.5 mg ai/L) the maximum application rate residues of penoxsulam were found in catfish up to 56 ppb (0.6 ppm) and in clams up to 141 ppb (0.14 ppm). Based upon the data as submitted, residues in bluegills at 10X were up to 39 ppb (0.04 ppm). As extrapolated from the rice field study, TRR in crayfish are expected to be up to up to 48 ppb (0.05 ppm). Tolerances are therefore required for fish. Based upon these studies the tolerance expression for fish should be penoxsulam, per se. A tolerance of penoxsulam residues on mollusc is tentatively recommended at 0.02 ppm; and a tolerance on finfish and crustacean (or crayfish) is tentatively recommended at 0.01 ppm.

In general, from the bluefish study, 5-hydroxy penoxsulam is present in penoxsulam residues at about 40% of the parent penoxsulam. Thus, residues of concern in fish (finfish, mollusc and crustacean) for risk assessment based upon these studies should be penoxsulam plus 5-hydroxy penoxsulam.

The petitioner is required to propose tolerances on fish and shellfish in a revised Section F. Based on the available residue data for freshwater clams and catfish treated at 0.15 mg ai/L, HED tentatively recommends tolerances of 0.02 ppm for mollusc, and 0.01 ppm for both fish and for crustaceans after a direct aquatic use. A registration using such tolerances will, of course, be dependent upon submission of required supporting information for the relevant studies. Based upon the reviewed studies the tolerance expression for fish should be penoxsulam, per se.

Conclusions: Additional confirmatory data/information must be submitted to upgrade the submitted sunfish study (MRID 46703506) to an acceptable status. Information is required regarding the chromatographic system (i.e., instrumentation and detection) and the LOD/LOQ of the methodologies used for identification/characterization of the residues. In addition, raw

data are required to support the reported characterization/identification of radioactive residues in the edible fish tissues. The petitioner must address the source of the discrepancy between recoveries of identified/characterized residues and TRR. The petitioner should consult OPPTS 860.1000 regarding the types of raw data required for this type of study submission.

Concurrent recoveries and raw data must also be submitted to support the catfish and clam study (MRID 46703507).

Because penoxsulam-treated water from lakes, ponds, canals, and reservoirs may unknowingly be used by a second party for irrigation of food/feed crops, the proposed use of GF-443 SC as an aquatic herbicide will also require magnitude of the residue data on crops that may potentially be irrigated, and certain such crops also will need processing data as appropriate. Technically, crops that may potentially be irrigated can include any U. S. grown crop and so selected crops for testing might need to include a representative crop from all crop groups.

HED's ChemSAC determined that some irrigation studies were needed to support direct use of penoxsulam on waterways because the treated water may be used on food crops. That information was conveyed to Dow. Dow responded with changes that they assert will preclude the need for irrigation studies. Dow proposed to remove treatment of irrigation canals from the label. The revised label would allow only treatment of lakes/ponds and potentially moving water, which would not be treated according to Dow because the product would not be effective in moving water (rivers and streams) and would be cost prohibitive as well. Dow asserts a label restricting use of the treated water for irrigation is practical because lakes and ponds can be effectively controlled by the user/applicator (e.g., through posting).

ChemSAC supported Dow's proposal to remove treatment of irrigation canals from the label. ChemSAC agreed that application of penoxsulam to lakes and ponds can be controlled through rigorous enforcement of Dow's proposed stewardship program. However, ChemSAC recommended that the registrant remove applications to slow moving rivers/streams from the label because applications to those water ways cannot be controlled and also because the use should not be needed if, as Dow asserts, treatment of these water is ineffective and uneconomical. ChemSAC also concluded that Dow's proposal to monitor treated lakes and ponds until concentrations are ≤ 1 ppb in any potential food-crop irrigation water using Enzyme-Linked ImmunoSorbant Assay (ELISA) analysis seems reasonable and that such limitation would provide an adequate basis to waive requirements for irrigated crop studies. In addition, the SAC recommended that the label be generalized to refer to "food/feed-crop irrigation water" rather than limited to food-crop irrigation water. ChemSAC concluded that it is reasonable to assume that the ELISA method proposed is reliable and a specific method validation is not required. Also, since it is not an enforcement method, an ILV is not required (ChemSAC 3/21/07).

5.1.11 International Residue Limits

There are no Codex, Canadian, or Mexican MRLs for penoxsulam; therefore, there are no international harmonization issues from this petition.

5.2 Dietary Exposure and Risk

5.2.1 Acute Dietary Exposure/Risk

There are no acute endpoints established for any population subgroup for exposure to penoxsulam; therefore, no acute dietary exposure assessment was conducted.

5.2.2 Chronic Dietary Exposure/Risk

HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID™ analyses estimate the dietary exposure of the US population and various population subgroups. The results reported in Table 5.2.3 are for the general U.S. population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and adults 50+ years old.

An unrefined (using tolerance-level residues and assuming 100% CT for all registered and proposed commodities), chronic dietary exposure assessment was conducted for the general U.S. population and various population subgroups. Drinking water was incorporated directly in the dietary assessment using the penoxsulam concentration as an aquatic herbicide in the water of lakes, ponds, canals, and reservoirs at 150 ppb. This assessment concludes that the acute dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (2% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is all infants (<1 year old), at 7% of the cPAD.

5.2.3 Cancer Dietary Risk

Penoxsulam was determined to be "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential;" therefore, a cancer dietary exposure assessment was not conducted.

Population Subgroup	Chronic Dietary		Cancer Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General US Population	0.003169	2	NA	
All Infants (<1 year old)	0.010380	7		
Children 1-2 years old	0.004708	3		
Children 3-5 years old	0.004407	3		
Children 6-12 years old	0.003040	2		
Youth 13-19 years old	0.002292	2		
Adults 20-49 years old	0.002959	2		
Adults 50+ years old	0.003112	2		

Population Subgroup	Chronic Dietary		Cancer Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
Females 13-49 years old	0.002946	2		

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

No %CT information was used in the penoxsulam dietary assessment.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. In the case of the proposed aquatic and turf scenarios, inhalation exposure is expected to be negligible and therefore only oral and dermal exposures will be considered for purposes of this assessment.

HED used the SWIMODEL from the Residential Standard Operating Procedures (SOPs) to assess dermal and oral exposure to recreational swimmers. Parameters used in calculating exposure and risk are based on information for competitive swimmers for both adults and children (6 years) in swimming pools which includes an exposure duration of 5 hours. Therefore, HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk (see characterization below) and therefore does not recommend that these MOEs be used when aggregating risk.

Residential exposure is considered to generally be short-term in duration; however, no short-term dermal endpoint was selected. Short-term exposure to adults during handling will include only an inhalation assessment. The only route of postapplication short-term exposure for turf to be aggregated for children is oral (hand-to-mouth, object-to-mouth, and ingestions of soil). The aggregate short-term MOE for adults and children were greater than the level of concern (Total MOE > 100) and therefore were not of concern to HED.

Since postapplication inhalation exposure is anticipated to be negligible and based on information which indicates that the amount of residues remaining on the turf after 30 days would be negligible, HED does not expect intermediate-term dermal exposure to result from application of penoxsulam to turf. No intermediate-term aggregate exposure assessment to turf is required.

6.1 Residential (Homeowner) Handler

6.1.1 Residential Handler Exposure to Turf

The Agency uses the term “Handlers” to describe those individuals who are involved in the pesticide application process. Four penoxsulam turf products (i.e., Penoxsulam GR 0.04%, Penoxsulam GR 0.014%, Penoxsulam FERT 0.04% granule, and Penoxsulam FERT 0.014% granule) can be applied by home owners. These granular products are to be applied using a drop or push rotary-type spreader, whirlybirds, cyclones and or shaker type applicators. The following use scenarios were used to assess handler exposure:

1. mixer/loader/applicator for push-type granular spreader using PHED
2. mixer/loader/applicator for low pressure hand wand and backpack sprayer using PHED
3. mixer/loader applicator for ORETF Granular Push Spreader

6.1.2 Turf Data and Assumptions

Unit Exposures: No chemical specific unit exposure data was provided in support of this submission; therefore, Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Guide and the Outdoor Residential Exposure Task Force (OREFT) study (MRID 44972201) unit exposures were used to estimate handler exposure.

Acres Treated: Information regarding area treated for the various use scenarios was provided by the registrant.

- 1000 ft² per day by low pressure hand wand or back pack sprayer for spot treatment of lawns,
- 0.5 acres per day by push-type granular spreader for broadcast treatment of lawns

Application Rate and Amount Handled:

- 0.06 lb ai per acre for broadcast treatment
- 0.0014 to 0.0016 lbs ai per 1000 ft² for spot treatment

Exposure Duration: Based on information provided in the proposed labels handler exposure is anticipated to be short-term in duration. The proposed labels indicate that, “additional applications should not be made within four weeks of a previous application.” Therefore, neither intermediate- nor long-term exposure to turf handlers is expected and was not assessed.

Body Weight: The average male body weight of 70 kilograms was used to assess handler exposure.

6.1.3 Turf Handler Exposure and Risk

HED’s level of concern for non-cancer risks (i.e., MOE) for penoxsulam is 100 for residential exposure. Since a short-term dermal point was not selected, the only route of exposure to be addressed is inhalation. Handler inhalation MOEs were significantly greater than 100 and therefore not of concern to HED. Short-term inhalation exposure for residential handlers is summarized in Table 6.1.3.

Turf Exposure Scenarios	Use Site	Mitigation Level	Inhalation Unit	Application Rate ^b	Area Treated	Inhalation Dose ^c	MOE ^d
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			Exposure (mg/lb) ^a	(lb ai/acre)	(A/day)	(mg/kg/day)	
Mixer/loader/Applicator							
ORETF Resident-applicator Granular Push Spreader	lawns		0.00078	0.06 lb ai/A	0.5	0.00000033	54,000,000
PHED Low Pressure handwand and Backpack			0.03	0.0016 lb ai/1000ft ²	1000ft ²	0.000686	26,000
PHED "Push-type" Granular Spreader			0.0063	0.06 lb ai/A	0.5	0.0000027	660,000

a. Inhalation Unit Exposure derived from PHED Version 1.1 and ORETF Handler Exposure Study MRID 44972201

b. Application Rate based on proposed labels

c. Inhalation Dose = Unit Exposure (mg/lb) x Application Rate (lb ai/day) x Area Treated/BW

d. Inhalation MOE = NOAEL (17.8 mg/kg/day) / Inhalation Dose

6.2 Residential (Homeowner) Postapplication

There is a potential for postapplication exposure from oral and dermal routes of exposure while swimming in aquatic and/or turf (lawns, golf courses, sports fields, and sod farms) sites treated with penoxsulam. The duration of exposure is expected to be of short- and/or intermediate-term in duration.

6.2.1 Postapplication Swimmer Exposure Scenario

6.2.1.1 Data and Assumptions

The following data, assumptions and calculations were used to assess post application exposure as a result of recreational swimming in aquatic sites treated with penoxsulam.

Data and Assumptions:

- Since penoxsulam is to be applied outdoors and its vapor pressure is very low (7.2 x 10⁻¹⁶ mmHg) inhalation exposure is expected to be negligible. Therefore inhalation exposure is not of concern.
- Standard Operating Procedures (SOPs) for Residential Exposure were used to assess oral, and dermal post application exposure to recreational swimmers.
- 100 percent (100%) of the application concentration is available in the water for dermal contact and oral ingestion. For purposes of this assessment the maximum concentration is 150 ppb in accordance with label restrictions.
- Assumed surface area is 20,900 cm² for adults and 9,000 cm² for children (age 6 years)
- Duration of exposure is assumed to be 5 hours a day for both adults (18-64 years) and children (6 years). This duration is based on the 90th percentile value for time spent at home in a swimming pool from the 1996 Exposure Factors Handbook.
- Mean ingestion rate for adult and children swimmers is 0.05 L/hour.

- Average body weight is 70 kg for adult male and 22 kg for 6 year old child.
- Penoxsulam permeability coefficient is 8×10^{-7} cm/hr.
- Galleon™ SC may be applied either directly to water using hoses or as a foliar application to post-emerged vegetation. For “in water” applications, the maximum sum of all applications is 150 ppb per annual growth cycle or a single maximum application rate of 150 ppb. For each ppb of penoxsulam, the label indicates that 0.174 fluid ounces of active ingredient should be applied per acre foot of treated water results in a concentration of 1 ppb, or:

$$1 \text{ ppb penoxsulam} = \frac{0.174 \text{ fl oz Galleon}}{\text{A/ft}}$$

Therefore, using that ratio, a concentration of 150 ppb would require 26.1 fluid ounces of product, or:

$$150 \text{ ppb penoxsulam} = \frac{26.1 \text{ fl oz Galleon}}{\text{A/ft}}$$

The Galleon™ SC label features instructions for depths of up to 10 feet, which is a typical depth most of the water bodies to be targeted for treatment with this EUP. The maximum application rate (in lb ai/A units) to reach a concentration of 150 ppb in a 10 foot body of water would be:

$$\frac{26.1 \text{ fl oz Galleon}}{\text{A-ft}} \times \frac{1 \text{ gal. Galleon.}}{128 \text{ fl oz Galleon}} \times \frac{2 \text{ lb ai}}{\text{gal Galleon}} \times 10 \text{ ft} = 4.1 \text{ lb ai/A}$$

- For “foliar applications post emergent”, Galleon™ SC is applied at the rate of 2.0 to 5.6 fl oz per acre (0.03125 to 0.0875 lb ai/A).
- For purposes of assessing residential exposure “in water” application was determined to be the worst case scenario (i.e. greatest application rate), and was therefore used to estimate exposure to swimmers.

Calculations:

The following calculations and equations were used to determine oral and dermal exposure as a result of swimming in aquatic areas treated with penoxsulam.

$$\text{Incidental Ingestion Dose} = \frac{C_w \times \text{IgR} \times \text{ET}}{\text{BW}}$$

Where:

C_w = concentration in water (150 ppb = 0.15 mg/L)

IgR = ingestion rate of water (0.05 L/hr)

ET = exposure time (5 hr/day)

BW = body weight (kg)

$$\text{Dermal Dose} = \frac{C_w \times \text{SA} \times \text{ET} \times K_p \times \text{CF}}{\text{BW}}$$

Where:

C_w = concentration in water (150 ppb = 0.15 mg/L)

SA = surface area exposed (cm²)
 ET = exposure time (5 hr/day)
 Kp = permeability coefficient (8 x 10⁻⁷ cm/hr)
 CF = unit conversion factor (L/1000 cm³)
 BW = body weight (kg)

Permeability coefficient (Kp) is chemical specific estimated using the following equation:

$$\text{Log Kp} = -2.72 + 0.71 \log k_{ow} - 0.0061 \text{ MW}$$

Where:

Kp = permeability coefficient (1.5 x 10⁻⁶ x 50% DA = 8.0 x 10⁻⁷ cm/hr)
 Log k_{ow} = octanol-water partition coefficient (-0.6 at pH of 7), and
 MW = molecular weight (438.38)

$$\text{MOE} = \frac{\text{NOAEL (17.8 mg/kg/day)}}{\text{Dose (mg/kg/day)}}$$

6.2.1.2 Exposure and Risk Estimates for Swimmers

The above factors were used in the SWIMODEL formulas for dermal and ingestion exposure. The SWIMODEL formulas for the other dermal pathways (aural, buccal/sublingual and orbital/nasal) were not used because these formulas are based upon recreational swimmers in swimming pools who swim with their heads partially immersed. It is anticipated that recreational swimmers in weed infested areas would be less likely to swim with their heads immersed than recreational swimmers in weed-free swimming pools. In addition, the formulas for the buccal/sublingual and orbital/nasal pathways contain a default absorption factor of 0.01 which is based upon the absorption of nitroglycerin. This factor would greatly overestimate the risk of penoxsulam exposure because penoxsulam is absorbed at a much lower rate.

Since the short-term postapplication assessment needs to address only oral exposure which results in the same estimated dose for intermediate-term exposure, a short-term aggregate exposure was not required. The intermediate-term postapplication exposure assessment combined oral and dermal exposures and is protective for short-term exposure. Short- and intermediate-term postapplication exposures resulted in MOEs > 100 and were therefore not of concern to HED. A summary of the short- and intermediate-term postapplication exposures for adults and children is provided in Table 6.2.1.2.

Characterization of Risk and Exposure

Duration of exposure is assumed to be 5 hours a day for competitive swimmers both adult (18-64 years) and children (6 years) in swimming pools. This duration is based on the 90th percentile value for time spent at home in a swimming pool from the 1996 Exposure Factors Handbook. HED considers this exposure period very conservative for recreational swimmers in weed infested ponds and lakes. Furthermore, the oral route of exposure is the main driver. A mean ingestion rate of 0.05 L/hour for adults and children was used to assess oral MOEs. This ingestion rate is based on HED's swimmer model typically used to assess competitive swimmers in pools who tend to swim with their heads partially immersed in the water and can ingest larger amounts of water. It is anticipated that recreational swimmers in weed infested waters would not immerse their heads as often and therefore would ingest smaller amounts of

water. Therefore HED concludes that the dermal and oral MOEs are over estimates of the actual risk.

HED considers the swimmer dermal and oral margins of exposure to be over estimates of the actual risk and therefore does not recommend that these MOEs be used when aggregating risk with food and drinking water.

Table 6.2.1.2: Short and Intermediate-Term Postapplication Exposure for Adults and Children Swimmers to Penoxulam

Exposure Scenarios	Cw ^a (mg/L)	IgR ^b (L/hr)	ET ^c (hr/day)	SA ^d (cm ²)	Kp ^e (cm/hr)	CF ^f (L/cm ³)	BW ^g (kg)	Oral Dose ^h (mg/kg/day)	Dermal Dose ⁱ (mg/kg/day)	Adult Total Dose ^j	Child Total Dose ^k	Adult Total MOE ^l	Child Total MOE ^m
Oral	0.15	0.05	5	NA	NA	NA	70	3.3 x 10 ⁻⁴	NA	3.3 x 10 ⁻⁴	1.1 x 10 ⁻⁴	21,000	33,000
Dermal	0.15	NA	NA	20,900	8E-7	L/1000	70	NA	1.8 x 10 ⁻⁷	1.8 x 10 ⁻⁷	2.5 x 10 ⁻⁷	21,000	33,000
				9,000			22						

- a. Cw = concentration in water (150 ppm = 0.15 mg/L)
- b. IgR = ingestion rate of water (0.05 L/hr)
- c. ET = exposure time (5 hr/day)
- d. SA = surface area exposed (cm²)
- e. Kp = permeability coefficient (8 x 10⁻⁷ cm/hr)
- f. CF = unit conversion factor (L/1000 cm³)
- g. BW = body weight = 70 kg for adults and 22 kg for children
- h. Oral Dose = $\frac{C_w \times IgR \times ET}{BW}$
- i. Dermal Dose = $\frac{C_w \times SA \times ET \times K_p \times CF}{BW}$
- j. Adult Total Dose (mg/kg/day) = Adult oral dose + Adult dermal dose
- k. Adult Total MOE = NOAEL (17.8 mg/kg/day)/Adult Total Dose (mg/kg/day)
- l. Child Total Dose (mg/kg/day) = Child oral dose + Child dermal dose
- m. Child Total MOE = NOAEL (17.8 mg/kg/day)/Child Total Dose (mg/kg/day)

6.2.2 Postapplication Dermal Exposure on Treated Turf

Postapplication dermal exposure resulting from contact with treated turf was assessed using a chemical specific turf transfer residue (TTR) study (MRID 46703508).

6.2.2.1 Data and Assumptions

Data:

Determination of Transferable Residue on Turf Treated with Penoxsulam; Robert, D.W. and G.E. Schelle; 2005; MRID 45013501.

This study was designed to characterize dissipation of penoxsulam transferable turf residues when applied to turf at 2 test sites in Georgia and Florida. GF-443 SC, formulated as a suspension concentrate containing 21.4% penoxsulam as the active ingredient, was applied once to each site using a tractor-mounted boom sprayer. (Note: The Study Report states the percent active ingredient is 21.4%; however, on the product label the percent active ingredient is stated to be 21.7%). Each application was made at a target application rate of 100 g ai/hectare (0.09 lb ai/A). The application method and application rate were relevant to the use pattern proposed; however, the application rate used in the study was higher than the maximum recommended application rate in the proposed label (0.06 lb ai/A). Transferable turf residues (TTR) were collected using the modified California Roller Technique. All untreated control samples were collected at each site prior to application of the test product. Each field site consisted of three replicate plots, each containing subplots for sampling.

The maximum average penoxsulam residues occurred immediately following the application at each site. At the Georgia site, the maximum average penoxsulam residue was 0.043 $\mu\text{g}/\text{cm}^2$, or 4.3% of the applied active ingredient. At the Florida site, the maximum average penoxsulam residue was 0.0068 $\mu\text{g}/\text{cm}^2$, or 0.7% of the applied active ingredient. A linear regression analysis using the natural logarithm of the individual TTR values was conducted. Residue data was collected after the application through the first day where all the TTR values were <LOQ (DAT 7 for both sites). The raw TTR values for field recoveries were not corrected, since the overall field recoveries were >90% for both sites. For values > LOD and <LOQ, HED used a value of $\frac{1}{2}$ the LOQ. For values < LOD, HED used a value of $\frac{1}{2}$ the LOD. It appears that the Registrant used the average residue data from only the sampling times when residues were greater than the LOD (DAT 7 for the Georgia site and DAT 4 for the Florida site). The Registrant corrected the raw TTR values using the average analytical set recovery values, all of which were >90%. It is not known if the Registrant used the LOQ value or $\frac{1}{2}$ LOQ in their calculations. The estimated half-life values were 1.3 days ($R^2=0.8217$) and 1.5 days ($R^2=0.9403$) for penoxsulam residues at the Georgia and Florida site, respectively.

The Registrant provided the residues in $\mu\text{g}/\text{cm}^2$ for the triplicate cloth dosimeter samples collected at each sampling interval. The cloth dosimeter penoxsulam residue levels and corresponding statistical summaries are shown in Tables 1 and 2. At the Georgia site, the average penoxsulam residues immediately following the application were 0.043 $\mu\text{g}/\text{cm}^2$, or

4.3% and at the Florida site, the average penoxsulam residues immediately following the application were 0.007 µg/cm², or 0.68% of the applied active ingredient (maximum average).

Table 6.2.2.1.a Penoxsulam Residues from Cloth Dosimeters – Georgia Site

Sampling Interval (Days After Last Treatment)	Residue (µg sample)	Residue (µg/cm ²)	Arithmetic Mean (µg/cm ²)	Standard Deviation (µg/cm ²)	Coefficient of Variance (%)	Geometric Mean (µg/cm ²)	% of Original Application Rate Transferred
0	337.7667	0.0606	0.0427	0.0157	36.8	0.0410	4.2995
	203.7761	0.0366					
	173.1338	0.0311					
	<LOQ	<LOQ					
	ND	ND					

LOD = 0.00036 µg/cm²
 LOQ = 0.00108 µg/cm²
 Actual Application Rate = 0.994 µg/cm²

Table 6.2.2.1.b Penoxsulam Residues from Cloth Dosimeters – Florida Site

Sampling Interval (Days After Last Treatment)	Residue (µg sample)	Residue (µg/cm ²)	Arithmetic Mean (µg/cm ²)	Standard Deviation (µg/cm ²)	Coefficient of Variance (%)	Geometric Mean (µg/cm ²)	% of Original Application Rate Transferred
0	42.2745	0.0076	0.0068	0.0007	10.7	0.0068	0.6818
	34.3044	0.0062					
	36.9867	0.0066					

LOD = 0.00036 µg/cm²
 LOQ = 0.00108 µg/cm²
 Actual Application Rate = 0.996 µg/cm²

- Postapplication must be assessed on the same day the pesticide is applied since it is assumed that homeowner could be exposed to turfgrass immediately after application. Therefore, exposures are based on day 0.
- The application rate used in the study (0.09 lb ai/A) was higher than the maximum recommended application rate in the proposed label (0.06 lb ai/A).

6.2.2.2 Dermal and Inhalation Postapplication Exposure and Risk Estimates to Turf

Since penoxsulam is applied outdoors inhalation postapplication exposure is expected to be negligible. HED does anticipate short-term dermal exposure to individuals entering turf areas treated with penoxsulam. However, a short-term dermal exposure endpoint was not determined since no dermal, systemic, neurological or developmental toxicity concerns were identified at the highest dose tested. An intermediate-term dermal exposure NOAEL of 17.8 mg/kg/day was selected based on multifocal hyperplasia of the pelvic epithelium of the kidney from a 1-year chronic feeding study in the dog.

Based on the following information: (1) proposed turf labels state that additional applications should not be made within four weeks of a previous application; (2) the average penoxsulam

residues dropped below the LOQ by DAT 7 (7 days after treatment) at both sites (Georgia and Florida) in the chemical specific TTR study; and (3) the estimated half-life values for penoxsulam residues at the Georgia and Florida sites ranged from 1.3 to 1.5 days, respectively; HED considers intermediate-term dermal exposure to be negligible.

6.2.3 Oral Postapplication Exposure

6.2.3.1 Non-dietary Ingestion (Hand-to-Mouth) Exposure from Treated Turf

Postapplication hand-to-mouth exposure was assessed using the SOP for Residential Exposure: 1.3.2. This SOP provides a method for estimating potential dose among toddlers from incidental ingestion of pesticide residues from previously treated turf. This scenario assumes that pesticide residues are transferred to the skin of toddlers playing on treated yards and subsequently ingested as a result of hand-to-mouth transfer.

Penoxsulam turf products formulated as both liquid and granules are applied as broadcast and spot treatment. For purposes of this assessment, broadcast application rates were considered to represent the worst case scenarios and therefore used in assessing oral exposure.

6.2.3.1.1 Data and Assumptions

Assumptions:

- On the day of application, it may be assumed that 5% of the application rate is available on turfgrass.
- Postapplication activities must be assessed on the same day that the pesticide is applied
- The median surface area of both hands is 20 cm² for children. This value is based on the February 1999 recommendation from the Scientific Advisory Panel (SAP).
- It is assumed that there is a one-to-one relationship between the transferable residues on the turf and on the surface area of the skin after contact.
- The mean rate of hand-to-mouth activity is 20 times/hour for short-term exposure scenarios. This value was provided by the 1999 SAP.
- Duration of exposure for children is assumed to be 2 hours per day for turf and 4 to 8 hours for indoor surfaces.
- The saliva extraction factor is 50%.
- Children are assumed to weigh 15 kg.

Equations, Calculations, and Risks:

$$TTR_0 = AR \times F \times (1-D)^0 \times CF2 \times CF3$$

- AR = application rate (lb ai/ft² or lb ai/A or mg ai)
 F = fraction of ai available on turf (unitless)
 D = fraction of residue that dissipates daily (unitless)
 0 = postapplication day on which exposure is being assessed
 CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for DFR value (4.54E⁸ ug/lb)
 CF3 = area unit conversion factor to convert the surface area units (ft²) in the application rate to cm² for the DFR value (1.08E⁻³ ft² /cm² or 2.47E⁻⁸ A/cm²)
 DFR = Dislodge able Foliar Residue

$$PDR = \frac{TTR_0 \times SA \times FQ \times ET \times SE \times CF1}{BW}$$

- PDR = potential dose rate on day "0" (mg/day)
 DFR0 = dislodgeable foliar residue on day 0 (ug/cm² turf)
 SA = surface area of the hands (cm²/event)
 FQ = frequency of hand-to-mouth activity (20 events/hr for short-term and 9.5 events/hr for intermediate-term), Reed et al 1999
 ET = exposure time (hr/day)
 CF1 = weight unit conversion factor to convert ug units in the DFR value to mg for the daily exposure (0.001 mg/ug for turf)
 SE = Saliva Extraction Factor (50%)
 BW = 15 kg

$$\text{Short-term Oral MOE} = \text{NOAEL (17.8 mg/kg/day)} \div \text{PDR}$$

6.2.3.1.2 Hand-To-Mouth Risk and Exposure

A total UF of 100 has been applied to all residential risk assessments HED's level of concern for risks (i.e., MOE) for penoxsulam is 100 for residential exposure. All hand-to-mouth MOEs were greater than 100. Residential exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. Table 6.2.3.1.2 summarizes the short- and intermediate-term MOEs for hand-to-mouth transfer of pesticide residues from broadcast lawn use.

Table 6.2.3.1.2 Post Application Oral Exposure from Hand-to-Mouth Activity on Penoxsulam Treated Turf

Data Source	Turf Transfer Residue ¹ (ug/cm ²)	Application Rate ² (lb ai/A)	Percent ai dislodgable	Surface Area (cm ²)	Hand to Mouth (events/hr)	Extraction by Saliva	Exposure Time (hours)	Body Weight (kg)	Daily Dose ³ (mg/kg/day)	MOE ⁴
HED Default	3.33E-2 ^a	0.06	5%	20	20	50%	2	15	8.88E-4	20,000
Georgia TTR	1.05E-2 ^b		NA						2.79E-4	64,000
Florida TTR	5.1E-3 ^b								1.36E-4	130,000

1a. Turf Transfer Residue (ug/cm²) = AR x F x (1-D)⁰ x 4.54E⁸ ug/lb x 2.47E⁻⁸ A/cm²
 1b. Determination of Transferable Residue on Turf Treated with Penoxsulam; Robert, D.W. and G.E. Schelle, 2005; MRID 45013501

2. Maximum application rate for turf use in accordance with proposed label

3. Oral Dose (mg/kg/day) = $\frac{AR (lb ai/A) \times F \times SA (cm^2) \times EXT \times EQ (events/hr) \times ET (mins/day) \times CF (0.001 mg/ug)}{BW (15kg)}$

4. Oral MOE = NOAEL (17.8 mg/kg/day) / Oral Dose (mg/kg/day)

6.2.3.2 Ingestion of Pesticide-Treated Turfgrass (Object-to-Mouth)

This scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The SOP 2.3.3, Postapplication Potential Dose Among Toddlers from the Ingestion of Pesticide-Treated Turfgrass, estimates doses among toddlers from incidental ingestion of residential turfgrass that has been previously treated with pesticides. This scenario assumes that turf is ingested by toddlers who play on treated areas.

6.2.3.2.1 Data and Assumptions

Assumptions and Factors

- on the day of application it may be assumed that 20% of the application rate is available to be ingested
- postapplication exposure is assessed on the same day pesticide is applied
- assumed ingestion rate for grass for children (3 years old) is 25 cm²/day
- children are assumed to weigh 15 kg

Equations and Calculations

$$GR_0 = AR \times F \times (1-D)^0 \times CF2 \times CF3$$

GR ₀	=	grass residue on day 0 (ug/cm ²)
AR	=	application rate (lb ai/A)
F	=	fraction of ai available on the grass (unitless)
D	=	fraction of residue that dissipates daily (unitless)
0	=	postapplication day on which exposure is being assessed
CF2	=	weight unit conversion factor to convert the lbs ai in the application rate to µg for grass residue value (4.54E8 µg/lb)
CF3	=	area unit conversion factor to convert surface area units (A) in the application rate to cm ² for grass residue value (2.47E-8 A/cm ²)

$$PDD = GR_0 \times IgR \times CF1$$

PDD	=	potential daily dose on day 0
GR ₀	=	grass residue on day 0 (ug/cm ²)
IgR	=	ingestion rate of grass (cm ² /day)
CF1	=	weight unit conversion factor to convert the µg of residues on the grass to mg to provide units of mg/day (1E-3 mg/µg)

$$\text{Short- and Intermediate-term Oral MOE} = \text{NOAEL (17.8 mg/kg/day)} \div \text{PDD}$$

6.2.3.2.2 Risk and Exposure

HED's level of concern for risks (i.e., MOE) for penoxsulam is 100 for residential exposure. The short and intermediate term object-to-mouth MOEs are greater than 100 and therefore are not of concern to HED. Table 6.2.3.2.2 summarizes the short- and intermediate-term object-to-mouth MOE for pesticide ingestion of treated turfgrass.

Scenario	AR (lb ai/A)	F	CF2 (ug/lb)	CF3 (A/cm2)	GR ₀ ^a (ug/cm2)	IgR (cm ² /day)	CF1 (mg/ug)	PDD ^b (mg/kg/day)	MOE ^c
GF-443 SC EPA Reg No. 62719-1.11A HED Default TTR	.06	0.2	4.54E8	2.47E-8	1.33E-1	25	0.001	2.22E-4	80,000
Georgia TTR		NA			1.05E-2			1.74E-5	1.02E6
Florida TTR					5.1E-3			8.5E-6	2.09E6

- a. $GR_0 = AR \times F \times (1-D)^0 \times CF2 \times CF3$
- b. $PDD = GR_0 \times IgR \times CF1 \div BW$
- c. $MOE = NOAEL (17.8 \text{ mg/kg/day}) / PDD$

6.2.3.3 Incidental Ingestion of Soil

This scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). The SOP 2.3.4, Postapplication Potential Dose Among Toddlers from Incidental Ingestion of Soil from Pesticide-Treated Residential Areas, estimates doses among toddlers from incidental ingestion of soil containing pesticide residues. This scenario assumes pesticide residues in soil are ingested by toddlers who play on treated areas as a result of normal mouthing activities.

6.2.3.3.1 Data and Assumptions

Assumptions and Factors

- on the day of application, it is assumed that 100% of the application rate is located within the soil's uppermost 1 cm;
- postapplication must be assessed on the same day the pesticide is applied;
- assumed soil ingestion rate for children is 100 mg/day;
- children are assumed to weigh 15 kg.

Equations, Calculations and Risks

$$SR_0 = AR \times F \times (1-D)^0 \times CF2 \times CF3 \times CF4$$

SR₀ = soil residue on day 0 (ug/g)
 AR = application rate (lb ai/A)

- F = fraction of ai available in uppermost cm of soil (1 cm)
- D = fraction of residue that dissipates daily (unitless)
- 0 = postapplication day on which exposure is being assessed
- CF2 = weight unit conversion factor to convert the lbs ai in the application rate to µg for soil residue value (4.54E8 µg/lb)
- CF3 = area unit conversion factor to convert surface area units (A) in the application rate to cm² for soil residue value (2.47E-8 A/cm²)
- CF4 = volume to weight unit conversion factor to convert the volume units (cm³) to weight units for the SR value (0.67 cm³/g soil)

$$PDD = SR_0 \times IgR \times CF1$$

- PDD = potential daily dose on day 0
- SR₀ = soil residue on day 0 (ug/g)
- IgR = ingestion rate of soil (mg/day)
- CF1 = weight unit conversion factor to convert the µg of residues on the soil to mg to provide units of mg/day (1E-6 g/µg)

$$Short- and Intermediate-term Oral MOE = NOAEL (17.8 mg/kg/day) \div PDD$$

6.2.3.3.2 Exposure and Risk

HED's level of concern for non-cancer risks (i.e., MOE) for penoxsulam is 100 for residential exposure. The short and intermediate term oral MOEs are greater than 100 and therefore are not of concern. Table 6.2.3.3.2 summarizes the short- and intermediate-term MOEs for incidental ingestion of soil by children.

Scenario	AR (lb ai/A)	F (cm)	CF2 (ug/lb)	CF3 (A/cm ²)	CF4 (cm ³ /g)	SR ₀ ^a (ug/g)	IgR (mg/day)	CF1 (mg/ug)	PDD ^b (mg/kg/day)	MOE ^c		
GF-443 SC EPA Reg No. 62719-LUA HED Default TTR	0.06	1	4.54E8	2.47E-8	0.67	4.51E-1	100	1.00E-6	3.01E-6	5.92E6		
Georgia TTR						1.05E-2					7.00E-8	2.54E8
Florida TTR						5.1E-3					3.4E-8	5.24E8

a. $SR_0 = AR \times F \times (1-D)^0 \times CF2 \times CF3 \times CF4$

b. $PDD = SR_0 \times IgR \times CF1 \div BW$

c. $MOE = NOAEL (1 mg/kg/day) \div PDD$

6.2.3.4 Episodic Incidental Ingestion of Granules

There are four proposed penoxsulam turf products formulated as granules (Penoxsulam FERT 0.04%, Penoxsulam FERT 0.014%, Penoxsulam GR 0.014% and Penoxsulam GR 0.04%). These products are applied using a drop or rotary-type spreader designed to apply granular herbicides turfgrass, lawns, recreational areas and golf courses. Although HED believe there is potential for incidental ingestion of pesticide applied to lawns no acute dietary endpoint attributable to a single exposure was identified in the available toxicology studies on

penoxsulam. Therefore, an episodic incidental ingestion of granules assessment was not performed.

6.3 Residential Aggregate Margins of Exposures for Aquatic and Turf Use

6.3.1 Short- and Intermediate term Aggregate Exposure for Swimmer

Since no short-term dermal endpoint was selected, and inhalation postapplication exposure is expected to be negligible, the only route of exposure is oral. The aggregate intermediate-term exposure assessment combined oral and dermal exposures and is protective for short-term exposure. The aggregate MOEs for adults and children swimmers were greater than 100 and therefore were not of concern to HED. A summary of the short- and intermediate-term swimmer aggregate exposure and risk is provided in Table 6.3.1.

Population	Oral Dose	Dermal Dose	Total MOE ^a
Adults	5.4E-4	1.8E-7	33,000
Children (6 yrs old)	1.7E-3	2.5E-7	10,000

$$a. \text{Total MOE} = \frac{\text{NOAEL (17.8 g/kg/day)}}{\text{Dose}_{\text{oral}} + \text{Dose}_{\text{dermal}}}$$

HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk and therefore does not recommend that these MOEs be used when aggregating risk.

6.3.2 Short- and Intermediate-Term Aggregate Exposure to Turf

Postapplication inhalation exposure is anticipated to be negligible and no short-term dermal endpoint was selected. As a result, the only residential exposure of concern for adults is inhalation exposure during turf application (worst case MOE of 26,000) and the only route of postapplication exposure to turf to be aggregated for children is oral (hand-to-mouth, object-to-mouth, and ingestions of soil). A summary of the turf residential aggregate exposure is provided in Table 6.3.2. The aggregate MOEs for children and adults were greater than 100 and therefore were not of concern to HED.

Population Data Source	Inhalation (mg/kg/day)	Hand-to-Mouth (mg/kg/day)	Object-to-mouth (mg/kg/day)	Soil Ingestion (mg/kg/day)	Total Dose (mg/kg/day)	Total MOE ^a
Adult	0.000686	NA	NA	NA	0.000686	26,000
Children – HED Default	NA	8.88E-4	2.22E-4	3.01E-6	0.001	18,000
Children – Georgia TTR	NA	2.79E-4	1.74E-5	7.0E-8	0.00029	61,000
Children – Florida TTR	NA	1.36E-4	8.5E-6	3.4E-8	0.000145	120,000

$$a. \text{Total MOE} = \frac{\text{NOAEL (17.8 g/kg/day)}}{\text{Dose}_{\text{inhalation}} + \text{Dose}_{\text{hand-to-mouth}} + \text{Dose}_{\text{object-to-mouth}} + \text{Dose}_{\text{soil ingestion}}}$$

Since postapplication inhalation exposure is anticipated to be negligible and based on information provided in the penoxsulam TTR study which indicates that the amount of residues remaining on the turf after 30 days would be negligible, HED does not expect intermediate-

term dermal exposure to result from application of penoxsulam to turf. No intermediate-term aggregate exposure assessment to turf is required.

6.4 Other (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for penoxsulam. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, ARIA must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, ARIA considers both the route and duration of exposure. In the case of penoxsulam, an acute aggregate (food + drinking water) was not conducted because no acute endpoint was determined for penoxsulam. Since HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk and does not recommend that these MOEs be used when aggregating risk, postapplication inhalation exposure is anticipated to be negligible, and no short-term dermal endpoint was selected, only the short- and intermediate-term residential exposure from oral (hand-to-mouth, object-to-mouth, and ingestions of soil) exposure was included with food and drinking water in the short- and intermediate-term aggregate risk assessments. For the chronic aggregate risk assessment, no chronic residential exposures are expected; therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only. A cancer aggregate risk assessment was not performed because penoxsulam has not been determined to be carcinogenic. All potential exposure pathways were assessed in the aggregate risk assessment.

7.1 Acute Aggregate Risk

Penoxsulam was classified by the HED CARC as Suggestive in 2004. There is some cancer concern but the data are judged not sufficient for a stronger conclusion or a quantitative cancer risk assessment. No acute aggregate risk assessment was conducted since an acute exposure endpoint was not determined for penoxsulam.

7.2 Short-Term Aggregate Risk

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to penoxsulam residues from food, drinking water, and residential pesticide uses. High-end estimates of the residential exposure are used in the short-term assessment, and average values are used for food and drinking water exposures. Penoxsulam common toxicological effects were selected for assessment of short-term exposures by oral and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure duration should include oral and inhalation exposures appropriate to the populations of concern. Short-term dermal exposure need not be aggregated because no toxicological endpoint was selected.

For adults, short-term exposure to penoxsulam can occur as a result of the residential use on turf. Because oral exposure from the residential use as a handler is not expected in adults and no short-term dermal endpoint was selected, only the short-term residential exposure by inhalation is expected in adults. The short-term residential exposure potential from turf can be found in Table 6.1.3. The worst-case MOE of 26,000 was aggregated with the chronic dietary (food + water) to provide a worst-case estimate of short-term aggregate risk for U.S. population (see Table 5.2.3). As the aggregate MOE is greater than 100, the short-term aggregate risk to adults does not exceed HED's level of concern.

For children/toddlers adults, short-term exposure to penoxsulam can occur as a result of the residential use on turf. Because postapplication inhalation exposure is anticipated to be negligible and no short-term dermal endpoint was selected, only the short-term residential exposure from oral (hand-to-mouth, object-to-mouth, and ingestions of soil) exposure was included with food and drinking water in the short-term aggregate risk assessment for children/toddlers. The aggregate short-term residential exposure potential from the turf uses for children/toddlers can be found in Table 6.3.2. The HED-default scenario resulted in the worst-case MOE for children (MOE = 16,000; post-application) which was aggregated with the chronic dietary (food + water) to provide a worst-case estimate of short-term aggregate risk for all infants (<1 year old), the child population subgroup with the highest estimated chronic dietary food exposure (see Table 5.2.3). As the aggregate MOE is greater than 100, the short-term aggregate risks to children do not exceed HED's level of concern.

Population Subgroups	Short-Term Scenario					
	NOAEL (mg/kg/day)	Level of Concern	Max Exposure ² (mg/kg/day)	Average Dietary Exposure (mg/kg/day)	Residential Exposure ³ (mg/kg/day)	Aggregate MOE (dietary and residential) ⁴
US Pop.	17.8	100	0.178	0.003169	0.000686	4600
All infants (<1 yr old)	17.8	100	0.178	0.010380	0.001	1600

¹ The level of concern (target MOE) includes 10X for interspecies extrapolation and 10X for intraspecies variation.
² Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
³ Residential Exposure = Adults [Inhalation], Children [Oral].
⁴ Aggregate MOE = [NOAEL ÷ (Avg Dietary Exposure + Residential Exposure)]

7.3 Intermediate-Term Aggregate Risk

The intermediate-term aggregate risk assessment estimates risks likely to result from 1- to 6-month exposure to penoxsulam residues from food, drinking water, and residential pesticide uses. High-end estimates of the residential exposure are used in the intermediate-term assessment, and average values are used for food and drinking water exposures.

Penoxsulam short-term exposures can result from the proposed aquatic and turf use scenarios. HED considers the swimmer dermal and oral MOEs to be over estimates of the actual risk and does not recommend that these MOEs be used when aggregating risk. Since penoxsulam is applied outdoors inhalation postapplication exposure is expected to be negligible. HED does not anticipate intermediate-term dermal exposure to individuals entering turf areas treated with penoxsulam. Since postapplication inhalation exposure is anticipated to be negligible and based on information provided in the penoxsulam TTR study which indicates that the amount of residues remaining on the turf after 30 days would be negligible, HED does not expect intermediate-term dermal exposure to result from application of penoxsulam to turf. No intermediate-term aggregate exposure assessment to turf is required.

7.4 Long-Term Aggregate Risk

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of penoxsulam (food and drinking water) and residential uses. However, due to the existing and proposed use patterns, no chronic residential exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (2% of the cPAD) and all population subgroups (see Table 5.2.3). The most highly exposed population subgroup is all infants (<1 year old), at 7% of the cPAD. 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.

7.5 Cancer Risk

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.

8.0 Cumulative Risk Characterization/Assessment

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/>.

9.0 Occupational Exposure/Risk Pathway

Since a short-term dermal point was not selected, the only route of short-term exposure to be addressed for handlers is inhalation. All turf and aquatic handler short-term exposure scenarios resulted in MOEs greater than 100 and therefore not of concern to HED.

Dermal and inhalation endpoints were selected for intermediate-term exposure. Since both endpoints were derived from the same study, toxicological effects were the same and therefore exposures could be combined to determine a total MOE for intermediate-term aquatic handler scenarios only. All intermediate-term aquatic handler scenarios resulted in Total MOEs greater than HED's level of concern (MOE > 100) when occupational handlers wore single layer of clothing plus gloves. Based on information provided in the proposed turf label, handler exposure is anticipated to only be short-term in duration. Therefore, neither a dermal nor inhalation intermediate-term handler exposure assessment was performed for turf uses.

For aquatic scenarios, postapplication exposure is expected to occur to only non-occupational individuals swimming in treated areas. Therefore an occupational postapplication exposure assessment is not required for aquatic scenarios.

No short-term dermal exposure endpoint was selected. Although an intermediate-term dermal endpoint was selected, intermediate-term dermal postapplication exposure is expected to be negligible based on information on the proposed turf labels and chemical specific turf transfer residue studies. Therefore, a dermal postapplication exposure assessment for turf was not performed.

9.1 Handler Aquatic Use Scenarios

Penoxsulam may be applied either directly into the water through submerged hoses trailing behind boats or as a foliar application to emergent or floating foliage of aquatic vegetation. For in-water uses (i.e. boat-mounted trailing hose), handler exposure is limited to the mixer/loader scenario only. Since the active ingredient is automatically applied to the water through hoses, there is no direct contact between the active ingredient and the applicator. However, foliar applications made from a helicopter or boat will result in exposure to mixer/loaders and applicators. Handheld equipment (i.e. right-of-way) generally involves one person mixing/loading and applying a dilute spray mixture into canals made from a truck. To achieve desired concentrations, trucks travel at 2 to 5 miles per hour. The following use scenarios were used to assess handler exposure:

1. mixer/loader of liquid formulation for helicopter-mounted boom
2. applicator of liquid formulation for helicopter-mounted boom
3. mixer/loader of liquid formulation for boat-mounted trailing hose
4. mixer/loader of liquid formulation for airboat-mounted boom

5. applicator of liquid formulation for airboat-mounted boom
6. mixer/loader/applicator of liquid formulation for right-of-way handheld equipment for foliar applications made from a truck

9.1.1 Data and Assumptions

Unit Exposures: No chemical specific unit exposure data was provided in support of this submission; therefore, Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Guide unit exposures were used to estimate handler exposure. Since there are no unit exposure values specific to applying foliar sprays from a boat, unit exposure for open cab groundboom application was used as a surrogate scenario to assess handler exposure.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposure. These include administrative controls, use of personal protective equipment (PPE), and the use of engineering controls. For the present scenarios occupational handler exposure assessments were completed by HED using baseline and PPE.

The baseline clothing level for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, shoes, socks, no chemical-resistant gloves, and no respirator. The first level of mitigation generally applied is PPE which include addition of chemical resistant-gloves, additional layer of clothing and a respirator. The next layer of mitigation considered in the risk assessment process is the use of appropriate engineering controls, which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading transfer systems, and water-soluble packets.

Acres Treated: Information regarding area treated for the various use scenarios was provided by the registrant.

- 100-150 acres treated per day by helicopter for foliar application
- 50-100 acres treated per day by boat-mounted trailing hose application
- 10-12 acres per day by airboat-mounted boom for foliar application
- 6-8 acres per day by handheld equipment (i.e. right-of-way spray) made from trucks for foliar application

Application Rate and Amount Handled: According to the Galleon™ SC, the maximum sum of all applications is 150 ppb per annual growth cycle or a single maximum application rate of 150 ppb. For “in water” applications, the maximum sum of all applications is 150 ppb per annual growth cycle or a single maximum application rate of 150 ppb. For each ppb of penoxsulam, the label indicates that 0.174 fluid ounces of product applied per acre foot of treated water results in a concentration of 1 ppb, or:

$$1 \text{ ppb penoxsulam} = \frac{0.174 \text{ fl oz Galleon}}{\text{A} / \text{ft}}$$

Therefore, using that ratio, a concentration of 150 ppb would require 26.1 fluid ounces of product, or:

$$150 \text{ ppb penoxsulam} = \frac{26.1 \text{ fl oz Galleon}}{\text{A/ft}}$$

The Galleon™ SC label features instructions for depths of up to 10 feet, which is a typical depth for most of the water bodies to be targeted for treatment with this EUP. The maximum application rate (in lb ai/A units) to reach a concentration of 150 ppb in a 10 foot body of water would be:

$$\frac{26.1 \text{ fl oz Galleon}}{\text{A-ft}} \times \frac{1 \text{ gal. Galleon.}}{128 \text{ fl oz Galleon}} \times \frac{2 \text{ lb ai}}{\text{gal Galleon}} \times 10 \text{ ft} = 4.1 \text{ lb ai/A}$$

For “foliar applications post emergent”, Galleon™ SC is applied at the rate of 2 to 11.2 fl oz per acre (11.2 fl oz/A x 2 lb ai/gal x 1 gal/128 oz = 0.175 lb ai/A).

Dermal Absorption Factor: Since the intermediate-term dermal endpoint was based on an oral study, a 50% dermal absorption factor was used to determine dermal exposure.

Exposure Duration: Periodic repeat applications of penoxsulam are anticipated in order to maintain efficacious concentrations in treated bodies of water over a minimum period of 45 days. The half-life of penoxsulam in water is about 21 days, which limits the frequency at which applications are made. Therefore, duration of exposure is expected to be both short- and intermediate-term in nature.

Body Weight: The average male body weight of 70 kilograms was used to assess handler exposure

9.1.2 Aquatic Handler Exposure and Risk

Since a short-term dermal point was not selected, the only route of exposure to be addressed is inhalation. Short-term inhalation exposure is summarized in Table 9.1.2.a. All short-term inhalation MOEs were greater than 100 and therefore not of concern to HED. Dermal and inhalation endpoints were selected for intermediate-term exposure. Since both endpoints were derived from the same study, toxicological effects were the same and therefore exposures could be combined to determine a total MOE. Intermediate-term handler exposure is summarized in Table 9.1.2.b. All short- and intermediate-term handler scenarios resulted in MOEs and Total MOEs greater than HED’s level of concern (MOE > 100).

Table 9.1.2.a Short-term Handler Exposure for Penoxsulam						
Exposure Scenario	Mitigation Level	Inhalation Unit Exposure (mg/lb)^a	Application Rate^b (lb ai/A)	Area Treated (A/day)	Inhalation Dose^c (mg/kg/day)	MOE^d
Mixer/loader						
Helicopter	Baseline	0.0012	0.175	150	0.00045	40,000

Boat trailing hose			4.1	100	0.007	2500
Boat-boom			0.175	12	0.000036	500,000
Applicator						
Helicopter	Baseline	0.0000018	0.175	150	0.00000067	26,000,000
Boatboom		0.00074		12	0.000022	800,000
Mixer/loader/Applicator						
Right of Way Sprayer	Single layer & gloves	0.0039	0.175	8	0.000078	230,000

- a. Inhalation Unit Exposure derived from PHED Version 1.1
- b. Application Rate = $10\text{ft} \times 150\text{ppb} \times 0.174\text{fl oz product} \times 1\text{gal.} \times 2\text{lb ai} = 4.1\text{ lb ai/A}$
 $\text{A-ft-ppb} \qquad \qquad \qquad 128\text{oz gal prod}$
- c. Inhalation Dose = Unit Exposure (mg/lb) x Application Rate (lb ai/day) x Area Treated/BW
- d. MOE = NOAEL (17.8 mg/kg/day) / Inhalation Dose

Table 9.1.2.b Intermediate-term Handler Exposure for Penoxsulam									
Exposure Scenario	Mitigation Level	Dermal Unit Exposure (mg/lb) ^a	Inhalation Unit Exposure (mg/lb) ^a	Application Rate ^b (lb ai/A)	Amount Handled ^c (acres/day)	Dermal Dose ^d (mg/kg/day)	Inhalation Dose ^e (mg/kg/day)	Total Dose ^f (mg/kg/day)	Total MOE ^g
Mixer/loader									
Helicopter	Single layer and gloves	0.023	0.0012	0.175	150	0.0086	0.00045	0.00475	3700
Boat-trailing hose				4.1	100	0.135	0.007	0.075	240
Boatboom				0.175	12	0.00069	0.000036	0.00038	47,000
Applicator									
Helicopter	Single layer & gloves	0.0019	0.0000018	0.175	150	0.00071	0.00000067	0.000356	50,000
Boat-boom		0.014	0.00074		12	0.00042	0.000022	0.00023	77,000
Mixer/loader/Applicator									
Right of Way Sprayer	Single layer & gloves	0.39	0.0039	0.175	8	0.0078	0.000078	0.004	4500

- a. Unit Exposures provided by PHED Version 1.1
- b. Application Rate provided by proposed label
- c. Amount handled provided by Registrant
- d. Dermal Dose (mg/kg/day) = Dermal unit exposure (mg/lb) x Application Rate (lb ai/day) x Amount Handled (acres/day)
- e. Inhalation Dose (mg/kg/day) = Inhalation unit exposure (mg/lb) x Application Rate (lb ai/day) x Amount Handled (acres/day)
- f. Total Dose (mg/kg/day) = [Dermal Dose (mg/kg/day) x 50% Dermal Absorption] + Inhalation Dose (mg/kg/day)
- g. Total MOE = NOAEL (17.8 mg/kg/day) / Total Dose (mg/kg/day)

9.2 Handler Turf Use Scenarios

Penoxsulam turf herbicide products are formulated as liquids and granules. These proposed products are for postemergence control of annual and perennial broadleaf weeds in established turfgrass, residential lawns, golf course, sport fields, sod farms and around commercial buildings. Penoxsulam may be applied as a ground broadcast or spot treatment. Spot treatment using liquid formulations may be applied by hand-held or back sprayers. Granular applications are to be applied using a drop or push rotary-type spreader, whirlybirds, cyclones and or shaker type applicators. The following use scenarios were used to assess handler exposure:

4. mixer/loader of liquid formulation for groundboom using PHED
5. applicator using groundboom using PHED
6. mixer/loader/applicator for push-type granular spreader using PHED
7. mixer/loader/applicator for low pressure hand wand and backpack sprayer using PHED
8. mixer/loader applicator for ORETF LOC Handgun Spray –Liquid Flowable
9. mixer/loader applicator for ORETF LCO Push Cyclone Granular Spreader

9.2.1 Turf Data and Assumptions

Unit Exposures: No chemical specific unit exposure data was provided in support of this submission; therefore, Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Guide and the Outdoor Residential Exposure Task Force (OREFT) study (MRID 44972201) unit exposures were used to estimate handler exposure.

Acres Treated: Information regarding area treated for the various use scenarios was provided by the registrant.

- 40 acres treated per day by groundboom of turf, lawns, golf courses and sports fields
- 80 acres treated per day by groundboom of sod farms
- 1000 ft² per day by low pressure hand wand or back pack sprayer for spot treatment of turf, lawns, golf courses and sports fields
- 0.5 acres per day by push-type (cyclone) granular spreader for broadcast treatment of turf, lawns, golf courses and sports fields

Application Rate and Amount Handled:

- 0.06 lb ai per acre for broadcast treatment
- 0.0014 to 0.0016 lbs ai per 1000 ft² for spot treatment

Exposure Duration: Based on information provided in the proposed labels handler exposure is anticipated to be short-term in duration. The proposed labels indicate that, “additional applications should not be made within four weeks of a previous application.” Therefore, neither intermediate- nor long-term exposure to turf handlers is expected and was not assessed.

Body Weight: The average male body weight of 70 kilograms was used to assess handler exposure.

9.1.2 Turf Handler Exposure and Risk

HED's level of concern for non-cancer risks (i.e., MOE) for penoxsulam is 100 for occupational exposure. Since a short-term dermal point was not selected, the only route of exposure to be addressed is inhalation. Handler inhalation MOEs were significantly greater than 100 and therefore not of concern to HED. Short-term inhalation handler exposure is summarized in Table 9.1.2.

Table 9.1.2 Short-term Turf Handler Exposure and Risk							
Turf Exposure Scenarios	Use Site	Mitigation Level	Inhalation Unit Exposure (mg/lb)^a	Application Rate^b (lb ai/A)	Area Treated (A/day)	Inhalation Dose^c (mg/kg/day)	MOE^d
Mixer/loader							
groundboom liquid	lawns, turf grass areas, sport fields and golf courses	Baseline	0.0012	0.06	40	0.000041	430,000
groundboom liquid	sod farm				80	0.0000823	200,000
Applicator							
groundboom liquid	lawns, turf grass areas, sport fields and golf courses	Baseline	0.00074	0.06	40	0.0000254	700,000
groundboom liquid	sod farm		0.00074		80	0.00005	360,000
Mixer/loader/Applicator							
ORETF LOC Handgun Spray Liquid Flowable	lawns, turf grass areas, sport fields and golf courses	Baseline	0.0018	0.0016 lb ai/1000ft ²	1000ft ²	0.000000041	430,000
ORETF LCO Push Cyclone Granular Spreader			0.0075	0.06 lb ai/A	0.5	0.0000032	5,600,000
PHED Low Pressure handwand and Backpack			0.03	0.0016 lb ai/1000ft ²	1000ft ²	0.000000686	26,000
PHED "Push-type" Granular Spreader			0.0063	0.06 lb ai/A	0.5	0.0000027	660,000

a. Inhalation Unit Exposure derived from PHED Version 1.1 and ORETF Handler Exposure Study MRID 44972201

b. Application Rate based on proposed labels

c. Inhalation Dose = Unit Exposure (mg/lb) x Application Rate (lb ai/day) x Area Treated/BW

d. Inhalation MOE = NOAEL (17.8 mg/kg/day) / Inhalation Dose

9.3 Turf Postapplication Exposure

No short-term dermal endpoint was determined since no dermal, systemic, neurological or developmental toxicity concerns were identified at the highest dose tested. An intermediate-term dermal exposure NOAEL of 17.8 mg/kg/day was selected based on multifocal hyperplasia

of the pelvic epithelium of the kidney from a 1-year chronic feeding study in the dog. The LOAEL was 46.2 mg/kg/day.

Based on the following information: (1) in accordance with proposed label, additional applications should not be made within four weeks of a previous application; (2) the average penoxsulam residues dropped below the LOQ by DAT 7 at both sites (Georgia and Florida) in the chemical specific TTR study summarized above; and (3) the estimated half-life values for penoxsulam residues at the Georgia and Florida site were 1.3 days ($R^2 = 0.8217$) and 1.5 days ($R^2 = 0.9403$), respectively; HED does believe that an intermediate-term dermal postapplication exposure assessment is required. Based on information provide in the penoxsulam TTR study, the amount of residues remaining on the turf after 30 days would be negligible based on half life data. Therefore, a dermal postapplication exposure assessment was not performed and postapplication dermal exposure is not of concern to occupational workers.

10.0 Data Needs and Label Recommendations

None.

10.1 Toxicology

None.

10.2 Residue Chemistry.

The petitioner must submit a label restricting uses on moving waters (canals, rivers, etc), and include suitable directions to control the residues on non-moving waters (lakes, ponds, etc).

Acceptable review of concurrent recoveries and raw data recently submitted to support the catfish and clam study.

Additional confirmatory data/information must be submitted to upgrade the submitted sunfish study (MRID 46703506) to an acceptable status.

Submit a revised Section F for penoxsulam residues in fish and fish - shellfish, crustacean at 0.01 ppm and fish- shellfish, mollusc at 0.02 ppm.

10.3 Occupational and Residential Exposure

None

References:

HIARC Report: TXR No. 0052273, E. Budd, 12/16/03
CARC Report: TXR No. 0050702, J. Kidwell, 3/24/04
MARC Report: TXR No. 0052740, W. Cutchin, 7/19/04
EFED Report: DP Num: 325468, L. Shanaman, 11/8/06

Residue Chemistry: PP#5F7012, DP Num: 326985, MRID: 46703504, 46703505, 46703506,
46703507, and 46703509, D. Soderberg, 1/30/07

ORE: DP Num: 339488, M. Collantes, 5/15/07

PP#3F6542, DP Num: 288152, MRID: 45830712, W. Cutchin, 8/11/04

PP#3F6542, DP Num: 288152, MRID: 45830713 & 46267601, W. Cutchin, 8/11/04

DP Num: 303172, C. Stafford, 9/17/04

DP Num: 288160, MRID: 45831101, L. Shanaman, 4/22/04

ChemSAC Minutes, 1/10/07 & 3/21/07

Appendices

Appendix A: Toxicology Data Requirements

GDIN	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

STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
<p>2-YR FEEDING/CARCINOGENIC, RAT (2002) MRID 45830901, 45830913</p> <p>M: 0, 5, 50, 250 mg/kg/d F: 0, 5, 50, 250 mg/kg/d</p> <p>Chronic toxicity- Acceptable/Guideline Carcinogenicity-- Acceptable/Guideline</p>	<p>M: 50</p> <p>F: 50</p>	<p>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.</p> <p>F: 250 In F based on ↓BW/BWG, ↑urine vol, ↑crystals/calculi in urinary bladder, hyperplasia of kidney pelvis epithelium and urinary bladder mucosa.</p>

Table A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
	<u>Carcinogenicity</u>	M: Possibly treatment-related ↑ incidence of Large Granular Lymphocyte (LGL) leukemia at 5, 50 & 250 m/k/d. Also ↑ severity at 250 m/k/d. Dosing was adequate. F: Negative for carcinogenicity, but dosing was only marginally adequate.
18-MN CARCINOGENIC, MOUSE (2002) MRID 45830915 M: 0, 10, 100, 375 m/k/d F: 0, 10, 100, 750 m/k/d Carcinogenicity-- <u>UNACCEPTABLE</u> / 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-week 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 A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
<p>DEVELOPMENTAL TOX. CD RAT (Sprague-Dawley derived) (2000) MRID 45830917</p> <p>F: 0, 100, 500, 1000 m/k/d On GD 6-20</p> <p>Acceptable/Guideline</p> <p>DER also includes results for a range-finding study in CD rats (MRID 45830916).</p>	<p><u>Mat Tox:</u> 500</p> <p><u>Dev Tox:</u> 1000 (HDT)</p>	<p><u>Mat Tox:</u> 1000 Based on ↓BWG, ↓food consumption, ↑kidney weights</p> <p><u>Dev Tox:</u> Not identified >1000 (HDT)</p>
<p>DEVELOPMENTAL TOX. RABBIT (2001) MRID 45830918</p> <p>F: 0, 5, 25, 75 m/kg On GD 7-27</p> <p>Acceptable/Guideline</p> <p>DER also includes results for a range-finding study in rabbits (MRID 45830919).</p>	<p><u>Mat Tox:</u> 25</p> <p><u>Dev Tox:</u> 75</p>	<p><u>Mat Tox:</u> 75 Based on death, clinical signs, ↓BWG, ↓food consumption.</p> <p><u>Dev Tox:</u> Not identified >75 (HDT)</p>
<p>13-WEEK FEEDING. RAT (2000) MRID 45830906</p> <p>M: 0, 5, 50, 250, 500 m/k/d F: 0, 5, 50, 250, 500 m/k/d</p> <p>With a 4-week recovery phase (0 and 500 m/k/d)</p> <p>Acceptable/Guideline</p> <p>DER also includes results for a 4-week range-finding study in rats (MRID 45830903).</p>	<p>M: 50</p> <p>F: 250</p>	<p>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.</p>
<p>13-WEEK FEEDING. DOG (2000) MRID 45830909</p> <p>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</p> <p>Acceptable/Guideline</p> <p>DER also includes results for a 4-week range-finding</p>	<p>M: 17.8</p> <p>F: 19.9</p>	<p>M: 49.4 In M based on histopathologic changes in kidney.</p> <p>F: 57.1 In F based on histopathologic changes in kidney.</p>

Table A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
study in dogs (MRID 45830908).		
<p>13-WEEK FEEDING, MOUSE (2001) MRID 45830905</p> <p>M: 0, 10.2, 102, 513, 1027 m/k/d F: 0, 10.4, 104, 524, 1029 m/k/d</p> <p>Acceptable/Guideline</p> <p>DER also includes results for a 4-week range-finding study in mice (MRID 45830904).</p>	<p>M: 1027 (HDT)</p> <p>F: 1029 (HDT)</p>	<p>M: Not determined >1027 (HDT)</p> <p>F: Not determined >1029 (HDT)</p>
<p>4-WEEK RANGE-FINDING, RAT (1998) MRID 45830903</p> <p>M: 0, 10, 100, 500, 1000 m/k/d F: 0, 10, 100, 500, 1000 m/k/d</p> <p>Acceptable/Non-Guideline (as a range-finding study)</p> <p>Review is in DER for 90-day rat feeding study.</p>	<p>M: 100</p> <p>F: 100</p>	<p>M: 500 In M based on ↓BW/BWG, ↓food consumption, ↓RBC parameters.</p> <p>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.</p>
<p>4-WEEK RANGE-FINDING, DOG (1998) MRID 45830908</p> <p>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</p> <p>Acceptable/Non-Guideline (as a range-finding study)</p> <p>Review is in DER for 90-day dog feeding study.</p>	<p>M: 29</p> <p>F: <32 (LDT)</p>	<p>M: 133 In M based on ↑liver weights; ↑ALT, ALK, AST; histo-pathologic changes in liver and kidneys.</p> <p>F: 32 In F based on histopathologic changes in kidneys. At 163 m/k/d, treatment-related effects very similar to those in males.</p>
<p>4-WEEK RANGE-FINDING, MICE (1998) MRID 45830904</p> <p>M: 0, 10.5, 103, 530, 1018 m/k/d F: 0, 10.8, 110, 545, 1069 m/k/d</p> <p>Acceptable/Non-Guideline (as a range-finding study)</p> <p>Review is in DER for 90-day mouse feeding study.</p>	<p>M: 1018 (HDT)</p> <p>F: 1069 (HDT)</p>	<p>M: Not determined >1018 (HDT)</p> <p>F: Not determined >1069 (HDT)</p>
<p>ACUTE NEUROTOXICITY, RAT (2000) MRID 45830902</p>	<p>M: 2000 (HDT)</p>	<p>M: Not determined >2000 (HDT)</p>

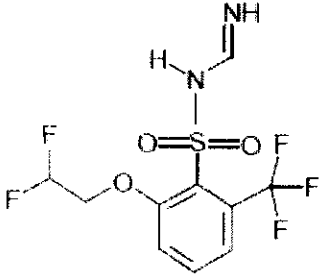
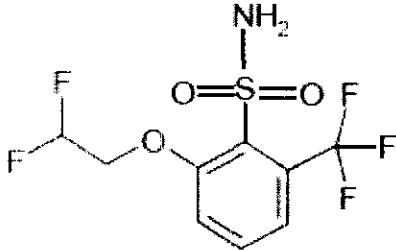
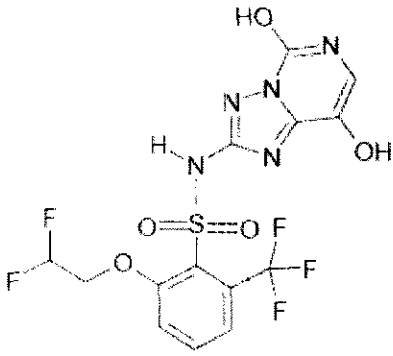
Table A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
M: 0, 500, 1000, 2000 mg/kg F: 0, 500, 1000, 2000 mg/kg Acceptable/Guideline	F: 2000 (HDT)	F: Not determined >2000 (HDT)
CHRONIC NEUROTOXICITY, RAT (2002) MRID 45830912, 45830901 M: 0, 5, 50, 250 m.k.d F: 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	<u>Systemic:</u> M: 1000 F: 1000 <u>Dermal:</u> M: 1000 F: 1000	<u>Systemic:</u> M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) <u>Dermal:</u> M: Not determined >1000 (HDT) F: Not determined >1000 (HDT)
28-DAY DERMAL TOXICITY, RAT (2002) MRID 45830911 <u>TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)</u> 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-443, and <u>not</u> in mg/kg/day of penoxsulam. Acceptable/Guideline	<u>Systemic:</u> M: 1000 F: 1000 <u>Dermal:</u> M: 500 F: 1000	<u>Systemic:</u> M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) <u>Dermal:</u> M: 1000 Based on very slight hyperplasia at test site F: Not determined >1000 (HDT)
GENERAL METABOLISM, RAT (2002) 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/day followed by	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	

Table A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
5.0 mg/kg orally on day 15. Biliary elimination was examined in additional rats following a single oral dose of 5.0 mg/kg. Acceptable/Guideline		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 MUTATION (1999) (<i>S. typhimurium</i> / <i>E. coli</i>) MRID 45830921 Acceptable/Guideline		Negative without and with rat S-9 activation.
MUTA-REVERSE GENE MUTATION (2002) (<i>S. typhimurium</i> / <i>E. coli</i>) MRID 45830922 <u>TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)</u> 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- <i>in vitro</i> MAMMALIAN CYTOGENETICS (Chromosomal aberrations in primary rat lymphocytes) (1999) MRID 45830924 Acceptable/Guideline		Negative without and with rat S-9 activation.
MUTA- <i>in vivo</i> 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- <i>in vivo</i> MICRONUCLEUS, MICE (2002) (Bone marrow cells)		Negative at oral doses (once per day on two consecutive days) of up to 2000 mg/kg.

Table A.2 Toxicology Study Summary		
STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
MRID 45830926 <u>TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)</u> Acceptable/Guideline		

Appendix B: Penoxsulam and Metabolites

Table B. Penoxsulam and Metabolite Structures.	
Name	Structure
<p>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</p>	
<p>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:</p>	
<p>2-amino TCA CAS name: 2-amino-1,2,4-triazole carboxylic acid Synonyms: Polars</p>	
<p>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</p>	

Table B. Penoxsulam and Metabolite Structures.	
Name	Structure
<p>SFA CAS name: 2-(2,2-difluoroethoxy)-N-(iminomethyl)-6-(trifluoromethyl)-benzenesulfonamide IUPAC name: 2-(2,2-difluoroethoxy)-N-[(E)iminomethyl]-6-</p>	
<p>sulfonamide CAS name: 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-benzenesulfonamide IUPAC name: 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-benzenesulfonamide</p>	
<p>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</p>	

Appendix C: International Residue Status Sheet.

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide	Common Name: Penoxsulam	<input checked="" type="checkbox"/> Proposed tolerance <input type="checkbox"/> Reevaluated tolerance <input type="checkbox"/> Other	Date: 4/30/07
Codex Status (Maximum Residue Limits)		U. S. Tolerances	
<input checked="" type="checkbox"/> No Codex proposal step 6 or above <input type="checkbox"/> No Codex proposal step 6 or above for the crops requested		Petition Numbers: 5F7012 DP Barcodes: 325461 Other Identifier: 119031	
Residue definition (step 8/CXL): N/A		Reviewer/Branch: W. Cutchin	
		Proposed Residue definition Penoxsulam per se	
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Fish	0.01
		Shellfish	0.02
Limits for Canada		Limits for Mexico	
<input checked="" type="checkbox"/> No Limits <input type="checkbox"/> No Limits for the crops requested		<input checked="" type="checkbox"/> No Limits <input type="checkbox"/> No Limits for the crops requested	
Residue definition: N/A		Residue definition: N/A	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions: S. Funk, 04/30/2007.			

Appendix D: Review of Human Research

No MRID - PHED Surrogate Exposure Guide



13544

R149520

Chemical: Penoxsulam

PC Code:
119031

HED File Code: 11000 Chemistry Reviews

Memo Date: 6/18/2007

File ID: DPD325461

Accession #: 000-00-0120

HED Records Reference Center
6/22/2007