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

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: November 16, 2005

**MEMORANDUM**

SUBJECT: Flazasulfuron: Human Health Risk Assessment for the Proposed Uses on Golf Courses, Sod Farms, Professionally Managed Athletic Fields (College and Professional), and Commercial Lawns. PC Code: 119011, DP Barcode: D303573 & D309442.

Regulatory Action: Section 3 Registration Action
Risk Assessment Type: Single Chemical/No Aggregate

FROM: Gerome V. Burke, Ph.D., Toxicologist and Risk Assessor
Kelly O'Rourke, Biologist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen C. Dapson, Ph.D., Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

TO: Jim Tompkins/Ching-Tsen Bien, RM25
Herbicide Branch
Registration Division (7505C)

Following is the HED risk assessment document which includes the Metabolism, Toxicology, and Hazard Assessment from Gerome V. Burke, Ph.D. and an occupational and residential exposure assessment conducted by Kelly O'Rourke (DP: D316614, 11/3/05). Information was also drawn from the Environmental Fate and Effects Division (EFED) Drinking Water Assessment (Tier I Modeling) (Keara Moore, DP: D317381 2/24/05).

## Table of Contents

## 1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the toxicity and exposure data bases for the new pesticide active ingredient, flazasulfuron, and has conducted a human health risk assessment in support of the Section 3 Registration Action for this new active ingredient.

*Use Information*

Flazasulfuron is a new active ingredient proposed for control of annual and perennial grasses, sedges, and broadleaf weeds on golf courses and other non-residential turf areas such as industrial parks, tank farms, sod farms, seed farms, professionally managed sports fields, and commercial lawns. The formulated end use product evaluated in this assessment is labeled under the trade name Flazasulfuron 25WG, a water dispersible granule, also called dry flowable, containing 25% flazasulfuron. There are no proposed food uses or tolerances for flazasulfuron.

*Toxicology*

Most of the toxicological studies utilized to support flazasulfuron have been submitted and found to be acceptable and within compliance of guidelines, with the exception of the acute neurotoxicity battery (Acceptable pending submission of analytical data verifying homogeneity and stability /Guideline).

Flazasulfuron exhibits low acute toxicity in rats and rabbits. The oral LD50 is greater than 5000 mg/kg and the acute inhalation LD50 is greater than 4.0 mg/L. All studies are in Toxicity Category III or IV. Flazasulfuron is not irritating to the skin or eyes and is not a sensitizer.

Metabolism studies in the rat indicate that flazasulfuron is rapidly distributed and excreted in the urine and feces. Excretion in urine occurred more slowly in males (73%) than females (90%). Fecal elimination was greater in males (23%) than females (10%).

In a 21-day dermal toxicity study in rabbits, no dermal or systemic effects were seen at the high dose of 1000 mg/kg/day, the dermal and systemic NOAEL.

Chronic studies in the rat and the dog indicate that the kidney and liver are the target organs for chronic oral exposure. Subchronic studies in animals indicated decreased body weight gain, slight anemia in rats and liver abnormalities in dogs.

The genotoxic potential of flazasulfuron has been assessed as negative by several *in vitro* and *in vivo* mutagenicity studies. The two-year combined chronic toxicity and carcinogenicity study showed no evidence of carcinogenicity.

Developmental toxicity has been investigated in two rat studies and one rabbit study. The effects on reproduction have been examined in one rat study. Reduced fetal weights and retardation in ossification were the effects observed in a Sprague-Dawley rat developmental study. A second

developmental rat study (Wistar) showed increased incidence of visceral malformations (interventricular septal defect). The developmental study in rabbits showed high incidences of abortion at the highest dose tested. Decreases in body weight and chronic nephropathy were observed in offspring in a 2-generation rat reproduction study.

Neurotoxicity was observed using an acute neurotoxicity battery. A transient decrease in motor activity on Day 0 (5 hours post-dosing) was observed at the mid dose of 1000 mg/kg.

Because this is a non-food use pesticide, consideration of an FQPA Safety Factor is not required.

*Dose Response Assessment*

An acute RfD was selected based on an acute neurotoxicity battery (ACN) in rat. A chronic RfD was selected based on 2-year combined chronic/carcinogenicity rat study. Uncertainty factors of 100 were used (10X intraspecies, 10X interspecies) for both the acute and chronic RfDs. Incidental oral and short-term (dermal, inhalation) endpoints were selected based on the ACN. The level of concern (LOC) for occupational and residential exposure is 100 based on traditional uncertainty factors.

*Exposure/Risk Assessment and Risk Characterization*

Risk assessments were conducted for drinking water, and occupational and residential exposure pathways. Acute and chronic dietary assessments were conducted for drinking water exposure only, because the active ingredient is not used on agricultural crops (i.e., there are no food uses). The quantitative assessment of risk from the drinking water pathways was based on a Tier 1 Drinking Water Assessment conducted by the Environmental Fate and Effects Division (EFED). EFED used the FIFRA Index Reservoir Screening Tool (FIRST) to estimate surface water concentrations and the Screening Concentration in ground water (SCI-GROW) model to estimate ground water concentrations for flazasulfuron and its degradates. The quantitative assessment of exposure from drinking water concluded that the acute and chronic exposure estimates are below HED's level of concern.

Short-term occupational and residential exposure assessments were conducted based on uses of flazasulfuron on golf courses and athletic fields. Intermediate-term and chronic exposures are not expected for the proposed use patterns associated with flazasulfuron because the application interval is 2 to 6 weeks, and the turf transferrable residue data indicated that the half-life is less than one day. Occupational handlers were assessed for dermal and inhalation exposure. Flazasulfuron will be applied by professional applicators only, so residential handlers were not assessed. Occupational and residential dermal post-application exposure was assessed based on golf course and athletic field applications. Risk estimates were conducted using maximum application rates and HED standard default assumptions for area of application and/or amount of product applied for most exposure scenarios. Exposure and risk estimates indicate that residential and occupation risks are not of concern (i.e., MOEs $\geq$ 100).

## 2.0 Ingredient Profile

Flazasulfuron [1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-trifluoromethyl-2-pyridylsulfonyl) urea] is the proposed common name of SL-160, a new active ingredient developed by ISK Biosciences Corporation. Flazasulfuron belongs to the pyrimidinylsulfonylurea class of herbicides. Flazasulfuron is a post-emergence herbicide with some pre-emergence activity that controls a large number of weeds in established warm-season bermudagrass and zoysiagrass turf. Flazasulfuron controls weeds by inhibiting the acetolactate synthase (ALS) biochemical process. Acetolactate synthase is the site of action of several new, structurally diverse classes of herbicides (sulfonylurea, imidazolinone, sulfonanilide or triazolopyrimidine and pyrimidinylthiobenzoate).

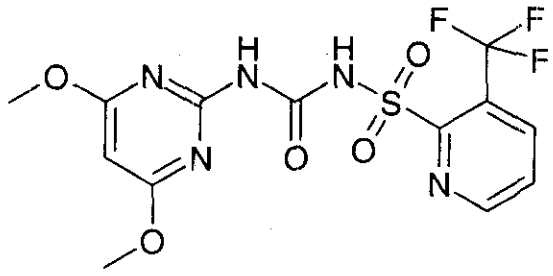
### 2.1 Summary of Registered/Proposed Uses

The proposed uses of flazasulfuron are for control of grass and broadleaf weeds, for early season crabgrass and sedge control, and for removal of overseeded cool-season grasses from professionally managed warm-season turf grass in the Southeastern and Southwestern regions of the United States. Flazasulfuron is not currently registered. This risk assessment covers the formulated end use product Flazasulfuron 25WG containing 25% ai.

**Table 2.1. Summary of Use Pattern/Formulation Information**

| Formulation Type (% ai) | Application Method | Use Site | Application Rate (lb ai/A) | Frequency of Application | Application Interval |
|---|---|---|---|---|---|
| Water-Dispersible Granule (i.e., Dry Flowable) (25% ai) | Groundboom, Handgun, Low-pressure Handwand, and Backpack Sprayer | Non-Residential Turf | 0.023 - 0.047 | 3 applications (at maximum rate) | 2 to 6 weeks |

## 2.2 Structure and Nomenclature

| TABLE 2.2. Test Compound Nomenclature | |
|---|---|
| Chemical Structure |  |
| Empirical Formula | $C_{13}H_{12}F_3N_5O_5S$ |
| Common name | Flazasulfuron |
| Company experimental name | SL-160 |
| IUPAC name | 1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-trifluoromethyl-2-pyridylsulfonyl) urea |
| CAS name | N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(trifluoromethyl)-2-pyridinesulfonamide |
| CAS Registry Number | 104040-78-0 |
| End-use product/EP | Flazasufluron 25 WG |
| Chemical Class | Pyrimidinylsulfonylurea herbicide |
| Known Impurities of Concern | none |

## 2.3 Physical and Chemical Properties

| TABLE 2.3. Physicochemical Properties | | |
|---|---|---|
| Parameter | Value | |
| Molecular Weight | 407.3 g/mol | |
| Melting point/range | 147 - 150 °C | |
| pH | 4.01 | |
| Density | 0.79 g/cm$^3$ | |
| Water solubility (20 °C) | pH | mg/ml |
| | 5 | 0.027 |
| | 7 | 2.1 |
| | 9 | Not Stable |
| Solvent solubility (25 °C) | Solvent | Solubility |
| | hexanes: | 0.50 µg/mL |
| | octanol: | 0.20 mg/mL |
| | methanol: | 4.2 mg/mL |
| | acetone: | 22.7 mg/mL |
| | toluene: | 0.56 mg/mL |
| | dichloromethane: | 22.1 mg/mL |
| | ethyl acetate: | 6.9 mg/mL |
| | acetonitrile: | 8.7 mg/mL |

| TABLE 2.3. Physicochemical Properties | |
|---|---|
| Parameter | Value |
| Vapor pressure (25 °C) | $< 1 \times 10^{-7}$ torr |
| Dissociation constant, pKa | 4.37 |
| Octanol/water partition coefficient, $\log P_{ow}$ (25 °C) | pH 5 Buffer: 20<br>pH 7 Buffer: <10 |
| UV/visible absorption spectrum | - |

Data from page 7, MRID 46220944.

## 3.0 Metabolism and Enviromental Fate Assessment

### 3.1 Comparative Metabolic Profile

#### 3.1.1 Rat Metabolism

Based on two metabolism studies in rats, radiolabeled flazasulfuron was rapidly distributed and excreted in urine and feces following multiple dosing. Elimination via the urine was the major route of excretion for study I (MRID 46220940), accounting for 74-80% and 90-94% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220938; 46220940). Elimination via the urine was the major route of excretion for study II (MRID 46220941), accounting for 73-79% and 89-91% in males and females, respectively, following both low- and high-dose and single and repeated dose administration up to 168 hours post dosing (MRID 46220939; 46220941). Time course data in both studies revealed that a significant portion of the radioactivity was excreted in urine by 48-72 hours post exposure. Feces were the secondary route of elimination in study I, accounting for 21-24% and 9-10% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220938; 46220940). Feces in study II, accounted for 18-24% and 9% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220939; 46220941). Tissue distribution in study I indicated that $^{14}$C-SL-160(P) is rapidly excreted from the system, with less than 4% (males) and 1% (females) of the administered radioactivity remaining in the tissues seven days after dosing. Tissue distribution in study II indicated that $^{14}$C-SL-160(Pm) is rapidly excreted from the system, with less than 2% (males) and 0.3% (females) of the administered radioactivity remaining in the tissues seven days after dosing.

The most prevalent metabolites (expressed as percent of administered dose) were HDTG+TPPG (~6.5-17.7% in urine, ~0.4-9.7% in feces, and ~6.5-14% in bile), with minor amounts (<5%) of other compounds (see metabolic pathway in Appendix 3). Individually, unidentified fractions generally accounted for less than 2% of the administered dose in the urine and biliary metabolite profile. The fecal metabolite profile had up to 35% unidentified of the recovered dose.

### 3.1.2 Environmental Degradation

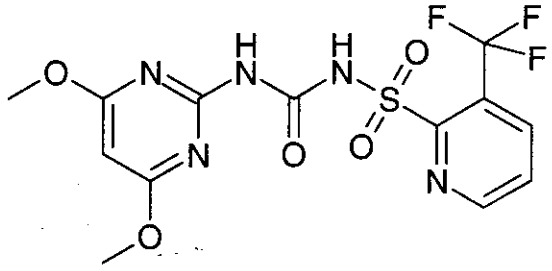
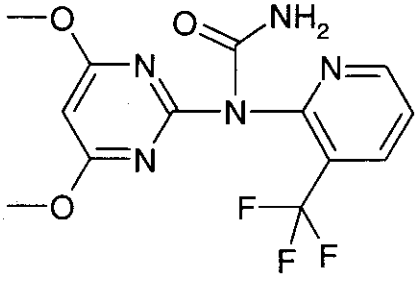
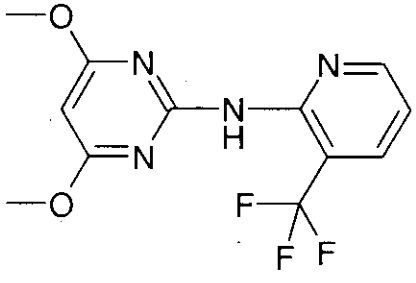
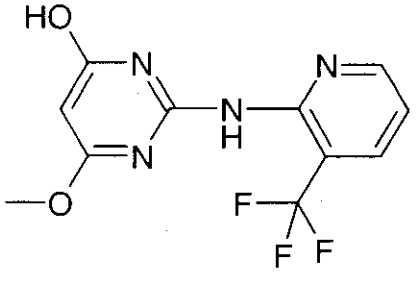
Flazasulfuron is non-persistent to moderately persistent in both aquatic and soil environments. The hydrolysis of flazasulfuron is pH dependent with half-lives at 22°C ranging from <1 days at pH 4 to 17 days at pH 7. Above pH 9, the rate of hydrolysis increases rapidly. The predicted environmental aquatic phototransformation half-life is 18 days. In an anaerobic aquatic metabolism study, flazasulfuron degraded with a half-life of 5 days in the whole system and in several aerobic aquatic metabolism studies, the system half-lives were 24 and 30 days. Aerobic soil metabolism half-lives ranged from 30 to 106 days in sandy loam and loam type soils. In a bare ground terrestrial field dissipation study, flazasulfuron degraded with a half-life of 8 days and in two terrestrial field dissipation studies on turf, flazasulfuron did not reach the soil in measurable quantities, and had half-lives in thatch of 5 and 7 days.

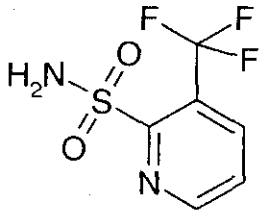
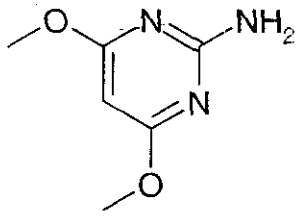
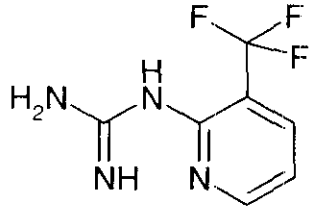
Several degradates were detected in the environmental fate studies reviewed, including DTPU, DTPP, TPSA, ADMP, HTPP, 2,3-GTP, bound residues, and carbon dioxide.

Currently, there are no environmental fate data available for any of the degradates of flazasulfuron. Studies of the parent compound do provide some information about the relative importance of these transformation byproducts, however. In most environments, DTPU is the most persistent degradate present at significant levels (44% to 86% of the applied amount) and still rising by the end of the aquatic photolysis study, and in all hydrolysis studies performed at pH ≤7, and decreasing slowly, but still high (>40% applied) in the aerobic soil studies. At the termination of the aerobic aquatic studies, DTPU was >30% of the applied dose and relatively steady or just beginning to decrease. In alkaline hydrolysis studies, DTPP is the major product, reaching a maximum of >70% of the applied on the final day of the pH 9 study. In aerobic soil studies, DTPP levels, although low (approximately 10% applied), appear to be still increasing at study termination. TPSA is also an important degradate in aerobic soil processes, remaining between 22% and 25% of the applied amount for the last six months of the study. HTPP is the most important degradate in aerobic aquatic environments, reaching levels >30% of the applied amount at the final day of the 100 day study. ADMP appears to be less persistent than the other degradates in all studies, and in an anaerobic aquatic environment, all degradates had been transformed to bound residues or minor polar products by the end of the 30-day study. (EFED, D317381 2/24/05)

## 3.2 Tabular Summary of Water Degradates

**Table 3.3. Water Degradates of Flazasulfuron**

| Degradate | Lab Results Max %AR (Study) | Chemical Structure |
|---|---|---|
| SL-160 (Flazasulfuron) | 97 (hydrolysis, pH = 4.5)<br>100 (hydrolysis, pH = 7)<br>100 (hydrolysis, pH = 9)<br>94 (aqueous photolysis)<br>(soil photolysis)<br>92 (aerobic soil)<br>97 (anaerobic aquatic)<br>(aerobic aquatic)<br>59 (terrestrial field dissipation) |  |
| DTPU N-(4,6-Dimethoxy-2-pyrimidinyl)-N-[3-(trifluoromethyl)-2-pyridinyl]urea | 85 (hydrolysis, pH = 4, 5)<br>59 (hydrolysis, pH = 7)<br>7 (hydrolysis, pH = 9)<br>44 (aqueous photolysis)<br>74 (soil photolysis)<br>61 (aerobic soil)<br>16 (anaerobic aquatic)<br>35 (aerobic aquatic)<br>12 (terrestrial field dissipation) |  |
| DTPP 4,6-Dimethoxy-N-[3-(trifluoromethyl)-2-pyridinyl]-2-pyrimidinamine | <3 (hydrolysis, pH = 4)<br>4 (hydrolysis, pH = 5)<br>9 (hydrolysis, pH = 7)<br>72 (hydrolysis, pH = 9)<br>6 (aqueous photolysis)<br>43 (soil photolysis)<br>10 (aerobic soil)<br>6 (anaerobic aquatic)<br>ND (aerobic aquatic)<br>13 (terrestrial field dissipation) |  |
| HTPP 6-Methoxy-2-[[3-(trifluoromethyl)-2-pyridinyl]amino]-4-pyrimidinol | ND (hydrolysis)<br>ND (aqueous photolysis)<br>4 (aerobic soil)<br>26 (anaerobic aquatic)<br>34 (aerobic aquatic)<br>N/A (terrestrial field dissipation) |  |

| Table 3.3. Water Degradates of Flazasulfuron | | |
|---|---|---|
| **Degradate** | **Lab Results Max %AR (Study)** | **Chemical Structure** |
| TPSA<br>3-Trifluoromethyl-2-pyridinesulfonamide | 14 (hydrolysis, pH = 4)<br>12 (hydrolysis, pH = 5)<br>3 (hydrolysis, pH = 7, 9)<br>5 (aqueous photolysis)<br>N/A (soil photolysis)<br>25 (aerobic soil)<br>8 (anaerobic aquatic)<br>6 (aerobic aquatic)<br>ND (terrestrial field dissipation) |  |
| ADMP<br>4,6-Dimethoxy-2-pyrimidinamine | 13 (hydrolysis, pH = 4)<br>4 (hydrolysis, pH = 7, 9)<br>ND (aqueous photolysis)<br>7 (soil photolysis)<br>10 (aerobic soil)<br>3 (anaerobic aquatic)<br>N/A (aerobic aquatic)<br>ND (terrestrial field dissipation) |  |
| 2,3-GTF<br>3-Trifluoromethyl-2-pyridylguanidine | 18 (anaerobic aquatic)<br>not analyzed for others |  |

## 3.3 Toxicity Profile of Major Metabolites and Degradates

Based on a review of the metabolites identified in the rat metabolism study and the degradates detected in environmental fate studies, HED has concluded that only compounds with the full sulfonylurea structure, such as parent flazasulfuron and HDPU (a minor rat metabolite comprising <5% of dose) are likely to contribute to the chronic endpoint of renal toxicity. The water degradates (HTPP), and the water degradates/rat metabolites (ADMP DTPU, DTPP), all of which lack the sulfonylurea structure, need not be included in the risk assessment. Because EFED included all metabolites and degradates in deriving estimated EDWC's as part of its Tier 1 assessment, all metabolites and degradates were conservatively included in the drinking water assessment. Because there is no data regarding the potential contribution of degradates to acute toxicity, equivalent toxicity to the parent is assumed. (Personal Communication, Alberto Protozel, 10/28/05)

## 3.4 Summary of Residues for Risk Assessment

### 3.4.1 Tabular Summary

| Table 3.6. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression | | |
|---|---|---|
| Matrix | | Residues included in Risk Assessment |
| Plants | Primary Crop | Not Applicable |
| | Rotational Crop | Not Applicable |
| Livestock | Ruminant | Not Applicable |
| | Poultry | Not Applicable |
| Drinking Water | | Parent, DTPU, DTPP, HTPP, TSPA, ADMP |

### 3.4.2 Rationale for Inclusion of Metabolites and Degradates

A conservative estimate of total pesticide residues in surface water, including the parent compound and all of its degradates, was approximated by assuming that flazasulfuron is stable to degradation and that it does not adsorb to soil, resulting in maximum runoff. This is a highly conservative assumption given HED's conclusion that only the parent should be included in estimated drinking water concentrations for risk assessment purposes.

## 4.0 Hazard Characterization/Assessment

### 4.1 Hazard Characterization

Most of the toxicological studies utilized to support flazasulfuron have been submitted and found to be acceptable and within compliance of guidelines, with the exception of the acute neurotoxicity battery (Acceptable pending submission of analytical data verifying homogeneity and stability /Guideline).

Flazasulfuron exhibits low acute toxicity in rats and rabbits. The oral LD50 is greater than 5000 mg/kg, the acute inhalation LD50 is greater than 4.0 mg/L, and the acute dermal LD50 is greater than 2000 mg/kg. All studies are in Toxicity Category III or IV. Flazasulfuron is not irritating to the skin or eyes and is not a sensitizer.

Metabolism studies in the rat indicate that flazasulfuron is rapidly distributed and excreted in the urine and feces. Excretion in urine occurred more slowly in males (73%) than females (90%). Fecal elimination was greater in males (23%) than females (10%).

In a 21-day dermal toxicity study in rabbits, no dermal or systemic effects were seen at the high dose of 1000 mg/kg/day, the dermal and systemic NOAEL.

Chronic studies in the rat and the dog indicate that the kidney and liver are the target organs for

chronic oral exposure. Subchronic studies in animals indicated decreased body weight gain, slight anemia in rats and liver abnormalities in dogs.

The genotoxic potential of flazasulfuron has been assessed as negative by several *in vitro* and *in vivo* mutagenicity studies. The two-year combined chronic toxicity and carcinogenicity study showed no evidence of carcinogenicity.

Developmental toxicity has been investigated in two rat studies and one rabbit study and the effects on reproduction have been examined in one rat study. Reduced fetal weights and retardation in ossification are the effects observed in a Sprague-Dawley rat developmental study. A second developmental rat study (Wistar) showed increased incidence of visceral malformations (interventricular septal defect). The developmental study in rabbits shows high incidences of abortion at the highest dose tested. Decreases in body weight and chronic nephropathy were observed in offspring in a 2-generation rat reproduction study.

Neurotoxicity was observed using an acute neurotoxicity battery. A transient decrease in motor activity on Day 0 (5 hours post-dosing) was observed at the mid-dose of 1000 mg/kg.

Because this is a non-food use pesticide, consideration of an FQPA Safety Factor is not required.

**Table 4.1a Acute Toxicity Profile - Test Substance**

| Guideline No. | Study Type | MRID(s) | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 | Acute oral [rat] | 46220908 | $LD_{50}$ > 5000 mg/kg (male and females) | IV |
| 870.1200 | Acute dermal [rat] | 46220909 | $LD_{50}$ > 2000 mg/kg (male and females) | III |
| 870.1300 | Acute inhalation [rat] | 46220910 | $LC_{50}$ > 5 mg/L (male and females) | IV |
| 870.2400 | Acute eye irritation [rabbit] | 46220911 | Minimal conjunctivitis through 48 hours. Free by 72 hours. | III |
| 870.2500 | Acute dermal irritation [rabbit] | 46220912 | No erythema, edema, or dermal effects observed at application site. | IV |
| 870.2600 | Skin sensitization [guinea pig] | 46220913 | Not a sensitizer | - |

| Table 4.1b Subchronic, Chronic and Other Toxicity Profile | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3100<br>90-Day oral toxicity (rat) | 46220920 (1988)<br>M/F: 0, 40, 200, 1000, 5000 ppm<br>M: 0, 2.31, 11.66, 57.1, 287 mg/kg/day<br>F: 0, 2.53, 12.8, 61.5, 309 mg/kg/day<br>Acceptable/Guideline | NOAEL (M/F) = 11.66/61.5 mg/kg/day<br>LOAEL (M/F) = 57.1/309 mg/kg/day based on depression of body weight gain (M/F) and slight anemia due to decrease in hemoglobin (F). |
| 870.3150<br>90-Day oral toxicity (dog)-capsule | 46220921 (1994)<br>M: 0, 2, 10, 50, 250 mg/kg/day<br>F:0, 2, 10, 50, 100 mg/kg/day<br>Acceptable/Guideline | NOAEL (M/F) = 2/10 mg/kg/day<br>LOAEL (M/F) = 10/50 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). |
| 870.3200<br>21-Day dermal toxicity (rabbit) | 46220922 (1994)<br>0, 250, 500, 1000 mg/kg/day<br>Acceptable/Guideline | NOAEL (M/F) = 1000/1000 mg/kg/day<br>LOAEL (M/F) = No systemic toxicity was observed at the limit dose. No localized dermal effects were observed. |
| 870.3700a<br>Prenatal developmental in (rat):<br>Wistar | 46220924 (1988)<br>0, 100, 300, 1000 mg/kg/day<br>Acceptable/Guideline | **Maternal** NOAEL = 100 mg/kg/day<br>LOAEL = 300 mg/kg/day based on increase in maternal relative liver weight and decreased body weight gain and food consumption.<br>**Developmental** NOAEL = 100 mg/kg/day<br>LOAEL = 300 mg/kg/day based on increased incidence of visceral malformations (interventricular septal defect). |
| 870.3700a<br>Prenatal developmental in (rat):<br>Sprague-Dawley | 46220925 (1996)<br>0, 100, 300, 1000 mg/kg/day<br>Acceptable/Guideline | **Maternal** NOAEL = 300 mg/kg/day<br>LOAEL =1000 mg/kg/day based on transient decreased body weight gain and food consumption.<br>**Developmental** NOAEL = 300 mg/kg/day<br>LOAEL = 1000 mg/kg/day based on reduced fetal weights and retardation in ossification. |
| 870.3700b<br>Prenatal developmental in (rabbit) | 46220923 (1988)<br>0, 50, 150, 450 mg/kg/day<br>Acceptable/Guideline | **Maternal** NOAEL = 150 mg/kg/day<br>LOAEL = 450 mg/kg/day based on high incidences of abortion and decrease in food consumption after initial administration.<br>**Developmental** NOAEL = 150 mg/kg/day<br>LOAEL = 450 mg/kg/day based on high incidences of abortion. |

| Table 4.1b Subchronic, Chronic and Other Toxicity Profile | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3800<br>Reproduction and fertility effects (rat) | 46220926 (1995)<br>0, 200, 2000, 10000 ppm<br>M: 0, 8.7, 87.5, 473.0 mg/kg/day<br>F: 0, 11.7, 124.5, 613.7 mg/kg/day<br>Acceptable/Guideline | **Parental/Systemic** NOAEL (M/F) = 8.7/124.5 mg/kg/day<br>LOAEL (M/F) = 87.5/613.7 mg/kg/day based on changes in kidney parameters (M/F: Bilateral discoloration, enlargement, mild nephropathy) and reductions in body weight in both generations ($F_0$, $F_1$).<br>**Reproductive** NOAEL (M/F) =473.0/613.7mg/kg/day<br>LOAEL (M/F) =not established.<br>**Offspring** NOAEL (M/F) = 87.5/124.5 mg/kg/day<br>LOAEL (M/F) = 473.0/613.7 mg/kg/day based on reduction in lactational body weights of the $F_1$ and $F_2$ offspring. |
| 870.4100b<br>Chronic toxicity (dog)-capsule | 46220927 (1995)<br>M: 0, 0.4, 2, 10, 50 mg/kg/day<br>F: 0, 2, 10, 50 mg/kg/day<br>Acceptable/Guideline | NOAEL = 2 mg/kg/day<br>LOAEL = 10 mg/kg/day based on changes in liver (increase in: inflammatory cell infiltration, hepatocellular necrosis, hepatocellular swelling, and bile duct proliferation). |
| 870.4300<br>Combined Chronic Toxicity/ Carcinogenicity (rat) | 46220929 (1995)<br>M: 0, 40, 400, 2000 ppm<br>F: 0, 40, 400, 4000 ppm<br>M: 0, 1.3, 13.3, 70.1 mg/kg/day<br>F: 0, 1.6, 16.4, 172.6 mg/kg/day<br>Acceptable/Guideline | NOAEL = 1.3 mg/kg/day<br>LOAEL = 13.3 mg/kg/day based on : Adverse change in kidney function (chronic nephropathy) and kidney physiology (enlargement, dark color of kidney)<br><br>**no evidence of carcinogenicity** |
| 870.4200<br>Carcinogenicity (mouse) | 46220928 (1995)<br>0, 500, 3500, 7000 ppm<br>M: 0, 77.3, 552.7, 1053.8 mg/kg/day<br>F: 0, 93.7, 659.8, 1208.2 mg/kg/day<br>Acceptable/Guideline | NOAEL (M/F) = 77.3/93.7 mg/kg/day<br>LOAEL (M/F) = 552.7/659.8 mg/kg/day based on decrease in body weight, body weight gain, food consumption and an increase in liver effects (liver weight and hepatocellular hypertrophy).<br><br>**no evidence of carcinogenicity** |
| 870.5500<br>*Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay | 46220933 (1987)<br>0, 20, 50, 100, 200, 500, 1000 µg/ plate (*S. typhimurium*); 0, 100, 200, 500, 1000, 2000, 5000 (*E. coli*) in the presence and absence of metabolic activation (± S9)<br>Acceptable/Guideline | Flazasulfuron was not cytotoxic with or without S9 activation in four *S. typhimurium* strains and one strain of *E. coli*, and did not induce a genotoxic response in any strain.<br><br>**Negative** |

| Table 4.1b Subchronic, Chronic and Other Toxicity Profile | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.5300<br>*in vitro* Mouse Lymphoma Mutagenesis Assay | 46220930 (1993)<br>0, 20, 30, 40, 50, 60, 70, 80, 90, 100, 500 µg/ml in the presence and absence of metabolic activation (± S9)<br>Acceptable/Guideline | There was no evidence of biologically significant induction of mutant colonies.<br><br>**Negative** |
| 870.5375<br>*in vitro*<br>Cytogenetics Test | 46220931 (1988)<br>0, $3.3 \times 10^{-4}$, $1.7 \times 10^{-4}$, $8.3 \times 10^{-5}$, $4.1 \times 10^{-5}$, $2.1 \times 10^{-5}$ M, with and without metabolic activation (± S9)<br>Acceptable/Guideline | Flazasulfuron did not induce chromosome aberrations in Chinese hamster lung cells, in the presence and absence of S9activation.<br><br>**Negative** |
| 870.5395<br>*in vivo* Mammalian Erythrocyte Micronucleus Test: Mouse | 46220932 (1995)<br>0, 1250, 2500, 5000 mg/kg<br>Acceptable/Guideline | There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or collection time.<br><br>**Negative** |
| 870.6200a<br>Acute neurotoxicity screening battery (rat) | 46220934 (2002)<br>0, 50, 1000, 2000 mg/kg/day<br>Acceptable pending data submission /Guideline | NOAEL (M/F) = 50 mg/kg<br>LOAEL = 1000 mg/kg based on: transient decrease in motor activity observed at Day 0 (5 hours post-dosing) |
| 870.7485<br>Metabolism and pharmacokinetics (rat) | 46220940 (1994), 46220941 (1995), 46220942 (1995), 46220943 (1995)<br>single dose: 2, 50 mg/kg<br>multiple dose: 2 mg/kg<br>Radiolabel:<br>(first ring: Pyridine second ring: Pyrimidine)<br>Acceptable/Guideline | Radiolabeled flazasulfuron (Pyridine/Pyrimidine) was rapidly distributed and excreted in the urine and feces following multiple dosing. Urinary elimination, calculated from a total collection of 168 hours, occurred slower in males (74/73%) compared to females (90/91%). Fecal elimination, calculated from a total collection of 168 hours, was greater in males (23/23%) than in females (10/9%). Radiolabel was detected at low concentrations in carcass (M:1.7/1.1%; F:0.30/0.23%)), blood (M: 0.74/0.35%; F: 0.16/0.02), liver (M: 0.23/0.14%; F: 0.04/0.04%), and kidney (M: 0.13/0.02%; F: 0.02/ <0.005%). Peak plasma concentration following single dose administration occurred at 6 hours in both sexes. |

## 4.2 FQPA Hazard Considerations

Flazasulfuron is a new active ingredient proposed for use on golf courses and other non-residential turf areas. This use is nonfood; therefore, an FQPA assessment of this chemical is not required.

## 4.3 Hazard Identification and Toxicity Endpoint Selection

A summary of the toxicology endpoints is in Table 4.3.

### 4.3.1 Acute Reference Dose (aRfD) - Female 13-49

In an acute neurotoxicity study (MRID 46220934), groups of 7-week old Sprague-Dawley rats (10/sex/group) were given a single oral dose by gavage of SL-160 (98.5 % a.i., batch/lot #303) in 0.5% aqueous methylcellulose at doses of 0, 50, 1000, or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 5 animals/sex/group. This assessment occurred on each of the four days, one week prior to the initiation of exposure, on Day 0 at five hours postdosing (the time of peak effect), and on Days 7 and 14 postdosing. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, all were subjected to histopathological evaluation of brain and peripheral nervous system tissues. No deaths occurred during the study.

No abnormal clinical observations were recorded in male animals. Anogenital staining, decreased feces and dried red material around the eyes, mouth, and forepaws were observed on Days 1 through 4 for two mid-dose and two high-dose females. Mean body weights for males and females in groups receiving the test material were not statistically significantly different from the controls at pre-test, pre-fast, or on Days 0, 7 and 14. There were no differences in the observations made as part of the FOB that were considered treatment related. Mean forelimb and hind limb grip strengths and mean foot-spread for males and females in groups receiving the test material showed no treatment-related differences from the controls at any of the observation times. Mean motor activity measurements for mid and high dose males and females were statistically significantly different from the respective control groups [Distance traveled measurement- M:(mid = 51.2% decrease), (high = 59.3% decrease); F: (high = 58.5% decrease)] on Day 0 (5 hours post-dosing). Animals were less active with more resting time than controls. The effect was reversed by the next scheduled observation (Day 7). Neurohistopathologic evaluation did not demonstrate any test material-related neurotoxic lesions following the examination of tissues from the central and peripheral nervous systems of high dose and control animals.

**Based on the transient loss of motor activity observed in this study, the NOAEL was 50 mg/kg bw. The LOAEL was 1000 mg/kg bw.**

This neurotoxicity study is classified as **Acceptable pending submission of analytical data verifying homogeneity and stability /Guideline**.

Dose and Endpoint for Establishing aRfD: **The NOAEL of 50 mg/kg bw based on the transient decrease in motor activity observed at Day 0 (5 hours post-dosing) at the LOAEL of 1000 mg/kg bw was selected for the acute RfD.**

Uncertainty Factor: The uncertainty factors used to determine RfD exposure limits of 100: 10X for interspecies variation; 10X for intraspecies variation.

Comments about Study/Endpoint/Uncertainty Factor: The NOAEL of 50 mg/kg is the lowest NOAEL for any available acute study. The endpoint selected is protective of the developmental effects seen in the prenatal developmental(Wistar) rat study with a NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day. Therefore, a separate endpoint for females 13-49 based on developmental effects is not considered necessary. The endpoint is appropriate for the exposure duration. The endpoint is considered conservative given the dose spacing. The NOAEL of 50 mg/kg could be significantly higher given that the LOAEL of 1000 mg/kg was the next highest dose tested.

**Acute RfD (General Population)** = $\frac{\text{50 mg/kg (NOAEL)}}{\text{100 (UF)}}$ = **0.5 mg/kg**

### 4.3.2 Chronic Reference Dose (cRfD)

In a 2-year combined chronic toxicity/carcinogenicity study (MRID 46220929), SL-160 technical (Lot/Batch No. 303, 97.3% a.i.) was administered in the feed to groups of 50 male Fischer (F344/DuCrj) rats at concentrations of 0, 40, 400, or 2000 ppm (0, 1.31, 13.26, and 70.1 mg/kg/day, respectively) and to groups of 50 female Fischer (F344/DuCrj) rats at concentrations of 0, 40, 400, or 4000 ppm (0, 1.60, 16.45, or 172.6 mg/kg/day) for up to 104 weeks. Satellite groups consisting of 10 male and female rats were administered the same dietary concentrations and were sacrificed after 26, 52, and 78 weeks for interim evaluations.

Treatment-related changes in clinical chemistry values in high-dose male rats were associated with renal toxicity (chronic nephropathy), the primary effect of SL-160 technical. Serum creatinine, blood urea nitrogen, total cholesterol, and potassium concentration were increased to 130, 178, 144, and 115%, respectively, of control levels at week 52 and increased to 369, 738, 216% , and 129%, respectively, of control levels at week 78. Hyperparathyroidism associated with chronic nephropathy induced hypercalcemia and hyperphosphatemia in high-dose males at weeks 52 and 78. Urine output was increased to 121% to 468% of control level in high-dose males from weeks 13-78, and the specific gravity was decreased and the urine was pale in color from weeks 52-78. Urine output by mid-dose males was increased to 122 to 160% of the control level from weeks 78-104.

Post-mortem examination revealed changes associated with renal toxicity that included increased absolute and relative kidney weights in mid-dose males from weeks 52-104 and in high-dose males from weeks 26-78. Increased incidences of gross kidney lesions were observed in high-dose males at weeks 52 and 78 and in the main study group and in mid-dose males at week 78 and in the main study group. Gross kidney lesions consisted of coarse surface, enlargement, pale color, dark color, and cysts. The enlarged parathyroid gland in high-dose male rats was associated with renal toxicity. Gross lesions in female rats included dark colored kidneys at weeks 52 and 78 and in the main study group.

Microscopic lesions in rats fed SL-160 technical were found primarily in the kidneys and in organs affected secondarily by kidney toxicity. Treatment-related microscopic kidney lesions included increased hyaline droplets in proximal tubular cells in mid-dose males and early

changes in chronic nephropathy, increased hyaline droplets, and luminal dilatation of proximal tubules in high-dose males at week 26. The incidences of the following kidney lesions were increased in mid- and high-dose males compared with control incidences: chronic nephropathy, increased hyaline droplets in proximal tubular cells, luminal dilatation of proximal tubules, increased brown pigment in proximal tubular cells, and pyelic (pelvic) epithelial hyperplasia. High-dose female rats had increased incidences of luminal dilatation of the proximal tubules (week 78 and main study), chronic nephropathy, and increased brown pigment in proximal tubular cells (main study) compared with control incidences.

**The lowest-observed-adverse-effect level (LOAEL) for SL-160 technical in rats is 400 ppm (13.3 mg/kg bw/day) for male and female rats based on renal toxicity (chronic nephropathy) in both sexes. The corresponding no-observed-adverse-effect level (NOAEL) is 40 ppm (1.3 mg/kg bw/day) for male and female rats.**

Dose and Endpoint for Establishing cRfD: The NOAEL of 1.3 mg/kg/day based on adverse change in kidney function (chronic nephropathy) at the LOAEL of 13.3 mg/kg/day was selected for the chronic RfD.

Uncertainty Factor: The uncertainty factors used to determine RfD exposure limits of 100: 10X for interspecies variation; 10X for intraspecies variation.

Comments about Study/Endpoint/Uncertainty Factor: The duration of dosing and the endpoint are appropriate for this study. The systemic NOAEL of 1.3 mg/kg/day is the lowest dose of any available chronic or subchronic study.

$$\textbf{Chronic RfD (all populations)} = \frac{\text{1.3 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.013 mg/kg/day}$$

### 4.3.3 Incidental Oral Exposure (Short and Intermediate Term)

*Short term.* (See Neurotoxicity (MRID 46220934) Executive Summary 4.3.1, p. 17) **The LOAEL of 1000 mg/kg is based on transient decrease in motor activity observed in the study at Day 0 (5 hours post-dosing). The NOAEL is 50 mg/kg.**

Dose and Endpoint for Risk Assessment: The NOAEL of 50 mg/kg bw based on the transient decrease in motor activity observed in this study at Day 0 (5 hours post-dosing) at the LOAEL of 1000 mg/kg bw.

Comments about Study/Endpoint: The NOAEL of 50 mg/kg is the lowest NOAEL for any available acute study. The endpoint is appropriate for the exposure duration. The endpoint is considered conservative given the dose spacing. The NOAEL of 50 mg/kg could be significantly higher given that the LOAEL of 1000 mg/kg was the next highest dose tested.

*Intermediate-term.* A 13-week dog study was used to select a dose and endpoint for evaluating intermediate-term incidental oral exposure. **The LOAEL of 10 mg/kg/day is based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic**

**transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). The NOAEL is 2 mg/kg/day.**

In a chronic toxicity study (MRID 46220927), SL-160 (Flazasulfuron; 97.3% a.i., batch/lot # 303) was administered to 4 beagle dogs/sex/dose by capsule. The dose levels of 0, 0.4, 2, 10, and 50 mg/kg/day in males and 0, 2, 10, and 50 mg/kg/day in females were administered for 52 weeks.

There were no deaths in any groups during the treatment period.

Almost all animals (34/36), including controls, had vomit of feed or foamy fluid during the treatment period. There was not a significant difference observed in the body weights of the treated groups when compared to the controls. No significant hematology toxicity occurred in the study. Clinical chemistry parameters were not statistically changed from controls in either males or females. There were no significant differences in organ weights between the treated and control groups.

Inflammatory cell infiltration (liver) was observed at 10 and 50 mg/kg/day in the male (4/4, 2/4) and female (3/4, 3/4) groups.

**In conclusion, the LOAEL (M/F) was 10 mg/kg/day based on inflammatory cell infiltration in the liver. The NOAEL (M/F) was 2 mg/kg/day.**

Dose and Endpoint for Risk Assessment: The NOAEL of 2 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas) at the LOAEL of 10 mg/kg/day.

Comments about Study/Endpoint: The systemic NOAEL of 2 mg/kg/day is the lowest dose of any subchronic available with the appropriate duration and route for the endpoint. Intermediate-term exposure is not expected based on the use pattern. Therefore, the intermediate-term endpoint will not be used in this assessment.

### 4.3.4 Dermal Absorption

No dermal absorption study is available for flazasulfuron. However, a 21-day dermal toxicity study (rabbit) was submitted. In this study, no systemic toxicity occurred at the limit dose (1000 mg/kg/day) and the primary toxic effects of concern were adequately assessed in the study. In the absence of a dermal absorption study, a conservative dermal absorption factor (DAF) was estimated based on available oral and dermal toxicity data. HED estimated a DAF of no more than 45% based on the ratio of the LOAEL from the oral rabbit developmental study (450 mg/kg/day) and the NOAEL from the 21-day dermal toxicity study in rabbits (1000 mg/kg/day). This is a conservative estimate because the 21-day dermal study did not present an adverse effect at the highest dose tested in order to produce a LOAEL.

$$\textbf{Dermal Absorption Factor (DAF)} = \frac{\text{450 mg/kg/day (LOAEL)}}{\text{1000 mg/kg/day (NOAEL)}} \times 100 = \textbf{45\%}$$

### 4.3.5 Dermal Exposure (Short, Intermediate and Long Term)

*Short-term.* (See Neurotoxicity (MRID 46220934) Executive Summary 4.3.1, p. 17) **The LOAEL of 1000 mg/kg is based on transient decrease in motor activity observed in the study at Day 0 (5 hours post-dosing). The NOAEL is 50 mg/kg.**

Dose and Endpoint for Risk Assessment: The NOAEL of 50 mg/kg bw based on the transient decrease in motor activity observed in this study at Day 0 (5 hours post-dosing) at the LOAEL of 1000 mg/kg bw.

Comments about Study/Endpoint: The NOAEL of 50 mg/kg is the lowest NOAEL for any available acute study. The endpoint selected is protective of the developmental effects seen in the prenatal developmental(Wistar) rat study with a NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day. Therefore, a separate endpoint for females 13-49 based on developmental effects is not considered necessary. The endpoint is appropriate for the exposure duration. The endpoint is considered conservative given the dose spacing. The NOAEL of 50 mg/kg could be significantly higher given that the LOAEL of 1000 mg/kg was the next highest dose tested.

*Intermediate-term.* (See 13-week dog (MRID 46220927) Executive Summary 4.3.3, p. 19) **The LOAEL of 10 mg/kg/day is based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). The NOAEL is 2 mg/kg/day.**

Dose and Endpoint for Risk Assessment: The NOAEL of 2 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas) at the LOAEL of 10 mg/kg/day.

Comments about Study/Endpoint: The systemic NOAEL of 2 mg/kg/day is the lowest dose of any subchronic study available with the appropriate duration and route for the endpoint. Intermediate-term exposure is not expected based on the use pattern. Therefore, the intermediate-term endpoint will not be used in this assessment.

*Long-term.* (See 2-year Combined Chronic Toxicity/Carcinogenicity (MRID 46220929) Executive Summary 4.4.3, p. 23) **A rat study was used to select a dose and endpoint for evaluating long-term dermal exposure. The LOAEL of 13.3 mg/kg/day is based on a decrease in body weight and adverse changes in kidney function (chronic nephropathy). The NOAEL is 1.3 mg/kg/day.**

Dose and Endpoint for Risk Assessment: The NOAEL of 1.3 mg/kg/day based on adverse change in kidney function (chronic nephropathy) at the LOAEL of 13.3 mg/kg/day.

Comments about Study/Endpoint: The duration of dosing and the endpoint are appropriate for this study. The systemic NOAEL of 1.3 mg/kg/day is the lowest dose of any available chronic or subchronic study. Long-term exposure is not expected based on the use pattern. Therefore, the long-term endpoint will not be used in this assessment.

### 4.3.6 Inhalation Exposure (Short, Intermediate and Long Term)

*Short-term.* (See Neurotoxicity (MRID 46220934) Executive Summary 4.3.1, p. 17) **The LOAEL of 1000 mg/kg is based on transient decrease in motor activity observed in the study at Day 0 (5 hours post-dosing). The NOAEL is 50 mg/kg.**

Dose and Endpoint for Risk Assessment: The NOAEL of 50 mg/kg bw based on the transient decrease in motor activity observed in this study at Day 0 (5 hours post-dosing) at the LOAEL of 1000 mg/kg bw.

Comments about Study/Endpoint: The NOAEL of 50 mg/kg is the lowest NOAEL for any available acute study. The endpoint is appropriate for the exposure duration. The endpoint is considered conservative given the dose spacing. The NOAEL of 50 mg/kg and LOAEL of 1000 mg/kg, which was the next highest dose tested, i.e. the NOAEL could be higher.

*Intermediate-term.* (See 13-week dog (MRID 46220927) Executive Summary 4.3.3, p. 19) **The LOAEL of 10 mg/kg/day is based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). The NOAEL is 2 mg/kg/day.**

Dose and Endpoint for Risk Assessment: The NOAEL of 2 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas) at the LOAEL of 10 mg/kg/day.

Comments about Study/Endpoint: The systemic NOAEL of 2 mg/kg/day is the lowest dose of any subchronic available with the appropriate duration and route for the endpoint. The intermediate-term exposure pattern is not expected to based on the use pattern. Therefore, the endpoint will not be of use in this assessment.

*Long-term.* (See 2-year Combined Chronic Toxicity/Carcinogenicity (MRID 46220929) Executive Summary 4.4.3, p. 23) A rat study was used to select a dose and endpoint for evaluating long-term dermal exposure. **The LOAEL of 13.3 mg/kg/day is based on a decrease in body weight and adverse changes in kidney function (chronic nephropathy, enlargement and dark color of kidney). The NOAEL is 1.3 mg/kg/day.**

Dose and Endpoint for Risk Assessment: The NOAEL of 1.3 mg/kg/day based on adverse change in kidney function (chronic nephropathy) at the LOAEL of 13.3 mg/kg/day.

Comments about Study/Endpoint: The duration of dosing and the endpoint are appropriate for this study. The systemic NOAEL of 1.3 mg/kg/day is the lowest dose of any available chronic or subchronic study. Long-term exposure is not expected based on the use pattern. Therefore, the long-term endpoint will not be used in this assessment.

### 4.3.7 Margins of Exposure for Occupational and Residential Exposure Assessments

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

| Route of Exposure | Duration of Exposure | | |
|---|---|---|---|
| | Short-Term (1-30 Days) | Intermediate-Term (1 - 6 Months) | Long-Term (> 6 Months) |
| Occupational Exposure | | | |
| Dermal | 100 | 100 | 100 |
| Inhalation | 100 | 100 | 100 |
| Residential (non-dietary) Exposure | | | |
| Incidental Oral | 100 | 100 | 100 |
| Dermal | 100 | 100 | 100 |
| Inhalation | 100 | 100 | 100 |

The MOE is based on 10x uncertainty factor (UF) for intraspecies variation and 10x UF for interspecies extrapolation. The (hazard-based) special FQPA safety factor is reduced to 1X due to non-food-use status of flazasulfuron.

### 4.3.8 Classification of Carcinogenic Potential

Based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies and lack of a mutagenicity concern, flazasulfuron can be classified as "No evidence of carcinogenicity to humans".

**Table 4.3. Summary of Toxicological Doses and Endpoints for Flazasulfuron for Use in Human Health Risk Assessments**

| Exposure Scenario | Dose Used in Risk Assessment, UF | Special FQPA SF* and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary (Female 13-49) | NOAEL =50 mg/kg<br>*UF = 100*<br>**Acute RfD** = 0.5 mg/kg | FQPA SF = 1X<br><br>aPAD = acute RfD / FQPA SF<br><br>= 0.5 mg/kg | Acute neurotoxicity (rat) LOAEL = 1000 mg/kg based on: transient decrease in motor activity observed at Day 0 (5 hours post-dosing). |
| Chronic Dietary (all populations) | Oral<br>NOAEL = 1.3 mg/kg/day<br>*UF = 100*<br>**Chronic RfD** = 0.013 mg/kg/day | FQPA SF = 1X<br><br>cPAD=chronic RfD / FQPA SF<br><br>= 0.013 mg/kg/day | Combined Chronic Toxicity/ Carcinogenicity rats<br>LOAEL= 13.3 mg/kg/day based on: Adverse change in kidney function (chronic nephropathy) |

**Table 4.3. Summary of Toxicological Doses and Endpoints for Flazasulfuron for Use in Human Health Risk Assessments**

| Exposure Scenario | Dose Used in Risk Assessment, UF | Special FQPA SF* and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Incidental Oral Short-Term (1 - 30 days) | NOAEL = 50 mg/kg | Occupational: LOC for MOE = 100 | Acute neurotoxicity (rat) LOAEL = 1000 mg/kg based on: transient decrease in motor activity observed at Day 0 (5 hours post-dosing). |
| Incidental Oral Intermediate-Term (1 - 6 months) | NOAEL = 2 mg/kg/day | Occupational: LOC for MOE= 100 | 90-Day oral toxicity in (dog) LOAEL= 10 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). |
| Dermal Short-Term (1 - 30 days) | Oral NOAEL = 50 mg/kg (dermal absorption rate = 45%) | Occupational: LOC for MOE= 100 | Acute neurotoxicity (rat) LOAEL = 1000 mg/kg based on: transient decrease in motor activity observed at Day 0 (5 hours post-dosing). |
| Dermal Intermediate-Term (1 - 6 months) | Oral NOAEL = 2 mg/kg/day (dermal absorption rate = 45%) | Occupational: LOC for MOE = 100 | 90-Day oral toxicity in (dog) LOAEL = 10 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). |
| Dermal Long-Term (> 6 months) | Oral NOAEL = 1.3 mg/kg/day (dermal absorption rate = 45%) | Occupational: LOC for MOE = 100 | Combined Chronic Toxicity/ Carcinogenicity rats LOAEL= 13.3 mg/kg/day based on: Adverse change in kidney function (chronic nephropathy) |
| Inhalation Short-Term (1 - 30 days) | NOAEL = 50 mg/kg (inhalation absorption rate = 100%) | Occupational: LOC for MOE = 100 | Acute neurotoxicity (rat) LOAEL = 1000 mg/kg based on: transient decrease in motor activity observed at Day 0 (5 hours post-dosing). |
| Inhalation Intermediate-Term (1 - 6 months) | NOAEL = 2 mg/kg/day (inhalation absorption rate = 100%) | Occupational: LOC for MOE = 100 | 90-Day oral toxicity in (dog) LOAEL = 10 mg/kg/day based on changes in liver (increase in: deposition of brown pigments, glutamic pyruvic transaminase, creatine phosphokinase, inflammatory cell infiltration, microgranulomas). |
| Inhalation Long-Term (> 6 months) | Oral NOAEL = 1.3 mg/kg/day (inhalation absorption rate = 100%) | Occupational: LOC for MOE = 100 | Combined Chronic Toxicity/ Carcinogenicity rats LOAEL= 13.3 mg/kg/day based on: Adverse change in kidney function (chronic nephropathy) and kidney physiology (enlargement, dark color of kidney) |

| Table 4.3. Summary of Toxicological Doses and Endpoints for Flazasulfuron for Use in Human Health Risk Assessments | | | |
|---|---|---|---|
| **Exposure Scenario** | **Dose Used in Risk Assessment, UF** | **Special FQPA SF* and Level of Concern for Risk Assessment** | **Study and Toxicological Effects** |
| Cancer (oral, dermal, inhalation) | **Classification:** No evidence of carcinogenicity to humans | | |

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable, * Refer to Section 4.5

### 4.4 Special FQPA Safety Factor

Because this is a non-food use pesticide, consideration of an FQPA safety factor is not required.

### 4.5 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). In the available toxicity studies on flazasulfuron, there was no estrogen, androgen, and/or thyroid mediated toxicity.

## 5.0 Public Health Data

Flazasulfuron is a new active ingredient. Public health information is not available.

## 6.0 Drink Water Exposure/Risk Pathway

### 6.1 Drinking Water Profile

#### 6.1.1 Environmental Fate Assessment

The proposed use of flazasulfuron is as an herbicide to control cool season grasses and weeds in professionally managed Bermudagrass and Zoysiagrass. This proposed use of flazasulfuron is the first use for this chemical in the United States. No adsorption/desorption

data are available for flazasulfuron and it will be assumed to be highly mobile. Estimations using Epi Suite software suggest that the degradates, with the exception ADMP, are generally less mobile. The degradate ADMP is also a degradate of other sulfonylurea herbicides and is known to be very mobile. Based on a low vapor pressure of $<1 \times 10^{-7}$ torr and a very low Henry's Law Constant , volatilization from soil or water is an unlikely route of dissipation for flazasulfuron.

Considered on its own, flazasulfuron is non-persistent to moderately persistent in both aquatic and soil environments, with hydrolysis (abiotic and/or microorganism mediated; abiotic hydrolysis half-life 0.5-11.3 d, MRID 46220949) and direct aqueous photolysis (18 d, MRID 46220950) being the fastest degradation pathways. Other routes of degradation include aerobic soil metabolism and aerobic and anaerobic aquatic metabolism, all of which have half-lives of less than 45 days (MRIDs 46220951, 46220953, 46220954). The rates of degradation and the major products depend on the environmental conditions (pH of the media, temperature, microbial population, etc). This low persistence will limit the availability of flazasulfuron for leaching and runoff regardless of its mobility and solubility.

Flazasulfuron is a weak acid (pKa = 4.37) like all of the sulfonylurea herbicides. Solubility and hydrophilicity increase with increasing pH. Flazasulfuron is unlikely to bioaccumulate.

An important characteristic of flazasulfuron is that not only the rates of abiotic hydrolysis are pH dependent, but also the mechanism of formation and chemical nature of degradates. Flazasulfuron degrades faster in acid than alkaline pHs. Cleavage products containing a single ring predominate in acid media. As pH increases, bridge elimination/bridge contraction products (Smiles rearrangement) become more predominant This type of products are also known for other sulfonylurea herbicides containing a pyridine ring (e.g., trifloxysulfuron, nicosulfuron, rimsulfuron). Those cleavage product containing only the pyrimidinyl ring are also known for other sulfonylurea herbicides. All degradates preserving the trifluromethyl group are unique to flazasulfuron.

The degradates of flazasulfuron are more stable. When considering total residues of flazasulfuron, direct aqueous photolysis remains an important degradation pathway (half-life 34 d) but total residues are stable to hydrolysis. The resistance to aerobic soil metabolism is also much higher (half-life 866 days, MRID 46220951), with DTPU and TPSA as the most persistent degradates. Despite the increased stability, in the field, most degradates are not detected below 30 cm and have dissipated by the end of the 119-137 day studies (MRIDs 46220957 - 46220959). The few, low-level exceptions to this involve DTPU, suggesting that it would be the most likely to persist.

### 6.1.2 Estimated Environmental Concentrations

EFED currently has no monitoring data for flazasulfuron in surface or ground water. Therefore, EFED conducted a Tier I drinking water assessment for flazasulfuron using the Tier I screening model, FIFRA Index Reservoir Screening Tool (FIRST) to determine estimated surface water concentrations of flazasulfuron from ground spray application to turf. The Screening Concentration in Ground water (SCI-GROW) model was used to estimate ground water concentrations for flazasulfuron. Modeling results are shown in Table 6.1.

| Table 6.1 Drinking Water EDWCs for Flazasulfuron | | |
|---|---|---|
| **Drinking Water Source** | **Peak (ug/L)** | **Annual Average(ug/L)** |
| Surface Water | 14.7 | 5.1 |
| Ground water | 92 | 92 |

### 6.1.2.1 Surface Water

Tier I EECs for surface were generated using FIRST, a screening model designed by the Environmental Fate and Effects Division (EFED, 2001a) of the Office of Pesticide Programs to estimate the concentrations found in drinking water from surface water sources for use in human health risk assessment. As such, it provides upper bound values on the concentrations that might be found in drinking water due to the use of a pesticide. FIRST is a single event model (one runoff event), but can account for spray drift from multiple applications. FIRST is hardwired to represent the Index Reservoir, a standard water body used by the Office of Pesticide Programs to assess drinking water exposure. It is based on a real reservoir, Shipman City Lake in Illinois, that is known to be vulnerable to pesticide contamination. The single runoff event moves a maximum percentage of the applied pesticide into the reservoir. This amount can be reduced due to degradation on the field and the effects of binding to soil in the field. FIRST also uses a Percent Cropped Area (PCA) factor to adjust for the area within the watershed that is planted to the modeled crop.

A summary of the model input parameter values used in FIRST is presented in Table 6.2. These parameters were selected in accordance with EFED's input parameter guidance (EFED, 2002). The application rate used represents the maximum label rate and half-lives are based on registrant-submitted data. In order to account for the degradates of flazasulfuron as well as the parent compound, half-lives were calculated using the total amount of all compounds remaining at each sampling event, including flazasulfuron, DTPU, DTPP, HTPP, TPSA, and ADMP.

Based on modeling results, EFED estimates an acute surface water EEC of 14.7 ug/L and a chronic EEC of 5.1 ug/L.

### 6.1.2.2 Ground water

EECs for groundwater generated with SCI-GROW 2.3 (EFED, 2001b), a screening tool for ground water used as drinking water. SCI-GROW was developed by regressing the results of Prospective Ground Water studies against the Relative Index of Leaching Potential (RILP). The RILP is a function of aerobic soil metabolism and the soil-water partition coefficient. The output of SCI-GROW represents the concentration that might be expected in shallow unconfined aquifers under sandy soils.

As with surface water modeling, model input parameter values used in SCI-GROW were selected in accordance with EFED's input parameter guidance. These input parameters represent the total residues of flazasulfuron at the maximum label application rate. The acute and chronic concentration of total residues of flazasulfuron in shallow ground water predicted by SCI-GROW under these conditions is 92 ug/L.

### 6.1.2.3 Input parameters for Drinking Water Models

Key parameters for the FIRST and SCI-GROW models are summarized in Table 6.2.

| Table 6.2 FIRST and SCI-GROW Input Parameters for **Flazasulfuron** | | |
|---|---|---|
| **Input parameters to FIRST** | | |
| **Parameter** | **Value** | **Source** |
| Application rate | 0.047 lb a.i./A | Label EPA Reg. # 71512-RE |
| Number of applications | 3 | Label EPA Reg. # 71512-RE |
| Minimum interval between applications | 14 Days | Label EPA Reg. # 71512-RE |
| Aerobic soil metabolism half-life | 2598 | MRID 46220951 |
| $K_d$ (mean) | 10 mL/g | MRID 46220954 |
| PCA | 100% | Default |
| Solubility | 2100 mg/L | Product Chemistry |
| Aerobic Aquatic Metabolism half-life | 156 | MRID46220954 |
| **Environmental Fate Input Parameters for SCI-GROW** | | |
| $K_{OC}$ | 10 mL/g | Lowest value for the parent compound or degradates |
| Aerobic soil metabolism half-life | 866 day | MRID 4622951 |

## 6.2 Acute and Chronic Drinking Water Exposure and Risk

Acute and chronic drinking water risk assessments were conducted using the DEEM (DEEM-FCID™, Ver 2.03) which use water consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute and chronic drinking water exposure/risk analyses for flazasulfuron were conducted using unrefined Tier 1 drinking water exposure assumptions for all uses. An estimated ground water concentration of 92 ppb was used for both the acute and chronic drinking water assessments.

Results of the Tier I DEEM acute drinking water exposure analyses are presented in Table 6.3. The results of the DEEM chronic drinking water exposure analyses for flazasulfuron are reported in the Table 6.4. These assessments conclude that the acute and chronic drinking water exposure estimates are below HED's level of concern. The DEEM acute drinking water exposure estimates at the 95$^{th}$ percentile for the highest exposed population subgroup, all infants (< 1 year old), is 4% of the aPAD.. The DEEM chronic drinking water exposure estimates for the highest exposed population subgroup, all infants (< 1 year old), is 49% of the cPAD. This is a highly conservative assessment in that all water metabolites were included in the assessment.

| Table 6.3 Results of Acute Drinking Water Exposure Analysis | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup | aPAD (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.5 | 0.0048 | 0.96 | 0.0090 | 2 | 0.0180 | 4 |
| All Infants (< 1 year old) | 0.5 | 0.0181 | 4 | 0.0260 | 5 | 0.0465 | 9 |
| Children 1-2 years old | 0.5 | 0.0075 | 2 | 0.0126 | 3 | 0.0183 | 4 |
| Children 3-5 years old | 0.5 | 0.0069 | 1 | 0.0108 | 2 | 0.0176 | 4 |
| Children 6-12 years old | 0.5 | 0.0048 | 1 | 0.0080 | 2 | 0.0109 | 2 |
| Youth 13-19 years old | 0.5 | 0.0039 | 1 | 0.0066 | 1 | 0.0118 | 2 |
| Adults 20-49 years old | 0.5 | 0.0044 | 1 | 0.0075 | 2 | 0.0135 | 3 |
| Females 13-49 years old | 0.5 | 0.0045 | 1 | 0.0072 | 1 | 0.0128 | 2 |
| Adults 50+ years old | 0.5 | 0.0040 | 1 | 0.0058 | 1 | 0.0093 | 2 |

| Table 6.4 Results of Chronic Drinking Water Exposure Analysis | | | |
|---|---|---|---|
| Population Subgroup | cPAD (mg/kg/day) | Exposure (mg/kg/day) | % cPAD |
| U.S. Population (total) | 0.013 | 0.0019 | 15 |
| All Infants (< 1 year) | 0.013 | 0.0064 | 49 |
| Children 1-2 years | 0.013 | 0.0029 | 22 |
| Children 3-5 years | 0.013 | 0.0027 | 21 |
| Children 6-12 years | 0.013 | 0.0019 | 14 |
| Youth 13-19 years old | 0.013 | 0.0014 | 11 |
| Adults 20-49 years old | 0.013 | 0.0018 | 14 |
| Females 13-49 years old | 0.013 | 0.0018 | 14 |
| Adults 50+ years old | 0.013 | 0.0019 | 15 |

## 7.0 Residential (Non-Occupational) Exposure/Risk Pathway

Flazasulfuron is proposed for use on golf courses and athletic fields. The registrant indicated that turf applications are intended to be made by professional pest control operators (PCOs) only (although the label does not state this). Therefore, non-occupational handler exposure was not evaluated. Recreational post-application exposure via the dermal route is likely for adults and children using golf courses or athletic fields. Toddler exposure was not assessed because the label specifically states that flazasulfuron is not for use in areas where children can contact treated turf. The postapplication risk assessment is based on generic assumptions from the Recommended Revisions to the Residential SOPs, and recommended approaches by HED's Science Advisory Council for Exposure (ExpoSAC).

A turf transferrable residue (TTR) study was submitted by the registrant (MRID#: 46220945) for use in assessing postapplication activities. The results of this study were useful for determining residue dissipation, however, the actual data were not used to estimate dermal exposure. The study was conducted using a modified version of the California roller, which was found to have a much lower transfer efficiency than the original version. These TTRs are not compatible with the transfer coefficients used in this assessment (which were derived using the original method); therefore, the assessment was conducted with the standard assumption for the initial fraction of residue available for turf.

### 7.1 Post-Application Exposure and Risk

Golf Course

Postapplication exposure is possible for recreational golfers who use the course after flazasulfuron has been applied. According to a 1992 report from *The Center For Golf Course Management*, 12.2 percent of the population are golfers (i.e., 28.5 million people). A discussion of the individual exposure factors used in the assessment follows:

- Turf Transferrable Residue = standard assumption of 5% of the application rate for the fraction initially available.
- Transfer coefficient = 500 $cm^2$/hour based on exposure data for two chemicals that quantified exposures to golfers. This transfer coefficient represents golfers wearing short pants and short-sleeved shirts.
- Duration is 4 hours for a chemical that can be used on all parts of a course (greens, tees, and fairways). This is an estimate of the average time it takes to play a round of golf which is based on the report completed by the Center For Golf Course Management *[1992 Golf Course Operations: Cost of Doing Business/Profitability*. Library of Congress GV975.G56 1992].

The short-term MOE was estimated for "Day 0" exposure (i.e., the day of application) because it is assumed that individuals could enter the course immediately after application. As shown in Table 7.1, the short-term MOE is greater than 100 on the day of application, and therefore, is not of concern.

| Table 7.1. Post-application Short-Term MOEs for Golfers | | | | | |
|---|---|---|---|---|---|
| Application Rate (AR) (lbs ai/A) | TTR ($\mu g/cm^2$)[a] | Transfer Coefficient (Tc) ($cm^2/hr$) | Exposure Time (ET) (hrs/day) | Short-Term Dermal | |
| | | | | ADD (mg/kg/day)[b] | MOE[c] |
| 0.047 | 0.026 | 500 | 4 | 0.00034 | 150,000 |

[1] Dislodgeable Foliar Residue $_{Postapplication\ day\ zero}$ ($ug/cm^2$) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage (0.05) x 4.54E+8 $\mu g$/lb x 2.47E-8 A/$cm^2$

[a] Default TTR value based on standard assumption of 5% of application rate for fraction of ai initially available.

[b] Average daily dose (ADD) (mg/kg/day) = [(TTR ($\mu g/cm^2$) * Tc ($cm^2$/hr) * 45% dermal absorption * mg/1,000 $\mu g$ * ET ( hrs/day)] / [70-kg BW]

[c] Short-Term MOE = NOAEL / ADD; Short-Term NOAEL = 50 mg/kg/day. The LOC is 100.

Athletic Fields

Postapplication exposure is also possible for people who use sports fields after flazasulfuron has been applied. Recreational postapplication dermal exposure was assessed.

The exposure and risk estimates for the exposure scenarios are assessed for the day of application (day "0") because it is assumed that the turf could be contacted immediately after application. The equations used for the exposure calculations and the results are presented in Table 7.2. The **short-term MOE** for this scenario is **above the LOC of 100, and is not of concern.**

| Table 7.2. Postapplication Dermal Exposure and Risk From Treated Turf | | | | | | |
|---|---|---|---|---|---|---|
| Subgroup Exposed | Application Rate (lb ai/A) | Dislodgeable Foliar Residue ($ug/cm^2$) | Dermal Transfer Coefficient ($cm^2$/hr) | Body Wt (kg) | Daily Dose[2] (mg/kg/day) | Dermal MOE[3] |
| | | | | | Short-term | Short-term |
| Adults | 0.047 | 0.026 | 43,000 | 70 | 0.015 | 3,400 |

[1] Dislodgeable Foliar Residue $_{Postapplication\ day\ zero}$ ($ug/cm^2$) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage (0.05) x 4.54E+8 $\mu g$/lb x 2.47E-8 A/$cm^2$

[2] Daily Dose = [Dislodgeable Foliar Residue x Absorption Factor (0.45) x 0.001 mg/ug x Dermal Transfer Coefficient x Exposure Time (2 hrs/day)]/Body weight

[3] Dermal MOE = Dermal NOAEL/Daily Dose; where Short-term NOAEL = 50 mg/kg/day.

The exposure estimate is based on some upper-percentile (i.e., maximum application rate, initial amount of TTR, transfer coefficient, dermal absorption factor, and duration of exposure) and a central tendency (i.e., body weight) assumptions and is considered to be representative of high-end exposure. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from turf and assumptions regarding transfer of chemical residues. The estimated exposure is believed to be a reasonable high-end estimate based on observations from chemical-specific field studies and professional judgement.

### 7.2 Other (Spray Drift, etc.)

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 flazasulfuron. 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. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/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 and risks associated with aerial as well as other application types where appropriate.

Please note that as indicated in this assessment, flazasulfuron is directly applied to golf course turf and athletic fields and does not result in exposures of concern. It is unlikely that the potential for risk of exposure to spray drift from these uses would be higher than that estimated for contact with treated turf.

## 8.0 Occupational Exposure/Risk Pathway

### 8.1 Short/Intermediate/Long-Term Handler Risk

There is a potential for exposure to flazasulfuron during mixing, loading, and application activities. Handlers' exposure and risk were estimated for the following scenarios: (1) mixing/loading water dispersible granule formulation (i.e., dry flowable) for groundboom application, (2) applying sprays with a groundboom sprayer, (3) mixing/loading dry flowable formulation and applying sprays with a handgun sprayer, and (4 and 5) mixing/loading/applying liquids with a low-pressure handwand and backpack sprayer, respectively. The label specifically states that flazasulfuron is not to be applied aerially, or through any type of irrigation system (chemigation).

The results of the handler occupational exposure and risk assessment indicate that risks are not of concern with baseline clothing, or when gloves are worn in cases where data are not available to demonstrate exposure with no gloves. The Total Short-Term MOEs range from 3,700 to 270,000; which exceed the LOC of 100, and therefore, are not of concern. Exposure assumptions and MOEs for occupational handlers are summarized in Table 8.1.

HED recognizes that it is feasible for the same individual to mix/load and apply formulations with the groundboom sprayer, however, appropriate data are not available in PHED for which unit exposure values for these combined activities can be derived. HED does not recommend simply adding the unit exposure values for each job function because any extrapolation error (i.e., exposure from the amount ai handled in the study to that of a real-life application) would be magnified, leading to greater uncertainty. For information and characterization purposes, even

with the over-estimation uncertainty, the MOEs for these combined activities for groundboom application of flazasulfuron would be well above the LOC of 100 (i.e., 50,000).

The minimum level of PPE for handlers is based on acute toxicity for the end-use products. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

| Table 8.1. Summary of MOEs for Occupational Handlers of Flazasulfuron | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario (Scenario #) | Dermal Unit Exposure (mg/lb ai) [1] | | Inhalation Unit Exposure (µg/lb ai) [2] | Application Rate (lb ai/A) [3] | Area Treated (A/day) [4] | Total Short-term MOE [5] | |
| | Baseline | PPE (gloves) | | | | Baseline | PPE (gloves) |
| Mixer/Loader | | | | | | | |
| (1) Mixing/Loading Dry Flowables for Groundboom application | 0.066 | - | 0.77 | 0.047 | 40 | 61,000 | - |
| Applicator | | | | | | | |
| (2) Applying Sprays with Open Cab Groundboom | 0.014 | - | 0.74 | 0.047 | 40 | 270,000 | - |
| Mixer/Loader/Applicator | | | | | | | |
| (3) Mixing/Loading Dry Flowables and Applying with Handgun Sprayer | no data | 0.59 | 2.2 | 0.047 | 5 | no data | 56,000 |
| (4) Mixing/Loading Dry Flowables and Applying with Low-Pressure Handwand | 100 | 0.43 | 30 | 0.00053 (lb ai/gal) | 40 (gal/day) | 3,700 | - |
| (3) Mixing/Loading Dry Flowables and Applying with Backpack Sprayer | no data | 2.5 | 30 | 0.00053 (lb ai/gal) | 40 (gal/day) | no data | 140,000 |

[1] Baseline dermal unit exposure values represent long pants, long sleeved shirts, shoes, and socks; PPE values represent the addition of chemical-resistant gloves for those scenarios for which data are not available without gloves. Values are reported in the PHED Surrogate Exposure Guide dated August 1998, except for the handgun value which was obtained from ORETF.

[2] Inhalation unit exposure values represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.

[3] Application rates are based on maximum values found in label: Flazasulfuron 25WG (Reg No: 71512-XXX).

[4] Daily area treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (standard EPA/OPP/HED values).

[5] Short-/Intermediate-Term MOE = NOAEL (50 mg/kg/day) / Total Daily Absorbed Short-Term Dose. The LOC is 100.

Total Daily Absorbed Dose (mg/kg/day) = {[(Dermal unit exposure * 45% Dermal absorption) + (Inhalation unit exposure * 100% absorption)] * Application rate * Area treated} / 70-kg Body weight.

## 8.2 Short/Intermediate/Long-Term Post-application Risk

This registration action for flazasulfuron involves application to golf courses, industrial parks, tank farms, sod farms, seed farms, professionally managed sports fields, and commercial lawns. Postapplication inhalation exposure is expected to be negligible, however, dermal exposure is possible for workers mowing/maintaining the turfgrass. A turf transferrable residue (TTR) study was submitted by the registrant (MRID#: 46220945) for use in assessing postapplication activities. The results of this study were useful for determining residue dissipation only. The actual data from the TTR study were not appropriate for use in estimating dermal exposure because the study was conducted using a modified version of the California roller. This version was found to have a much lower transfer efficiency than the original version, which results in TTR measurements that are incompatible with the transfer coefficients used in this assessment (which were derived using the original roller method). Therefore, the assessment was conducted with the standard assumption for the initial fraction of residue available for turf.

In addition to turf residue, transfer coefficients (Tc) are used to relate the turf residue values to activity patterns to estimate potential human exposure. The transfer coefficient used in this assessment is from an interim transfer coefficient guidance document developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP# 3.1). The Tc of 3,400 $cm^2$/hr was used in this assessment for mowing and all other maintenance activities associated with turf that take place after application.

As a screening-level approach, the short-term MOE was estimated for "Day 0" exposure (i.e., the day of application). As shown in Table 8.2, the short-term MOE is greater than 100 on the day of application, and therefore, is not of concern.

**Table 8.2. Post-application Short-Term MOEs for Turf Maintenance Workers**

| Scenario | TTR ($\mu g/cm^2$)[a] | Transfer Coefficient (Tc) ($cm^2$/hr) | Exposure Time (ET) (hrs/day) | Short-Term Dermal | |
|---|---|---|---|---|---|
| | | | | ADD (mg/kg/day)[b] | MOE[c] |
| Maintenance Activities Turfgrass | 0.026 | 3,400 | 8 | 0.0046 | 11,000 |

[a] Default TTR value based on standard assumption of 5% of ai initially available from the application rate of 0.047 lb ai/A.

[b] Average daily dose (ADD) (mg/kg/day) = [(TTR ($\mu g/cm^2$) * Tc ($cm^2$/hr) *45% dermal absorption * mg/1,000 $\mu g$ * ET (hrs/day)] / [70-kg BW]

[c] Short-Term MOE = NOAEL / ADD; Short-Term NOAEL = 50 mg/kg/day. The LOC is 100.

The flazasulfuron technical material has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III/IV. The Flazasulfuron 25WG label indicates and REI of 4 hrs, which is not in compliance with the WPS. This product is intended for use on sod and seed farms, which are within the scope of the WPS, therefore, **the REI on the label needs to be corrected to 12 hours.** Flazasulfuron is also intended for non-agricultural use sites to which the WPS does not

apply, and correctly contains language cautioning unprotected persons to keep out of treated areas until sprays have dried.

## 9.0 Data Needs and Label Requirements

### 9.1 Toxicology

Acute neurotoxic study: HED is requesting historical positive control data, analytical data verifying homogeneity, and stability of formulated test material for this study.

### 9.2 Occupational and Residential Exposure

The registrant is requested to amend the label to more prominently state that flazasulfuron is not for use in areas where children can contact treated turf. (Currently located on p.5 of the label.)

# Appendices

## 1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for non-food use for flazasulfuron are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

**Table 1.**

| Test | | Technical | |
|---|---|---|---|
| | | Required | Satisfied |
| 870.1100 | Acute Oral Toxicity | yes | yes |
| 870.1200 | Acute Dermal Toxicity | yes | yes |
| 870.1300 | Acute Inhalation Toxicity | yes | yes |
| 870.2400 | Primary Eye Irritation | yes | yes |
| 870.2500 | Primary Dermal Irritation | yes | yes |
| 870.2600 | Dermal Sensitization | yes | yes |
| 870.3100 | Oral Subchronic (rodent) | yes | yes |
| 870.3150 | Oral Subchronic (nonrodent) | yes | yes |
| 870.3200 | 21-Day Dermal | yes | yes |
| 870.3250 | 90-Day Dermal | no | - |
| 870.3465 | 90-Day Inhalation | no | - |
| 870.3700a | Developmental Toxicity (rodent) | yes | yes |
| 870.3700b | Developmental Toxicity (nonrodent) | yes | yes |
| 870.3800 | Reproduction | yes | yes |
| 870.4100a | Chronic Toxicity (rodent) | no | - |
| 870.4100b | Chronic Toxicity (nonrodent) | yes | yes |
| 870.4200a | Oncogenicity (rat) | no | - |
| 870.4200b | Oncogenicity (mouse) | yes | yes |
| 870.4300 | Chronic/Oncogenicity | yes | yes |
| 870.5100 | Mutagenicity—Gene Mutation - bacterial | yes | yes |
| 870.5300 | Mutagenicity—Gene Mutation - mammalian | yes | yes |
| 870.5xxx | Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5xxx | Mutagenicity—Other Genotoxic Effects | yes | yes |
| 870.6100a | Acute Delayed Neurotox. (hen) | no | - |
| 870.6100b | 90-Day Neurotoxicity (hen) | no | - |
| 870.6200a | Acute Neurotox. Screening Battery (rat) | yes | yes |
| 870.6200b | 90 Day Neuro. Screening Battery (rat) | no | - |
| 870.6300 | Develop. Neuro | no | - |
| 870.7485 | General Metabolism | yes | yes |
| 870.7600 | Dermal Penetration | no | - |
| Special Studies for Ocular Effects | | | |
| | Acute Oral (rat) | no | - |
| | Subchronic Oral (rat) | no | - |
| | Six-month Oral (dog) | no | - |

## 2.0 NON-CRITICAL TOXICOLOGY STUDIES

### 870.3100 90-Day oral toxicity (rat)

In a 90-day oral toxicity study (MRID 46220920) SL-160 (Flazasulfuron; 96.3% a.i., batch/lot #8706) was administered to 12 rats (SPF Fisher, F344/DuCrj)/sex/dose in the diet at dose levels of 0, 40, 200, 1000, or 5000 ppm (equivalent to (M: 0, 2.31, 11.66, 57.1, 287; F: 0, 2.53, 12.8, 61.5, 309 mg/kg bw/day).

There were no deaths in any group during the treatment period except for one male (No. 40; 1000 ppm) that was sacrificed in extremis due to malocclusion.

An adverse effect due to toxicity by SL-160 consists of a decrease in body weight in males (4-6%) and females (5-13%) in the high dose. Food consumption and efficiency was not significantly changed during the study. No significant hematology toxicity occurred in the study. Organ abnormalities at necropsy included an increase in relative/absolute weight of the liver and kidney (Male group: 5000 ppm) and kidneys that were swollen and pale in color (Male group: 5000 ppm). Histopathology displayed moderate focal tubular atrophy in the kidney of all males in the high dose group. Clinical chemistry parameters were not statistically changed from controls in either males or females. No adverse effects were observed in urinalysis examination. Dilation of the proximal tubules in the kidney was observed in the male 5000 ppm group.

**The LOAEL is (mg/kg/day): M = 287, F = 309, based on a decrease in body weight (M/F), an increase in relative/absolute weight of the liver and kidney (M), swollen and pale kidneys (M), moderate focal tubular atrophy in the kidney (M), and dilation of proximal tubules in the kidney (M). The NOAEL is (mg/kg/day): M = 57.1, F = 61.5.**

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

### 870.3200 21-Day dermal toxicity (rabbit)

In a 21-day dermal toxicity study (MRID 46220922), SL-160 (96.3% a.i., Batch #303) was applied to the shaved skin of five New Zealand white rabbits/sex/dose at dose levels of 0 (water), 250, 500, or 1000 mg/kg bw/day, 6 hours/day for 21 (males) or 22 (females) consecutive days.

There were no treatment-related deaths, clinical observations, dermal reactions, or effects on body weight, food consumption, hematology, clinical chemistry, organ weight, or gross or histopathology. **Based on the results of this study, the systemic and dermal LOAELs for Flazasufulron in male and female rabbits are not identified, and the systemic and dermal NOAELs are the limit dose of 1000 mg/kg/day.**

This 21-day dermal toxicity study in the rabbit is **Acceptable/Guideline**. It satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

## 870.3700a Developmental Toxicity Study (rat)

Two developmental rat studies were presented for review: (MRID 46220924) with Wistar rats and (MRID 46220925) with Sprague-Dawley rats.

*Study #1:*

**EXECUTIVE SUMMARY:** In a developmental toxicity study (MRID 46220924), SL-160 Technical (96.3% a.i., lot # 8706) was administered to 23 female Wistar rats/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day on days 6 through 15 of gestation. On GD 21, all surviving dams were sacrificed and examined grossly. Each fetus was weighed and examined externally for abnormalities and for sex determination. Approximately one-half of the fetuses in each litter were examined viscerally after fixation in Bouin's solution. The remaining one-half of the fetuses in each litter were eviscerated and processed for skeletal examination.

No treatment-related deaths or clinical signs of toxicity were observed in any animal and gross necropsy was unremarkable. Body weight, body weight change, and food consumption values for the low-dose group were not adversely affected by treatment. Mid-dose animals had transient decreases in body weight gain (50% of controls; $p \leq 0.01$) and food consumption (89% of controls; $p \leq 0.05$) during GDs 6-9. Absolute body weight of the high-dose group was significantly less (93-94% of controls; $p \leq 0.01$) than that of the controls beginning on GD 9 and continuing until termination. Body weight gain by the high-dose group was significantly ($p \leq 0.01$) less than that of the controls for the GDs 6-9 and 12-15 intervals. The most pronounced effect on body weight gain occurred during GDs 6-9 when the high-dose group had a net weight loss (-6 g) compared with a net weight gain (+12 g) by the control group. Food consumption by the high-dose group was significantly ($p \leq 0.01$; 64-80% of controls) less than that of the control group for the intervals of GDs 6-9, 9-12, and 12-15. Recovery was apparent for the high-dose group during the post-dosing interval with food consumption 113% of the control level for GDs 18-21.

**Therefore, the maternal toxicity LOAEL for SL-160 Technical in Wistar rats is 300 mg/kg/day based on transient decreased body weight gain and food consumption, and the maternal toxicity NOAEL is 100 mg/kg/day.**

No treatment-related differences were noted between the treated and control groups for numbers of corpora lutea and implantations, placental weight, fetal sex ratios, and pre-implantation losses. Male and female fetal body weights of the high-dose group were significantly less ($p \leq 0.01$) than those of the control. The high-dose group had increased fetal mortality (20.8% vs 5.5% for controls), a greater number of resorptions (69 vs 19 for controls), and increased post-implantation loss (21.6% vs 6% for controls), which resulted in 11.6 live fetuses/litter compared with 14.0 fetuses/litter for the control group. Two high-dose females had complete litter resorption of 16 and 17 implantations, respectively.

The number of fetuses (litters) examined for external malformations/variations in the control, low-, mid-, and high-dose groups was 323 (23), 320 (23), 310 (23), and 256 (20), respectively. The number of fetuses (litters) examined viscerally was 156 (23), 153 (23), 149 (23), and 122 (20), respectively, and the number of fetuses (litters) examined for skeletal malformations/variations was 167 (23), 167 (23), 161 (23), and 134 (20), respectively.

No treatment-related external or skeletal malformations/variations were observed in low- or mid-dose groups. In the high-dose group, two fetuses from different litters had a short trunk due to the absence of lower vertebrae, a vestigial or absent tail, anal atresia, and one of the fetuses had club foot. A significantly ($p \leq 0.05$) greater number of high-dose litters contained fetuses with visceral malformations compared with the control group [3(2), 1(1), 7(7), and 11(9) fetuses(litters) in the control, low-, mid-, and high-dose groups, respectively].

Interventricular septal defect occurred in 2(1), 1(1), 6(6), and 8(7) fetuses (litters) in the control, low-, mid-, and high-dose groups, respectively, with statistical significance ($p \leq 0.5$) attained for the litter incidence in both the mid- and high-dose groups compared with the controls. Other visceral malformations observed in one or two fetuses from the mid- and high-dose groups included dilatation of the renal pelvis and ureter and diaphragmatic hernia.

One fetus from a high-dose litter had multiple malformations involving the sternebrae, vertebrae, and ribs. Reduced ossification of high-dose fetuses was indicated by a significantly ($p \leq 0.05$) lower percentage of fetuses with 5 ossified metacarpals (72.8% vs 99.4% for the controls). The high-dose group also had a significantly greater ($p \leq 0.05$) number of litters containing fetuses with 14$^{th}$ rib compared with the controls (15 fetuses from 5 litters vs none of the controls).

**Therefore, the developmental toxicity LOAEL for SL-160 Technical in Wistar rats is 300 mg/kg/day based on increased incidence of visceral malformations (interventricular septal defect). The developmental toxicity NOAEL is 100 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/Guideline.**

*Study #2:*

**EXECUTIVE SUMMARY:** In a developmental toxicity study (MRID 46220925), SL-160 Technical (97.3% a.i., lot # 303) was administered to 24 female Sprague-Dawley rats/dose by gavage at dose levels of 0, 100, 300, or 1000 mg/kg bw/day on days 6 through 15 of gestation. On GD 20, all surviving dams were sacrificed and examined grossly. Each fetus was weighed and examined externally for abnormalities and for sex determination. Approximately one-half of the fetuses in each litter were examined viscerally by fresh dissection. The remaining one-half of the fetuses in each litter were examined viscerally, and then processed for skeletal examination.

No treatment-related deaths occurred and gross necropsy was unremarkable except for an increase in maternal relative liver weight. In the high-dose group, six animals showed anogenital stains and four had general alopecia. Alopecia was observed in one control animal. No other treatment-related clinical signs of toxicity were observed in any animal from the treated or control groups.

Body weight, body weight change, and food consumption values for the low-and mid-dose groups were similar to the control group throughout the study. Absolute body weight of the high-dose group was significantly less than that of the controls (93-94% of controls; $p \leq 0.01$) beginning on GD 9 and continuing until termination. Body weight gain by the high-dose group was significantly ($p \leq 0.01$) less than that of the controls for the GDs 6-9 interval during which the high-dose group had a net weight loss (-2 g) compared with a net weight gain (+8 g) by the control group. The initial weight loss by the high-dose group after the start of dosing resulted in a weight change only 71% of the control level for the entire dosing period. Food consumption by the high-dose group was significantly less than that of the controls ($p \leq 0.01$; 80-87% of controls) for the intervals of GDs 6-9 and 9-12. Recovery was apparent for the high-dose group during the

post-dosing interval with food consumption 113% of the control level for GDs 16-20.

**Therefore, the maternal toxicity LOAEL for SL-160 Technical in Sprague-Dawley rats is 1000 mg/kg/day based on increase in maternal relative liver weight and decreased body weight gain and food consumption, and the maternal toxicity NOAEL is 300 mg/kg/day.**

No treatment-related differences were noted between the treated and control groups for numbers of corpora lutea, implantations, or resorptions, fetal mortality, fetal sex ratio, and pre- and post-implantation losses. Male and female fetal body weights from the high-dose group were significantly less ($p \leq 0.01$) than those of the controls. No dam had compete litter resorption.

The number of fetuses (litters) examined for external and visceral malformations/variations in the control, low-, mid-, and high-dose groups was 316 (23), 301 (22), 341 (24), and 304 (23), respectively. The number of fetuses (litters) examined for skeletal malformations/variations was 153 (23), 144 (22), 166 (24), and 146 (23), respectively. No treatment-related external or visceral malformations/variations were found in any fetus of any group. Skeletal malformations were observed as retardation of ossification in the fetuses.

**Therefore, the developmental toxicity LOAEL for SL-160 Technical in Sprague-Dawley rats is 1000 mg/kg/day based on decreased fetal body weight and retardation in ossification. The developmental toxicity NOAEL is 300 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 870.3700; OECD 414) in rats.

**870.3700b Developmental Toxicity (rabbit)**

In a developmental toxicity study (MRID 46220923), SL-160 Technical (96.3% a.i., lot # 8706) was administered to 17 New Zealand White rabbits/dose by gavage at dose levels of 0, 50, 150, or 450 mg/kg bw/day from days 6 through 18 of gestation. On gestation day (GD) 28, does were sacrificed and subjected to cesarean section and gross necropsy. All fetuses were examined for external, visceral, and skeletal malformations/variations. The total numbers of fetuses examined (number of litters) were 101(12), 81(12), 123(14), and 53(8) for the 0, 50, 150, and 450 mg/kg bw/day groups, respectively. The number of litter/number of fetuses examined has been assessed as a low pregnancy rate in the rabbits for this study.

Treatment with 450 mg/kg bw/day resulted in maternal toxicity as evidenced by an increased number of does that stopped eating (7/17 [total animals dosed]), abortion (5/14 [total animals pregnant]) and mortality in one nonpregnant doe. Of the five does that aborted, 4 stopped eating for 6 or more days prior to aborting, and gross necropsy revealed that three of these does had empty intestines and a stomach filled with food and white muddy materials. The death of the nonpregnant doe was ascribed to treatment because this doe stopped eating for 15 days and had gross necropsy findings of a stomach filled with food and white muddy materials and a bloated gall bladder. It was determined that the death of an additional doe was due to gavage trauma.

No adverse effects of treatment were noted in the mid- or low-dose groups. Mean absolute body weight was comparable between the treated and control groups throughout the study. However, three of the does that aborted in the 450 mg/kg/day group lost weight over the dosing interval.

**Therefore, the maternal toxicity LOAEL for SL-160 Technical in rabbits is 450 mg/kg/day**

**based on cessation of eating and high incidences of abortion, and the maternal toxicity NOAEL is 150 mg/kg bw/day.**

Treatment of pregnant rabbits with 450 mg/kg bw/day resulted in an increased number of abortions (5/14 pregnant does) compared to one each in the control, low-dose, and mid-dose groups. No other effects of treatment were noted including pregnancy rate, number of corpora lutea, pre- or postimplantation losses, resorptions/dam, fetuses/litter, fetal body weight, or fetal sex ratio. One doe each in the control and low-dose group had complete litter resorptions.

No treatment-related external, visceral, or skeletal malformations/variations were observed in any groups. Although the high-dose group did not have the recommended number of litters for fetal evaluation (8 litters available for examination compared to recommended 12 litters), exposure of pregnant does to higher concentrations would likely result in only more abortions. Therefore, the 450 mg/kg bw/day test concentration is deemed adequate despite the low number of litters for evaluation.

**Therefore, the developmental toxicity LOAEL for SL-160 Technical in rabbits is 450 mg/kg/day based on an increased number of abortions, and the developmental toxicity NOAEL is 150 mg/kg bw/day.**

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline**. The guideline requirement for a rabbit developmental toxicity study (OPPTS 870.3700b; OECD 414) is upgradable if the laboratory methods and actual data for concentration and homogeneity analyses of the test substance in the dosing solution are provided.

**870.3800 2-Generation Reproduction Study (rat)**

In a two-generation reproduction study (MRID 46220926) technical SL-160 (97.3%, lot # 303) was administered to 30 Sprague-Dawley CRL:CD® BR VAF/Plus® rats/sex/dose in Purina® Certified Rodent Chow®, at nominal concentrations of 0, 200, 2000, or 10,000 ppm. Premating doses for the $F_0$-generation parental animals were 8.7, 87.5, and 473.0 mg/kg/day, respectively, for males and 11.7, 124.5, and 613.7 mg/kg/day, respectively, for females. Premating doses for the $F_1$ parental animals were 14.6, 147.8, and 760.5 mg/kg/day, respectively, for the males and 16.3, 164.9, and 841.5 mg/kg/day, respectively, for the females. One litter was produced for each generation. Parental animals of the $F_0$ and $F_1$ generations received test or control diets for 10 weeks and 12 weeks, respectively, prior to mating, and throughout mating, gestation, lactation, and to termination.

Treatment-related systemic effects in the parental generations included significant reductions in body weight and body weight gain that occurred at 10,000 ppm in both generations of males and females throughout their respective premating periods and until termination. Compared to control values, the statistically and biologically significant decreases in premating body weight ranged from about 14% to 17% for the $F_0$ males, 11% to 14% for the $F_0$ females, 21% to 23% for the $F_1$ males, and 14% to 17% for the $F_1$ females ($p \leq 0.01$ for all values). Cumulative body weight gain reductions were most severe for the 10,000-ppm $F_0$ males and females during week one of premating (reductions of 75% and 71%, respectively). Significant decreases were also observed in cumulative body weight gain of the 2000-ppm $F_0$ males, particularly during the first five weeks of the study ($p \leq 0.01$, decreases of about 12% to 22%). For the $F_1$ males and females, reductions in cumulative body weight gain were constant during premating (~21-26% for the males and ~12-18% for the females) and, at the end of premating (weeks 0-12) averaged 23%

and 14% for the males and females, respectively. Food consumption was reduced only for the 10,000-ppm $F_0$ males and females during week 1 of premating (33.6% and 28%, respectively; $p \leq 0.01$). Efficiency of food utilization was significantly reduced ($p \leq 0.01$) at the beginning of premating for the mid- and high-dose $F_0$ males and females and the high-dose $F_1$ males.

Treatment-related macroscopic and microscopic abnormalities of the kidneys were observed in the $F_0$ males and the $F_1$ males and females. The findings included nephropathy, tubular dilatation and cystic tubules and were dose-related with regard to incidence and severity. The increased incidence of nephropathy was statistically and biologically significant at ≥200 ppm for the $F_0$ males, at ≥2000 ppm for the $F_1$ males, and at 10,000 ppm for the $F_1$ females. Although nephropathy occurred in the low-dose $F_0$ males, but not in the $F_1$ males and females, severity ratings of all lesions were generally higher for the $F_1$ males than for $F_0$ males and the $F_1$ females. The incidence (severity rating in parentheses) of nephropathy in the $F_0$ males, were as follows: 18/30 (1.22), controls; 25/30 (1.36) at 200 ppm ($p \leq 0.05$); 28/30 (1.39) at 2000 ppm ($p \leq 0.01$); and 30/30 (2.13) at 10,000 ppm ($p \leq 0.01$).

The incidence of tubular dilatation in the kidney was significantly increased at 2000 and 10,000 ppm in the $F_0$ males and the $F_1$ males and at 10,000 ppm in the $F_1$ females. The incidence (severity rating) of tubular dilatation in the $F_1$ males was as follows: 0/30, controls; 1/30 (1.00) at 200 ppm; 30/30 (3.43) at 2000 ppm ($p \leq 0.01$); and 30/30 (4.27) at 10,000 ppm ($p \leq 0.01$). The incidence of cystic tubules was significantly increased in the $F_1$ males at 2000 and 10,000 ppm and in the $F_1$ females at 10,000 ppm. The incidence (severity rating) of cystic tubules in the $F_1$ males was as follows: 0/30, controls; 0/30 at 200 ppm; 11/30 (2.27) at 2000 ppm; and 30/30 (3.77) at 10,000 ppm ($p \leq 0.01$).

**The parental LOAEL for the systemic toxicity of technical SL-160 in male rats is 200 ppm (8.7 mg/kg/day), based on increased incidences of nephropathy in $F_0$ males. The systemic NOAEL for male rats is not identified. The parental LOAEL for the systemic toxicity of technical SL-160 in female rats is 10,000 ppm (613.7 mg/kg/day), based on kidney abnormalities in the $F_1$ females and decreased body weights in both generations of females. The systemic toxicity NOAEL for female rats is 2000 ppm (124.5 mg/kg/day).**

Viability, developmental parameters, and sex ratios of the $F_1$ and $F_2$ pups were not affected by exposure to technical SL-160. Statistically and biologically significant decreases ($p \leq 0.01$) were observed in mean body weights of the 10,000-ppm $F_1$ pups, starting at day 7 of lactation (decreases of 10-18%) and of the 10,000-ppm $F_2$ pups, starting at day 4 of lactation (decreases of 11-20%). The body weight effects occurred earlier and were slightly more pronounced in the $F_2$-generation pups.

**The offspring systemic LOAEL for technical SL-160 in rats is 10,000 ppm (473.0 mg/kg/day for the males and 613.7 mg/kg/day for the females), based on reduced lactational body weights of the $F_1$ and $F_2$ offspring. The NOAEL is 2000 ppm (87.5 mg/kg/day for males and 124.5 mg/kg/day for females).**

Mating performance and fertility of males and females of the $F_0$ and $F_1$ parental generations were not affected by treatment with technical SL-160. Therefore:

**The reproductive NOAEL for technical SL-160 in rats is >10,000 ppm (>473.0 mg/kg/day for males and >613.7 mg/kg/day for females), and the reproductive toxicity LOAEL is not identified.**

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

**870.4100b Chronic toxicity (dog)-capsule**

In a 90-day oral toxicity study (MRID 46220921), SL-160 (Flazasulfuron; 97.3% a.i., batch/lot # 303) was administered to 4 beagle dogs/sex/dose by capsule at dose levels of 0, 2, 10, 50, and 250 mg/kg/day for males and 0, 2, 10, 50, and 100 mg/kg/day for females.

All animals survived to study termination with the exception of one male at 250 mg/kg/day (number 18) killed in extremis at Week 11 due to reduced spontaneous motor activity, poor health including weight loss, and a large decrease in food intake at Week 10. Clinical signs occurred sporadically in the study (regurgitation of feed, diarrhea, mucous in the stool, and swelling of the foreleg). Males of the high-dose group (250 mg/kg/day), had a decrease in mean body weight of about 5-6% (compared to controls) starting at Week 6. Hematology measurements were not statistically changed from control in either males or females. No adverse liver functions in either males or females were shown in the clinical chemistry. Absolute and relative liver weights were increased in the 250 mg/kg/day male group (173%, 181%) and the 100 mg/kg/day female group (122%, 122%).

The histopathology of male dogs in the 250 mg/kg/day group included a slight increase in deposition of brown pigments, slight hepatocellular swelling, moderate atrophy of the thymus, and moderate atrophy/degeneration of the skeletal muscle. In the 50 mg/kg/day group, all male dogs had a slight increase in deposition of brown pigments, moderate inflammatory cell infiltration, hepatocellular degeneration/necrosis, and bile duct proliferation in the liver. The 10 mg/kg/day male group had a slight increase in the deposition of brown pigments, inflammatory cell infiltration and microgranulomas in the liver. The 100 mg/kg/day female group displayed increased deposition of brown pigments, inflammatory cell infiltration, hepatocellular degeneration/necrosis, bile duct proliferation, and microgranulomas in the liver. Atrophy/degeneration of the skeletal muscle was also observed in this group.

**In conclusion, the LOAEL was established in male dogs at 10 mg/kg/day and in female dogs at 50 mg/kg/day based on liver changes (hepatocellular swelling, hepatocellular degeneration/necrosis, inflammatory cell infiltration, hepatic microgranulomas, increased deposition of brown pigment) and atrophy/degeneration of the skeletal muscle. The NOAEL is 2 mg/kg/day for males and 10 mg/kg/day for females.**

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

**870.4200 Carcinogenicity (mouse)**

In an 18-month oral carcinogenicity study (MRID 46220928), SL-160 (97.3% a.i., Batch # 303) was administered to 60 Crl: CD-1 (ICR)BR VAF/PLUS® mice/sex/dose in the diet at concentrations of 0, 500, 3500, or 7000 ppm (equivalent to 0, 70.4, 497.8, or 987.4 mg/kg bw/day for males and 0, 88.5, 596.4, or 1165.5 mg/kg bw/day for females).

There were no significant treatment-related effects on mortality or clinical signs. Mean body weight was slightly decreased in males and females at 7000 ppm, but the decreases relative to

control weight did not exceed 8%. Cumulative weekly weight gain was decreased in male and female mice at 3500 and 7000 ppm compared with that of controls, but the decreases were not dose related and did not appear treatment related. Food consumption and food efficiency were not significantly affected by treatment of male mice with the test material. Food consumption and food efficiency were decreased in females at 3500 and 7000 ppm compared with the control values, but the differences were small (less than 8%).

The 2.4- and 1.7-fold (males) and 1.7- and 1.8-fold (females) increases in percent eosinophil count in the 7000-ppm group compared with controls at 12 months and 78 weeks were not associated with other pathological effects, had no known toxicological significance, and were not considered adverse.

The increased absolute and/or relative (to body) liver weights and the increased incidence of centrilobular hepatocyte hypertrophy in males and females at 3500 and 7000 ppm were considered adaptive rather than adverse responses to test material administration. The increased incidence of hepatocellular pigment accumulation seen in males at 7000 ppm (15%) compared to the controls (3%) was not considered adverse. The increased incidence of fibro-osseous lesions in the femur in males (18%) and females (25%) at 7000 ppm compared to the controls (males, 7%; females, 13%) had no known toxicological significance. The incidence of chronic alveolar inflammation in the lungs (32%) in females at 7000 ppm compared to the control group (13%) was likely due to aspiration of the feed. Therefore, these lesions were not adverse or had no known toxicological significance.

**The lowest-observed-adverse-effect-level (LOAEL) for SL-160 in male and female mice was not established. The no-observed-adverse-effect-level (NOAEL) was ≥7000 ppm (987.4 mg/kg/day for males and 1165.5 mg/kg/day for females).**

Treatment of CD-1 mice with a dietary levels up to 7000 ppm SL-160 for up to 78 weeks did not result in a significant treatment-related increase in the incidences of neoplasms at any anatomical site. Although no adverse effects were observed in male or female mice administered the test material, the animals in this study were adequately dosed. The high dose for males approximated the limit dose of 1000 mg/kg/day and the high dose for females exceeded the limit dose.

This carcinogenicity study in the mice is **Acceptable/Guideline** and satisfies guideline requirements for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

**870.7485 Metabolism and pharmacokinetics (rat)** - 2 studies

*(MRID 46220940)*
A series of studies were conducted to evaluate the absorption, distribution, metabolism, and excretion of $^{14}$C-SL-160(P) in groups of 4 or 5 rats (CRL: CD BR VAF/Plus)/sex. In these studies, $^{14}$C-SL-160(P) (CP-1385; 55.8 mCi/mMole; radiolabel purity variously reported as 97.29%, 97.5%, 98.49%, 99.2% and >98%) was administered orally by gavage at doses of 2 or 50 mg/kg (MRID 46220936; 46220938; 46220942) or 2 mg/kg (MRID 46220940). In MRID 46220940, rats had received daily oral gavage doses of nonlabeled SL-160 (Y-920205; 98.9% purity) for 14 days, prior to oral dosing with $^{14}$C-SL-160(P) on Day 15. Metabolism (MRID 46220935) was evaluated in animals used in studies MRID 46229038, 46220940, and 46220936.

Mass balance was excellent for the studies, ranging from 100.61-105.49% in the single oral dose

study (MRID 46220938), 100.06-101.70 in the repeated oral dose study (MRID 46220940), and 97.97-101.94% in the biliary excretion study (MRID 46220936). Mass balance was not provided for the pharmacokinetic study (MRID 46220942).

Differences were generally not noted between dose levels or between single versus repeated dose administration, but were noted between males and females. The studies demonstrated that $^{14}$C-SL-160(P) is rapidly absorbed following a single oral dose of 2 or 50 mg/kg. By 48 hours post exposure, males and females absorbed 94% and 93% of the low dose, respectively, and 86% and 93% of the high dose, respectively (MRID 46220936). A similar pattern was observed when low- and high-dose animals were followed up to 168 hours (MRID 46220938), with little difference noted between a single or repeated exposure (MRID 46220938; MRID 46220940). Elimination via the urine was the major route of excretion, accounting for 74-80% and 90-94% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220938; 46220940). Time course data revealed that a significant portion of the radioactivity in urine was excreted by 48-72 hours post exposure. Feces were the secondary route of elimination, accounting for 21-24% and 9-10% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220938; 46220940). The biliary excretion study determined that ~9.5% of the administered dose appeared in bile by 48 hours in low-dose males and females and high-dose females, with ~16.5% in high-dose males (MRID 46220936). Tissue distribution studies indicated that $^{14}$C-SL-160(P) is rapidly excreted from the system, with less than 4% (males) and 1% (females) of the administered radioactivity remaining in the tissues seven days after dosing. In general, the pattern of the radiolabel distribution in tissues was similar between the low- and high-dose groups in the single oral dose study (MRID 46220938) and between the low-dose groups in the single and repeated dose groups (MRID 46220938; 46220940).

Pharmacokinetic studies confirmed the rapid absorption and elimination of $^{14}$C-SL-160(P). Following a single oral dose of $^{14}$C-SL-160(P), $t_{max}$ values (provided only for individual animals; mathematically determined value not provided) ranged from 30 minutes (3/5 animals/sex) or 4 hours (2/5 animals/sex) at 2 mg/kg, while the median $t_{max}$ was 6 hours in males and 4 hours in females at the 50 mg/kg dose. At 2 and 50 mg/kg, males had slightly longer elimination half-times for the blood than females (males: 27 and 36 hours, respectively; females: 18.8 and 33.8 hours, respectively). Likewise, males had a greater AUC (304 and 4440 $\mu$g-eq/g ·hr, respectively) than females (189 and 3080 $\mu$g-eq/g ·hr, respectively).

In the single and repeated dose studies, parent compound was the primary component in the metabolite profiles for urine (males: 19-40%; females: 51-67% of administered dose), with lesser amounts in feces (males and females: 2-5% of administered dose), and bile (males and females: 0.6-2% of administered dose). Including parent compound, up to 11 fractions were detected among these matrices. The most prevalent metabolite (expressed as percent of administered dose) were HDTG+TPPG (~6.5-12% in urine, ~0.4-2% in feces, and ~6.5-14% in bile), with minor amounts (<5%) of DTPU, HDPU, HTTP, TPSA, and MTMG. Individually, unidentified fractions generally accounted for less than 2% of the administered dose in the urine and biliary metabolite profile. The fecal metabolite profile had up to 35% unidentified of the recovered dose.

These metabolism studies (MRID 46220935, 46220936, 46220938, 46220940, 46220942) are classified **Acceptable/Guideline** and satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in the rat. The studies collectively provided data regarding the absorption, distribution, metabolism, and excretion of the test article following administration of a single low dose (2 mg/kg) or single high dose (50 mg/kg), as well as the effect of oral

pretreatment with the test article.

*(MRID 46220941)*
A series of studies were conducted to evaluate the absorption, distribution, metabolism, and excretion of $^{14}$C-SL-160(Pm) in groups of 4 or 5 rats (CRL: CD BR VAF/Plus)/sex. In these studies, $^{14}$C-SL-160(Pm) (CP-1386; 49.7 mCi/mMole; radiolabel purity variously reported as >97%- 98.9%) was administered orally by gavage at doses of 2 or 50 mg/kg (MRID 46220937; 46220939; 46220943) or 2 mg/kg (MRID 46220941). In MRID 46220941, rats received daily oral gavage doses of nonlabeled SL-160 (Y-920205; 98.9% purity) for 14 days, prior to oral dosing with $^{14}$C-SL-160(Pm) on Day 15. Metabolism (MRID 46220935) was evaluated in animals used in studies MRID 46229039 and 46220941.

Mass balance was excellent for the studies, ranging from 98.7-103.7% in the single oral dose study (MRID 46220939), 98.9-101.01% in the repeated oral dose study (MRID 46220941), and 98.8-107.1% in the biliary excretion study (MRID 46220937). Mass balance was not provided for the pharmacokinetic study (MRID 46220943).

Differences were generally not noted between dose levels or between single versus repeated dose administration, but were noted between males and females. The studies demonstrated that $^{14}$C-SL-160(Pm) is rapidly absorbed following a single oral dose of 2 or 50 mg/kg. By 48 hours post exposure, males and females absorbed 98.5% and 95.4% of the low dose, respectively, and 84.2% and 92.5% of the high dose, respectively (MRID 46220937). A similar pattern was observed when low- and high-dose animals were followed up to 168 hours (MRID 46220939), with little difference noted between a single or repeated exposure (MRID 46220939; MRID 46220941). Elimination via the urine was the major route of excretion, accounting for 73-79% and 89-91% in males and females, respectively, following both low- and high-dose and single and repeated dose administration up to 168 hours post dosing (MRID 46220939; 46220941). Time course data revealed that a significant portion of the radioactivity in urine was excreted by 48-72 hours post exposure. Feces were the secondary route of elimination, accounting for 18-24% and 9% in males and females, respectively, following both low- and high-dose and single and repeated dose administration (MRID 46220939; 46220941). The biliary excretion study determined that 13.5-17.0% and 8.4-10.9% of the administered dose appeared in bile by 48 hours in males and females, respectively, following low- and high-dose administration (MRID 46220937). Tissue distribution studies indicated that $^{14}$C-SL-160(Pm) is rapidly excreted from the system, with less than 2% (males) and 0.3% (females) of the administered radioactivity remaining in the tissues seven days after dosing. In general, the pattern of the radiolabel distribution in tissues was similar between the low- and high-dose groups in the single oral dose study (MRID 46220939) and between the low-dose groups in the single and repeated dose groups (MRID 46220939; 46220941).

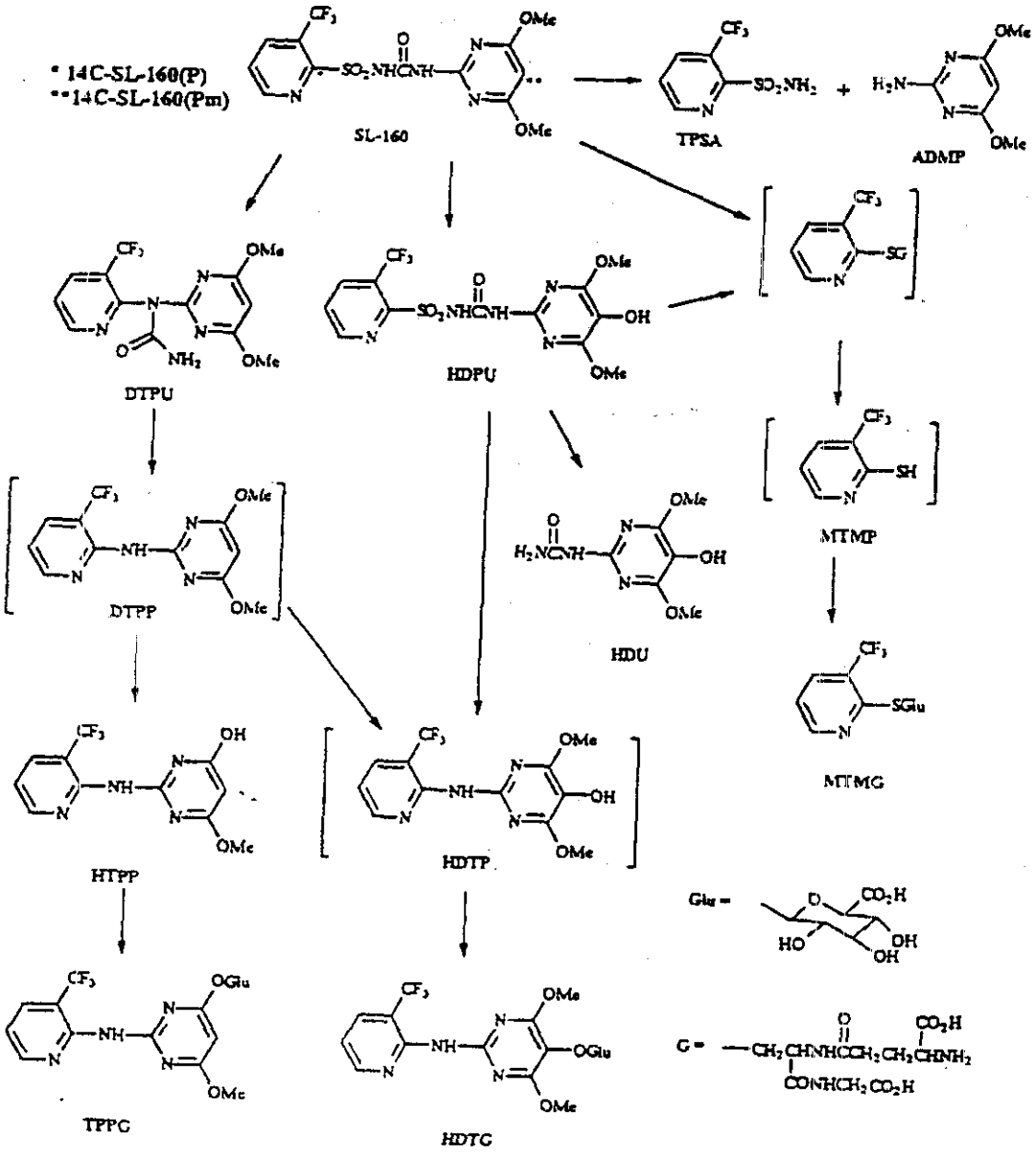
Pharmacokinetic studies confirmed the rapid absorption and elimination of $^{14}$C-SL-160(Pm). Median blood $t_{max}$ values were 6 hours in both males and females at the low-dose, and 4 hours in males and females at the high dose (MRID 46220943). At 2 and 50 mg/kg, males had slightly longer blood elimination half-lives than females (males: 28 and 26 hours, respectively; females: 17 hours at both doses). Likewise, males had a greater AUC (361 and 6630 $\mu$g-eq/g·hr, respectively) than females (259 and 5710 $\mu$g-eq/g·hr, respectively).

In the single and repeated dose studies, parent compound was the primary component in the metabolite profiles for urine (males: 28-35%; females: 61-66% of administered dose), with lesser amounts in feces (males and females: 1-4% of administered dose). Including parent compound,

up to 8 fractions were detected among these matrices. The most prevalent metabolites (expressed as percent of administered dose) were HDTG+TPPG (~9.5-17.7% in urine and ~2.4-9.7% in feces), with minor amounts (<5%) of DTPU, HDPU, HTTP, ADMP, and HDU (with the exception of DTPU accounting for 12.7% of the administered dose in low dose males). Individually, unidentified fractions accounted for less than 12% and 35% of the recovered dose in the urine and feces, respectively.

These metabolism studies (MRID 46220935, 46220937, 46220939, 46220941, 46220943) are classified **Acceptable/Guideline** and satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in the rat. The studies collectively provided data regarding the absorption, distribution, metabolism, and excretion of the test article following administration of a single low dose (2 mg/kg) or single high dose (100 mg/kg), as well as the effect of oral pretreatment with the test article.

## 3.0 METABOLIC PATHWAY



13544

# R124315

| | |
|---|---|
| **Chemical:** | **Flazasulfuron** |
| | **PC Code:** 119011 |
| **HED File Code:** | **14000 Risk Reviews** |
| **Memo Date:** | **11/16/2005** |
| **File ID:** | **DPD303573** |
| | **DPD309442** |
| **Accession #:** | **412-06-0013** |

**HED Records Reference Center**
**3/30/2006**