



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

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

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**MEMORANDUM**

DATE: 28-FEB-2008

SUBJECT: **AMENDMENT TO:** Sulfosulfuron. PP#6F7031. Human Health Risk Assessment for Proposed Uses of the Herbicide Sulfosulfuron on Grass Forage, Fodder and Hay (Crop Group 17), Forestry Conifer Release and Non-crop Areas. DP#: 327363.

**DP#: 349702      Decision#: 206919      PC Code: 085601**

FROM: Sarah J. Levy, Chemist *Sarah J. Levy*  
Kelly M. Lowe, Environmental Scientist *Kelly M. Lowe*  
P.V. Shah, Ph.D., Toxicologist *P.V. Shah*  
Registration Action Branch 1 (RAB 1)  
Health Effects Division (HED) (7509P)

THRU Dana Vogel, Branch Chief  
HED/RAB1 (7509P) *Dana Vogel*

TO: Jim Tompkins, Risk Manager  
and  
Vickie Walters, Risk Manager Reviewer  
PM Team 25  
Registration Division (RD) (7505P)

The last risk assessment for sulfosulfuron was conducted on 30-JUL-2007 (Memo, M. Clock-Rust, DP#: 327363). Subsequent to this assessment, the HED Cancer Assessment Review Committee (CARC) reclassified sulfosulfuron as "not likely to be carcinogenic" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD is considered protective of cancer and non-cancer effects (electronic communication, P.V. Shah to S. Levy, 27-FEB-2008). HED has revised the last risk assessment to reflect this cancer reclassification decision.

*Rec'd in Rec  
3/4/2008  
Mary C. Simmons*

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed tolerances for sulfosulfuron on winter/spring wheat, Bermudagrass and Bahiagrass pastures, forestry conifer release and non-crop areas. A summary of the findings and an assessment of human-health risk resulting from the proposed tolerances for sulfosulfuron are provided in this document. The risk assessment, residue chemistry data review, and dietary exposure assessment were provided by Sarah Levy (RAB1), the occupational exposure assessment by Kelly Lowe (RAB1), the toxicology evaluation by PV Shah (RAB1), and the drinking water exposure assessment by Jim Wolf of the Environmental Fate and Effects Division (EFED).

## TABLE OF CONTENTS

<b>1.0</b>	<b>EXECUTIVE SUMMARY</b> .....	<b>5</b>
<b>2.0</b>	<b>INGREDIENT PROFILE</b> .....	<b>8</b>
2.1	Identification of Active Ingredient.....	8
2.2	Physical and Chemical Properties.....	9
<b>3.0</b>	<b>HAZARD CHARACTERIZATION/ASSESSMENT</b> .....	<b>9</b>
3.1	Hazard and Dose-Response Characterization .....	9
3.1.1	Database Summary.....	11
3.2	FQPA Considerations.....	11
3.3	Hazard Identification and Toxicity Endpoint Selection.....	11
3.3.1	Acute Reference Dose (aRfD) .....	11
3.3.2	Chronic Reference Dose (cRfD).....	12
3.3.3	Incidental Oral Exposure (Short- and Intermediate-Term).....	12
3.3.4	Dermal Absorption .....	12
3.3.5	Dermal Exposure (Short- and Intermediate-Term).....	13
3.3.6	Dermal Exposure (Long-Term) .....	13
3.3.7	Inhalation Exposure (Short-, Intermediate- and Long-Term).....	13
3.3.8	Level of Concern for Margins of Exposure .....	13
3.3.9	Recommendation for Aggregate Exposure Risk Assessments.....	13
3.3.10	Classification of Carcinogenic Potential .....	14
3.4	Endocrine Disruption .....	15
<b>4.0</b>	<b>EXPOSURE ASSESSMENT AND CHARACTERIZATION</b> .....	<b>15</b>
4.1	Summary of Proposed Uses .....	15
4.2	Dietary Exposure/Risk Pathway.....	16
4.2.1	Residue Profile .....	17
4.3	Environmental Degradation .....	22
4.4	Drinking Water Residue Profile.....	23
4.5	Dietary Exposure and Risk.....	23
4.5.1	Chronic Dietary Exposure/Risk.....	24
<b>5.0</b>	<b>RESIDENTIAL EXPOSURE/RISK</b> .....	<b>24</b>
5.1	Residential Risk for Children .....	25

5.2 Spray Drift ..... 25

6.0 AGGREGATE RISK ..... 26

6.1 Short-term Aggregate Risk ..... 26

6.2 Chronic Aggregate Risk ..... 27

7.0 CUMULATIVE RISK ..... 27

8.0 OCCUPATIONAL EXPOSURE/RISK ..... 27

8.1 Restricted-Entry Level (REI) ..... 29

9.0 DATA NEEDS/LABEL CHANGES ..... 29

9.1 Chemistry ..... 29

APPENDIX A: TOXICOLOGY ASSESSMENT ..... 31

APPENDIX B: SULFOSULFURON AND METABOLITE STRUCTURES ..... 36

## 1.0 EXECUTIVE SUMMARY

The Monsanto Company has proposed to amend the use pattern for the 75% water-dispersible granule (WDG) formulation of sulfosulfuron (Maverick® Herbicide; EPA Reg. No. 524-500) to include uses on grasses. The proposed uses include postemergence broadcast application to grasses at a maximum seasonal rate of 0.125 pounds active ingredient per acre (lb ai/A), with a 0-day pre-harvest interval (PHI) for forage and a 14-day PHI for hay. Sulfosulfuron is a selective pre- and post-emergent herbicide for the control of various annual grasses and broadleaf weeds in winter and spring wheat and non-food crops and a variety of other uses including ornamentals, roadsides, airports, lumber yards, recreational areas, parks, golf courses, residential areas (lawns), industrial rights of way, etc. Sulfosulfuron uses on turf are to be made by professional applicators only. Sulfonylurea herbicides disrupt amino acid biosynthesis in susceptible plants by binding to the acetolactate synthase (ALS) enzyme.

A previous risk assessment for sulfosulfuron was performed in 2004 (Memo, M. Clock-Rust, et al., 07-OCT-2004; DP#: 304483) for a Section 18 specific Emergency Exemption request for use on pastures and hayfields to control Johnsongrass in Georgia, Oklahoma, Louisiana and Mississippi. HED recommended granting the exemption and proposed time-limited tolerances for Bermudagrass and Bahiagrass.

### *Hazard Assessment*

Sulfosulfuron has low acute oral, dermal, and inhalation toxicity. It is non-irritating to skin and slightly irritating to eyes. It is not a skin sensitizer.

In subchronic studies, the primary target system was the urinary tract with lesions including urinary calculi (bladder stones), hemorrhage, ulceration, inflammation and/or mucosal epithelial hyperplasia in the urinary bladder depending on the species. There were no signs of systemic toxicity following dermal exposure. In the chronic rat, dog, and mouse toxicity studies, urolithiasis and associated pathology of the urinary bladder, kidney and ureter were also observed at high doses. There was evidence of treatment related urinary tract tumors in both rats and mice.

The results of the 2-generation reproduction and developmental toxicity studies indicated that sulfosulfuron is not a developmental or reproductive toxicant. The acute and subchronic neurotoxicity studies showed that sulfosulfuron is not neurotoxic. Sulfosulfuron is rapidly excreted, primarily unmetabolized. Excretion at low dose occurred primarily in the urine, whereas at high dose, a large percentage of the administered dose was excreted in the feces. Sulfosulfuron was not retained in tissues to any significant extent.

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (10-APR-1996), the CARC classified sulfosulfuron as "not likely to be carcinogenic" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD based on the no-observed adverse effect level (NOAEL) of 500 ppm (24.4 mg/kg/day) from the carcinogenicity study in rats is considered protective of cancer and non cancer effects.

RAB1 toxicologists and the risk assessment team recommended that the Food Quality Protection Act (FQPA, 1996) factor for increased sensitivity to infants and children (as required by FQPA) be **reduced to 1X**. The rationale for selection of the FQPA factor was based on a complete toxicological database, lack of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure seen in developmental and reproductive studies, no neurotoxicity concerns, low exposure through food and residential sources and low acute toxicity.

#### *Dietary Exposure Analysis*

An acute dietary assessment was not conducted because an endpoint of concern attributable to a single dose was not identified for sulfosulfuron. A cancer dietary assessment was not conducted because sulfosulfuron was classified as “not likely to be carcinogenic” at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD is considered protective of cancer and non-cancer effects.

An unrefined chronic dietary risk assessment was conducted for sulfosulfuron. Dietary exposure from food and drinking water was included in the dietary assessment. The Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03) chronic exposure estimates were <1.0% chronic population-adjusted dose (cPAD) for all population subgroups, and are therefore not of concern to HED.

#### *Residential Risk*

Since there are registered residential uses of sulfosulfuron (commercial application to residential lawns), the results of a post-application risk assessment were included in this assessment (and the results were used in the aggregate risk assessment). Since dermal and inhalation endpoints of concern were not identified for sulfosulfuron, only an incidental oral (for toddlers) risk assessment was necessary to assess residential risk. The results of the residential risk assessment are not of concern to HED.

No short-, or intermediate-term dermal or inhalation endpoints were chosen; therefore, short- and intermediate-term assessments were not conducted. Additionally, long-term exposure for the proposed uses is not expected. Cancer risk estimates were not calculated as sulfosulfuron was classified by the CARC as “not likely to be carcinogenic” (CARC report pending, electronic communication, P.V. Shah to S. Levy, 27-FEB-2008). Furthermore, the cancer effects were seen only after a prolonged exposure at very high doses; therefore, quantification of cancer risk is not conducted based on this use pattern.

#### *Aggregate Risk*

Aggregate risk is comprised of dietary (food and water) and residential sources of exposure. Endpoints for risk assessment through exposure via acute and cancer dietary were not identified; therefore, aggregate risk assessments for these scenarios were not required. Additionally, no hazard via the dermal or inhalation routes was identified (for any duration). Short-term aggregate exposure is expected for adults resulting from dietary exposure (food and water), and for children

resulting from dietary (food and water) and incidental oral exposure (from residential turf). Further, no aggregate intermediate-term assessment is required because intermediate-term incidental oral exposure is not expected based on the use pattern (30-day application interval).

#### *Occupational Risk*

HED assessed occupational handler and post-application risk for sulfosulfuron. For handlers, mixer/loaders supporting aerial application and applicators using right-of-way sprayers and mixer/loader/applicators using low-pressure handwands or backpack sprayers were assessed.

No short-, or intermediate-term dermal or inhalation endpoints were chosen; therefore, short- and intermediate-term assessments were not conducted. Additionally, long-term exposure for the proposed uses is not expected. Cancer risk estimates were not calculated as sulfosulfuron was classified by the CARC as "not likely to be carcinogenic" (CARC report pending, electronic communication, P.V. Shah to S. Levy, 27-FEB-2008). Furthermore, the cancer effects were seen only after a prolonged exposure at very high doses; therefore, quantification of cancer risk is not conducted based on this use pattern.

#### *Regulatory Recommendations*

Pending submission of revised Sections B and F and submission of analytical standards for the ethyl sulfone chemophore metabolite of sulfosulfuron to the National Pesticide Standards Repository, there are no residue chemistry or toxicology issues that would preclude granting a conditional registration for the requested uses of sulfosulfuron on grasses, or establishment/revision of tolerances for residues of sulfosulfuron and metabolites as follows:

Grass, forage, fodder and hay, group 17, forage .....	14	ppm
Grass, forage, fodder and hay, group 17, hay.....	25	ppm
Cattle, fat .....	0.02	ppm
Cattle, meat.....	0.01	ppm
Cattle, meat byproducts.....	0.30	ppm
Goat, fat.....	0.02	ppm
Goat, meat .....	0.01	ppm
Goat, meat byproducts.....	0.30	ppm
Horse, fat.....	0.02	ppm
Horse, meat.....	0.01	ppm
Horse, meat byproducts.....	0.30	ppm
Sheep, fat.....	0.02	ppm
Sheep, meat .....	0.01	ppm
Sheep, meat byproducts.....	0.30	ppm
Milk.....	0.02	ppm

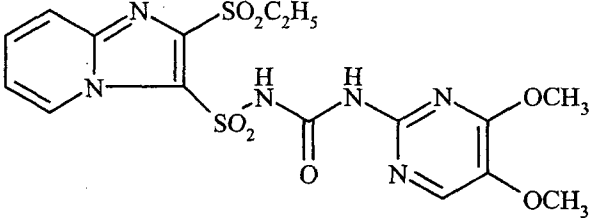
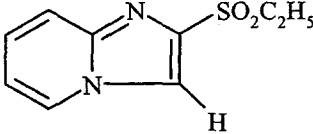
Conversion from a conditional to an unconditional registration is contingent upon completion of a petition method validation (PMV) by the Analytical Chemistry Laboratory (ACL).

## 2.0 INGREDIENT PROFILE

Tolerances for residues of sulfosulfuron in/on raw agricultural and livestock commodities are established under 40 CFR §180.552 and are expressed in terms of residues of sulfosulfuron and its metabolites converted to 2-(ethylsulfonyl)-imidazo[1,2-*a*]pyridine, calculated as sulfosulfuron.

Sulfosulfuron is a systemic herbicide previously registered for pre- and postemergence control of annual and perennial grasses and broadleaf weeds in wheat, forestry, and other noncrop sites. As with other SU herbicides, sulfosulfuron apparently inhibits the enzyme ALS, which in plants is involved in the synthesis of several amino acids. Suppression of ALS stops cell growth and division, followed by death of the growing point of the plant.

### 2.1 Identification of Active Ingredient

<b>Table 2.1. Sulfosulfuron Nomenclature.</b>	
Chemical structure	
Common name	Sulfosulfuron
Company experimental name	MON 37500; TKM-19
IUPAC name	1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-ethylsulfonylimidazo[1,2- <i>a</i> ]pyridin-3-ylsulfonyl)urea
CAS name	<i>N</i> -[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-2-(ethylsulfonyl)imidazo[1,2- <i>a</i> ]pyridine-3-sulfonamide
CAS registry number	141776-32-1
End-use product (EP)	75% WDG (Maverick® Herbicide; EPA Reg. No. 524-500)
Chemical structure of ethyl sulfone chemophore	 <p>2-(ethylsulfonyl)-imidazo [1,2-<i>a</i>]pyridine</p>



## 2.2 Physical and Chemical Properties

Table 2.2. Physical and Chemical Properties of Sulfosulfuron.	
Parameter	Value
Melting range	180.9-184.1°C
pH	4.76
Density	1.55 g/mL at 20°C
Water solubility	<u>ppm at 20°C</u>
	pH 5 17.60 ± 2.71
	pH 7 1626.8 ± 39.8
	pH 9 482.44 ± 8.35
Solvent solubility	<u>ppm at 20°C</u>
	Heptane <1
	Xylene 160
	Methanol 330
	Ethyl acetate 1010
Dichloroethane 4350	
Vapor pressure	2.29 x 10 <sup>-10</sup> mm Hg at 20°C
	6.61 x 10 <sup>-10</sup> mm Hg at 25°C
Dissociation constant, pK <sub>a</sub>	pK <sub>a</sub> = 3.51 at 20°C
Octanol/water partition coefficient, Log (K <sub>ow</sub> )	pH 5: K <sub>ow</sub> = 6.38; pK <sub>ow</sub> = 0.81
	pH 7: K <sub>ow</sub> = 0.14; pK <sub>ow</sub> = -1.01
	pH 9: K <sub>ow</sub> = 0.036; pK <sub>ow</sub> = -1.37
UV/visible absorption spectrum	UV <sub>MAX</sub> = 208 nm ε = 187,150 L/mol cm (pH >10.0, 1.06% by weight in water, 26°C)

Reference: MRID 44295704; Memo, S. Chun, 28-SEP-1998; DP#: 237683

## 3.0 HAZARD CHARACTERIZATION/ASSESSMENT

A summary of the toxicology/hazard assessment for sulfosulfuron is presented below. For more information, see the 1998 risk assessment (Memo, S. Chun, et al., 02-NOV-1998; DP#: 245035) or the HIARC Report (Memo, L. Hansen and J. Rowland, 16-OCT-1998; HED Document No. 012915).

### 3.1 Hazard and Dose-Response Characterization

Sulfosulfuron has low acute oral, dermal, and inhalation toxicity (Acute Toxicity Category 4 for oral, dermal and inhalation). It is nonirritating to skin and slightly irritating to eyes (Category 3). It is not a skin sensitizer.

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral	44295737	LD50 >5,000 mg/kg	IV
81-2	Acute Dermal	44295739	LD50 >5,000 mg/kg	IV
81-3	Acute Inhalation	44295745	No mortality at 3.0 mg/l	IV
81-4	Primary Eye Irritation	44295741	Moderately irritating	III
81-5	Primary Skin Irritation	44295743	Not an irritant	IV
81-6	Dermal Sensitization	44295747	Not a sensitizer	N/A

The subchronic toxicity studies in rats, mice, and dogs demonstrate that the primary effects of sulfosulfuron were observed at high doses, and included urinary crystals, bladder stones and associated pathology of the urinary bladder, kidney and ureter.

In the chronic rat and mouse toxicity studies, urinary crystals, bladder stones and associated pathology of the urinary bladder, kidney and ureter were also observed at high doses. In the rat, single incidences of rarely observed urinary bladder transitional cell papilloma and carcinoma were reported in 2 different females at 5,000 ppm (314.1 mg/kg/day) and in the mouse there was an increased incidence of benign mesenchymal bladder tumors in the male and a single renal adenoma in both high dose males and females.

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (10-APR-1996), the CARC classified sulfosulfuron as "not likely to be carcinogenic" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD based on the NOAEL of 500 ppm (24.4 mg/kg/day) from the carcinogenicity study in rats is considered protective of cancer and non cancer effects.

The results of the 2-generation reproduction and developmental toxicity studies indicate that sulfosulfuron is not a developmental or reproductive toxicant.

The acute and subchronic neurotoxicity studies show that sulfosulfuron is not neurotoxic.

The mutagenic test battery demonstrated that sulfosulfuron is not mutagenic at non-cytotoxic concentrations. An *in vitro* Chinese hamster lung point mutation assay was positive, only under conditions of non-activation and at levels that caused precipitation.

The toxicity of sulfosulfuron appears to be dependent on saturation in the urine, followed by precipitation and formation of urinary crystals and bladder stones. The metabolism study in the rat shows that sulfosulfuron is excreted largely unmetabolized (80%-90% of administered dose). Excretion at a low dose (10 mg/kg) occurs primarily in the urine (77%-87% of dose); whereas, at a high dose (1,000 mg/kg), a large percentage of the administered dose is excreted in the feces (55%-63%). Sulfosulfuron is rapidly excreted and is not retained in tissues to any significant extent.

### 3.1.1 Database Summary

The toxicology data base on sulfosulfuron is adequate as defined for a food-use chemical in 40 CFR Part 158.

### 3.2 FQPA Considerations

The HED Food Quality Protection Act (FQPA) Safety Factor Committee met on 22-JUN-1998 (Memo, B. Tarplee and J. Rowland, 01-JUL-1998) to evaluate the hazard and exposure data for sulfosulfuron and recommend application of the FQPA Safety Factor (as required by FQPA of August, 1996), to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the **10x factor** for enhanced sensitivity to infants and children (as required by FQPA) be **reduced to 1x**.

The rationale for reduction of the FQPA factor was:

- The toxicology database for sulfosulfuron is complete.
- The developmental and reproductive toxicity data did not indicate increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure.
- A developmental neurotoxicity (DNT) study is not required.
- Any detectable residues in food or drinking water would be expected at low levels since application rates are low.
- There are currently no registered homeowner handler uses for sulfosulfuron.
- Concern for post-application exposure to infants and children through commercial application of the pesticide is tempered by the low acute oral, dermal, and inhalation toxicity of this pesticide.

### 3.3 Hazard Identification and Toxicity Endpoint Selection

#### 3.3.1 Acute Reference Dose (aRfD)

A dose and endpoint was not selected for acute dietary risk assessment because there were no effects attributable to a single dose (exposure) observed in oral toxicology studies [including developmental toxicity studies in the rat and the rabbit (at up to 1,000 mg/kg/day) and an acute neurotoxicity study in the rat (at up to 2,000 mg/kg)]. The acute oral toxicity of sulfosulfuron is also very low ( $LD_{50} > 5,000$  mg/kg). An acute dietary risk assessment is NOT required for sulfosulfuron.

### 3.3.2 Chronic Reference Dose (cRfD)

The chronic RfD was based on the results of a 2-year chronic toxicity/carcinogenicity in rats in which increased incidence of urinary tract gross/microscopic lesions, mineralization in several tissues (males), abnormal urine crystals and possibly decreased albumin (males, termination) was observed at the lowest-observed adverse effect level (LOAEL) of 5,000 ppm (244.2 mg/kg/day). The NOAEL is 500 ppm (24.4 mg/kg/day).

Dose and Endpoint for Establishing cRfD: NOAEL = 24 mg/kg/day, based on urinary tract pathology at 244.2 mg/kg/day (males) and 314.1 mg/kg/day (females) (LOAEL).

Uncertainty Factor (UF): A UF of 100 was applied to account for both inter-species extrapolation and intra-species variability.

$$\text{Chronic RfD} = \frac{24 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.24 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: This NOAEL is the lowest NOAEL established in the available long-term oral toxicity studies conducted with this chemical.

Chronic dietary risk assessments are required.

### 3.3.3 Incidental Oral Exposure (Short- and Intermediate-Term)

In HED's risk assessment for the 2004 Section 18, HED used the NOAEL of 24 mg/kg/day from the combined chronic toxicity/carcinogenicity study in rats to address the short-term or intermediate-term residential risk to children from incidental exposure (since the HIARC did not identify an endpoint for this risk assessment in 1998). This NOAEL is considered conservative and health protective for this assessment because it represents the lowest NOAEL in the most sensitive species (the basis for the cRfD). The 2004 memo stated that the NOAEL was chosen for the purposes of the Section 18 assessment only. However, for the current action, the sulfosulfuron risk assessment team decided that it is appropriate to use this dose and endpoint to address toddler's incidental oral risk. Therefore, post-application incidental oral risk was assessed using the NOAEL of 24 mg/kg/day from the chronic toxicity/carcinogenicity study in rats.

### 3.3.4 Dermal Absorption

A dermal-absorption study is not available for sulfosulfuron. Therefore, for estimating cancer risk, 100% dermal absorption is assumed.

### 3.3.5 Dermal Exposure (Short- and Intermediate-Term)

No dermal or systemic toxicity was seen following 20 repeated dermal applications of sulfosulfuron at up to 1,000 mg/kg/day. Therefore, these risk assessments are not required.

### 3.3.6 Dermal Exposure (Long-Term)

There is no long-term exposure expected with this use pattern. Further, a hazard has not been identified through the dermal route (see 3.3.5 above). Therefore, this risk assessment is not required.

### 3.3.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

This risk assessment is not required based on the low toxicity (Toxicity Category IV), very low vapor pressure ( $2.29 \times 10^{-10}$  mm Hg at 20°C) and low use application rates via the inhalation route and the use pattern (ranging from 10 to 28 g ai/acre). The potential inhalation exposure is also expected to be a small fraction of the potential dermal exposure, the major route of exposure.

### 3.3.8 Level of Concern for Margins of Exposure

<b>Table 3.3.8. Summary of Levels of Concern for Risk Assessment.</b>			
<b>Route</b>	<b>Short-Term MOE (1 - 30 Days)</b>	<b>Intermediate-Term MOE (1 - 6 Months)</b>	<b>Long-Term MOE (&gt; 6 Months)</b>
<b>Occupational (Worker) Exposure</b>			
Dermal	-	-	-
Inhalation	-	-	-
<b>Residential Exposure</b>			
Dermal	-	-	-
Inhalation	-	-	-
Incidental Oral	100	100	100

### 3.3.9 Recommendation for Aggregate Exposure Risk Assessments

No endpoints were selected for dermal or inhalation exposure risk assessments; therefore, aggregate exposure risk assessment will be limited to oral exposure from food and water.

### 3.3.10 Classification of Carcinogenic Potential

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (10-APR-1996), the CARC classified sulfosulfuron as "not likely to be carcinogenic" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD based on the NOAEL of 500 ppm (24.4 mg/kg/day) from the carcinogenicity study in rats is considered protective of cancer and non cancer effects.

### 3.3.11 Summary of Toxicological Doses and Endpoints

<b>Exposure Scenario</b>	<b>Dose Used in Risk Assessment</b>	<b>Uncertainty/FQPA Factor, LOC</b>	<b>Study and Toxicological Effects</b>
Acute Dietary; all populations	A dose and endpoint was not selected for acute dietary risk assessment because there were no effects attributable to a single dose (exposure) in the oral toxicology studies including developmental toxicity studies in the rat and the rabbit and an acute neurotoxicity study in the rat.		
Chronic Dietary all populations	NOAEL= 24 mg/kg/day Chronic RfD = 0.24 mg/kg/day	FQPA SF = 1 cPAD = cRfD ÷ FQPA SF UF <sup>1</sup> = 100 cPAD = 0.24 mg/kg/day	Chronic toxicity/carcinogenicity - rat; LOAEL = 244.2 mg/kg/day based on urinary tract pathology, abnormal crystals and urinary calculi (both sexes); mineralization in heart, lung, pancreas, and skeletal muscles (male).
Short-, Intermediate- Long-Term Dermal	No dermal or systemic toxicity was seen following repeated dermal application at the limit dose in a 21-day dermal toxicity study in rats. Therefore, this risk assessment is not required.		
Short-term Incidental Oral	NOAEL=24 mg/kg/day	FQPA SF = 1 UF <sup>1</sup> = 100 LOC=100	Chronic toxicity/carcinogenicity - rat; LOAEL = 244.2 mg/kg/day based on urinary tract pathology, abnormal crystals and urinary calculi (both sexes); mineralization in heart, lung, pancreas, and skeletal muscles (male).
Inhalation (Any time period)	Based on the low acute inhalation toxicity (Category IV; no mortality at 3 mg/L), the formulation of the product as wettable granules, and the low application rates for the proposed use patterns ranging from 25 - 70 g ai/hectare (10-28 g ai/acre), there is minimal concern for potential inhalation exposure and risk. Therefore, a separate inhalation risk assessment is not required.		
Cancer	<b>Not likely to be carcinogenic</b> at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The current endpoint selected for chronic RfD based on the NOAEL of 500 ppm (24.4 mg/kg/day) from the carcinogenicity study in rats is considered protective of cancer and non-cancer effects.		

LOC=Level of concern for HED risk assessment. NOAEL= No-observed adverse effect level; LOAEL=Lowest-observed adverse effect level; PAD=Population-adjusted dose.

<sup>1</sup> uncertainty factor; 10x for intraspecies variation and 10x for interspecies extrapolation

### 3.4 Endocrine Disruption

EPA is required under the FFDCFA, 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, FFDCFA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

## 4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

### 4.1 Summary of Proposed Uses

**Proposed Use:** Monsanto Company has proposed to amend the use pattern for the 75% WDG formulation of sulfosulfuron (Maverick® Herbicide; EPA Reg. No. 524-500) to include uses on grasses. The proposed uses include postemergence broadcast application to Bermudagrass and Bahiagrass at a maximum seasonal rate of 0.125 pounds active ingredient per acre (lb ai/A), with a 0-day PHI for forage and a 14-day PHI for hay.

The supplemental label also contains the following statement concerning rotational crops: “No crop, except wheat, may be planted into pastures that have been treated with this product within 12 months after application. All crops other than wheat may be seeded only after completion of a successful field bioassay.”

The master label for the 75% WDG formulation (accepted 7/11/05) includes the following general use directions. Applications may be made using ground or aerial (fixed-wing or helicopter) equipment. Ground applications are to be made in 5-20 gallons of water per acre or 10-40 gallons of liquid fertilizer solution per acre, and aerial applications are to be made in 5-15 gallons of water per acre. Spray solutions of pH 6-8 are optimum; 7% ammonia solution may be used to increase the pH of the spray solution to the optimum range. Applications through any type of irrigation systems are prohibited. In addition, HED notes that the master label states that a nonionic surfactant is required in the spray solution for postemergence applications.

<b>Table 4.1. Summary of Directions for Use of Sulfosulfuron.</b>						
<b>Applic. Timing, Type, and Equip.</b>	<b>Formulation [EPA Reg. No.]</b>	<b>Applic. Rate (lb ai/A)</b>	<b>Max. No. Applic. per Season</b>	<b>Max. Seasonal Applic. Rate (lb ai/A)</b>	<b>PHI (days)</b>	<b>Use Directions and Limitations</b>
Bermudagrass and Bahiagrass <sup>1</sup>						
Postemergence; Broadcast; Ground or Aerial	75% WDG [524-500]	0.094	<b>2</b>	0.125	0 forage 14 hay	For use in well-established pastures. Applications may be made from early spring through the fall; follow-up applications may be made after suitable regrowth of weeds but no sooner than 40 days after initial application. Addition of a nonionic surfactant (NIS) at 0.25% by volume is required. Use only NISs containing ≥90% active ingredient which will not alter the pH of the spray solution to <5.

<sup>1</sup> **Bolded** information appears in Section B, but not on the proposed supplemental labeling.

*Conclusions.* The submitted information concerning the proposed use pattern is adequate to allow evaluation of the submitted data for grasses. The submitted crop field trial data for grasses do not support the proposed use directions because the supplemental label states that use of a nonionic surfactant is required, and, based on the information contained in MRID 46753801, no adjuvant was used in the field trials. The petitioner should amend the proposed supplemental label for grasses by removing directions for use of a nonionic surfactant, or provide residue data that includes use of a nonionic surfactant.

In addition, the supplemental labeling should be revised to reflect the information contained in Section B of the petition materials concerning the maximum number of applications per season (two) and the timing of applications (from early spring through the fall). **A revised Section B should be submitted.**

#### **4.2 Dietary Exposure/Risk Pathway**

The residue chemistry data submitted in support of the proposed petition were evaluated by HED on 24-JUL-2007 (Memo, S. Levy; DP#: 328450). The drinking water assessment was completed by EFED (Memo, J. Wolf, et al., 24-MAY-2007; DP#: 327364). The dietary exposure assessment was completed by HED (Memo, S. Levy, 28-FEB-2008; DP#: 349704).



#### 4.2.1 Residue Profile

##### Background

Sulfosulfuron (*N*-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-2-(ethylsulfonyl)imidazo [1,2-*a*]pyridine-3-sulfonamide) is a selective broadleaf SU herbicide registered for control of grass and broadleaf weeds in spring and winter wheat. Sulfosulfuron exhibits systemic postemergence herbicidal activity on a broad spectrum of annual and perennial sedges, grasses, and broadleaf weeds, but does not injure many warm-season and some cool-season grasses. Data for sulfosulfuron were originally reviewed by HED under a petition for use on wheat (Memo, S. Chun, 28-SEP-1998; DP#: 237683). SU herbicides disrupt amino acid biosynthesis in susceptible plants by binding to the ALS enzyme.

Monsanto Company has proposed to amend the use pattern for the 75% WDG formulation of sulfosulfuron (Maverick® Herbicide; EPA Reg. No. 524-500) to include uses on grasses. The proposed uses include postemergence broadcast application to Bermudagrass and Bahiagrass at a maximum seasonal rate of 0.125 lb ai/A, with a 0-day PHI for forage and a 14-day PHI for hay.

In conjunction with the amended use request, Monsanto has proposed (PP#6F7031) the establishment of permanent tolerances for the residues of sulfosulfuron and its metabolites calculated as sulfosulfuron, in/on the following RACs:

Grass forage.....	13 ppm
Grass hay .....	14 ppm

As a result of the proposed uses on grass forage and hay, Monsanto has also proposed revisions to the established tolerances for sulfosulfuron and its metabolites calculated as sulfosulfuron for the following livestock commodities:

Cattle, fat .....	0.03 ppm
Cattle, meat.....	0.01 ppm
Cattle, meat byproducts.....	0.4 ppm
Goat, fat.....	0.03 ppm
Goat, meat .....	0.01 ppm
Goat, meat byproducts.....	0.4 ppm
Horse, fat .....	0.03 ppm
Horse, meat.....	0.01 ppm
Horse, meat byproducts .....	0.4 ppm
Sheep, fat.....	0.03 ppm
Sheep, meat .....	0.01 ppm
Sheep, meat byproducts.....	0.4 ppm
Milk.....	0.02 ppm

Permanent and time-limited tolerances for residues of sulfosulfuron in/on raw agricultural and livestock commodities are established under 40 CFR §180.552(a) and 40 CFR §180.552(b),

respectively and are expressed in terms of residues of sulfosulfuron and its metabolites converted to 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine, calculated as sulfosulfuron. Permanent tolerances are established for wheat commodities at 0.02-4.0 ppm, and tolerances for milk, and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep are established at 0.005-0.05 ppm. Time-limited tolerances are established for Bahiagrass and Bermudagrass forage and hay commodities at 11-40 ppm, and tolerances for milk, and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep are established at 0.02-0.50 ppm, set to expire 31-DEC-2009.

#### Meat, Milk, Poultry, and Eggs

The proposed uses on grasses include ruminant feed items. Because residues in/on grass forage and hay resulting from the proposed use were significantly higher than those observed for wheat commodities, there is an appreciable increase in the maximum theoretical dietary burden (MTDB) for ruminants. Based on the results of the available feeding study and the recommended tolerances for grass forage and hay, the established tolerances for livestock commodities (*i.e.*, of cattle, goat, horse, and sheep), the following livestock tolerances are appropriate: 0.02 ppm for fat and milk, 0.01 for meat, 0.30 ppm for meat byproducts. The proposed tolerances should be revised to reflect the recommended tolerance levels as specified in Table 4.2.1.2. **A revised Section F should be submitted.**

#### Magnitude of the Residue

Crop field trial data have been submitted for grasses. The results from these studies are discussed below and summarized in Table 4.2.1.1.

<b>Table 4.2.1.1. Summary of Residue Data from Crop Field Trials with Sulfosulfuron.</b>										
Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Combined residues of sulfosulfuron and its metabolites containing the intact imidazopyridine ring (ppm) <sup>1</sup>							
			n	Min.	Max.	HAFT <sup>4</sup>	Median	Mean	Std. Dev.	
<b>Grass Forage, Fodder, and Hay (Crop Group 17)</b>										
<b>(proposed use = 0.125 lb ai/A total application rate, 0-day PHI for forage, 14-day PHI for hay)</b>										
Grass, forage	0.061-0.064 <sup>2</sup>	0	26	2.95	8.53	8.41	4.59	5.00	1.58	
		14	26	0.05	2.23	2.20	0.55	0.76	0.63	
	0.091-0.098 <sup>3</sup>	0	26	4.10	12.4	11.65	6.16	6.95	2.46	
		14	26	0.07	3.56	3.52	0.81	1.21	0.98	
	0.122-0.129 <sup>2</sup>	0	24	1.91	11.7	11	4.68	5.16	2.6	
		7	2	0.94	1.01	0.975	-	0.975	-	
		14	24	0.02	5.7	5.38	0.350	1.14	1.84	
	0.123-0.129 <sup>3</sup>	21	2	0.35	0.36	0.355	-	0.355	-	
		0	24	0.99	4.70	4.60	2.32	2.67	1.04	
		7	2	0.50	0.54	0.52	-	0.52	-	
		14	24	0.01	2.9	2.54	0.175	0.487	0.731	
	21	2	0.17	0.23	0.20	-	0.20	-		
Grass, hay		0.061-0.064 <sup>2</sup>	14	14	0.16	3.38	3.17	1.49	1.47	1.11
21			4	0.12	0.60	0.56	0.33	0.34	0.25	
0.091-0.098 <sup>3</sup>		14	14	0.22	5.13	4.93	1.93	2.24	1.60	

<b>Table 4.2.1.1. Summary of Residue Data from Crop Field Trials with Sulfosulfuron.</b>									
Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Combined residues of sulfosulfuron and its metabolites containing the intact imidazopyridine ring (ppm) <sup>1</sup>						
			n	Min.	Max.	HAFT <sup>4</sup>	Median	Mean	Std. Dev.
<b>Grass Forage, Fodder, and Hay (Crop Group 17)</b> <b>(proposed use = 0.125 lb ai/A total application rate, 0-day PHI for forage, 14-day PHI for hay)</b>									
		21	4	0.17	1.43	1.40	0.78	0.79	0.70
	0.122-0.129 <sup>2</sup>	14-17	18	0.24	7.23	7.14	1.11	2.80	2.72
		19-21	6	0.10	0.72	0.67	0.285	0.352	0.262
		28	2	0.54	0.62	0.58	-	0.58	-
	0.123-0.129 <sup>3</sup>	14-17	20	0.02	3.67	3.60	0.625	0.998	1.14
		19-21	6	0.09	0.44	0.43	0.09	0.203	0.176
		28	2	0.35	0.38	0.365	-	0.365	-

<sup>1</sup> Residues reported as parent equivalents; note that results were not reported in this table for trials with RTIs > 56 days.

<sup>2</sup> Treatment 2 = 1 application at ~0.062 lb ai/A (or two applications at ~0.062 lb ai/A).

<sup>3</sup> Treatment 3 = 1 application at ~0.094 lb ai/A (or one application at ~0.094 lb ai/A + one application at ~0.031 lb ai/A).

<sup>4</sup> HAFT = Highest-Average Field Trial.

In support of the proposed uses, the petitioner has proposed to establish tolerances for residues of sulfosulfuron and its metabolites calculated as sulfosulfuron on grass forage and hay. The proposed, and HED-recommended, tolerances are presented in Table 4.2.1.2.

The submitted grass crop field trial data adequately reflect the proposed use pattern with respect to application rate, timing of applications, and harvest intervals; geographic representation is adequate. However, the proposed use pattern specifies that a nonionic surfactant is required, and the submitted data do not reflect use of a spray adjuvant. Provided the petitioner amends the proposed supplemental labeling for grasses by removing directions for use of a nonionic surfactant, or provides residue data that include use of a nonionic surfactant, the available field trial data will support tolerances for residues of sulfosulfuron and its metabolites in/on grass forage at 14 ppm and grass hay at 25 ppm (the tolerance calculator was used to derive tolerances for this action). HED notes that the tolerance for grass forage was based on examination of residue results reflecting a single application at 0.094 lb ai/A because the highest residues observed in the field trials occurred following this use pattern. These data indicate that the proposed tolerances of 13 ppm for grass forage and 14 ppm for grass hay are too low. The proposed tolerances should be revised to reflect the recommended tolerance levels and correct commodity definitions as specified in Table 4.2.1.2. **A revised Section F should be submitted.**

<b>Commodity</b>	<b>Established Tolerance (ppm)</b>	<b>Proposed Tolerance (ppm)</b>	<b>Recommended Tolerance (ppm)</b>	<b>Comments; Correct Commodity Definition</b>
Grass forage	--	13	14	<i>Grass, forage, fodder and hay, group 17, forage</i>
Grass hay	--	14	25	<i>Grass, forage, fodder and hay, group 17, hay</i>
Cattle, fat	0.005	0.03	0.02	
Cattle, meat	0.005	0.01	0.01	
Cattle, meat byproducts	0.05	0.4	0.30	
Goat, fat	0.005	0.03	0.02	
Goat, meat	0.005	0.01	0.01	
Goat, meat byproducts	0.05	0.4	0.30	
Horse, fat	0.005	0.3	0.02	
Horse, meat	0.005	0.01	0.01	
Horse, meat byproducts	0.05	0.4	0.30	
Sheep, fat	0.005	0.03	0.02	
Sheep, meat	0.005	0.01	0.01	
Sheep, meat byproducts	0.05	0.4	0.30	
Milk	0.006	0.02	0.02	

#### *Storage Stability*

The maximum storage intervals of crop samples from harvest to analysis were 326 days (10.7 months) for grass forage and 300 days (9.9 months) for grass hay. Acceptable storage stability data are available which indicate that residues of sulfosulfuron are stable under frozen storage conditions in/on fortified samples of wheat forage for up to 17.5 months. These data may be translated to grass forage and hay, and are adequate to support the storage intervals of samples from the grass field trials.

#### *Nature of the Residue*

The qualitative nature of the residue in cereal grains and livestock is adequately understood based on acceptable wheat, goat, and hen metabolism studies. In all studies, the primary residues were the parent and those metabolites containing the intact imidazopyridine ring.

Based on the results of the previously reviewed metabolism studies and the proposed common moiety enforcement method, the HED Metabolism Assessment Review Committee (MARC) determined that the residues of concern in wheat and livestock commodities, for tolerance expression and risk assessment purposes, are sulfosulfuron and all metabolites which are converted to 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine (D249043, S. Chun, 23-Nov-1998).

The HED risk assessment team concludes that the results of the wheat metabolism study may be translated to grass and that the residues of concern in grass, for tolerance expression and risk assessment purposes, are sulfosulfuron and all metabolites which are converted to 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine.

Based on wheat, ruminant, and poultry metabolism studies and the proposed common moiety enforcement method, the HED MARC determined that the residues of concern in wheat and livestock, for tolerance expression and risk assessment purposes, are sulfosulfuron and all metabolites which are converted to 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine. For drinking water, the residues of concern are sulfosulfuron and its ethyl sulfone metabolites [including 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine-3-sulfonic acid (sulfonic acid), 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine-3-sulfonamide (sulfonamide), 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine (sulfone)] (Memo, S. Chun, 11/21/1998; DP#: 249043).

#### *Rotational Crops*

The nature of the residue in rotational crops is understood. HED concluded that the residues of concern in rotational crops for tolerance expression and risk assessment purposes are sulfosulfuron and all metabolites which are converted to 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine (or the ethyl sulfone chemophore).

A limited field rotational crop study (MRID 44821802) on sulfosulfuron has been submitted and reviewed to support the registration on wheat (Memo, P. Errico, 21-JAN-2000; No DP#). This study, along with a confined rotation study (MRID 44295735), showed that uptake of sulfosulfuron residues from the soil by root and tuber, leafy vegetable, and small cereal grain crops is minimal. Even with a plant-back interval (PBI) of 7 days (root/tuber crop), no residues of sulfosulfuron or its metabolites were detected above the limit of detection (LOD) of 0.006 ppm in the field rotational crop study, when planted into soil that had been treated at 0.035 lbs ai/A. For grass pastures, the seasonal application rate is 1.2 lbs ai/A, or ~ 4 times greater than the study conditions. At the seasonal application rate, and assuming a linear application rate/residue concentration correlation, the expected residue concentrations at the higher application rate would be less than 0.024 ppm. Because the label has a 12 month minimum PBI, residues in rotational crops are not expected.

#### *Analytical Methods*

In support of the petition for use on wheat, the petitioner proposed two common-moiety high-performance liquid chromatography (HPLC) methods with fluorescence detection for enforcement of tolerances in wheat and livestock commodities. In these methods, residues of sulfosulfuron and its metabolites containing the intact imidazopyridine ring are converted by acid hydrolysis to the ethyl sulfone chemophore. Samples from the submitted grass field trials were analyzed for residues of sulfosulfuron and metabolites containing the intact imidazopyridine ring using a common moiety liquid chromatograph/mass spectrometry/mass spectrometry (LC/MS/MS) method that was adapted from the proposed enforcement method for wheat. The validated limit of quantitation (LOQ) was 0.005 ppm, and the LOD was 0.0026 ppm. The method is adequate for data collection based on acceptable concurrent recovery data.

The revision of the original HPLC enforcement method to use LC/MS detection resolves the previous deficiencies related to specificity and confirmatory method. These deficiencies are no longer outstanding. The plant LC/MS/MS method was sent to ACL for a PMV (Memo, S. Levy, 17-OCT-2006; DP# 332807). The final decision regarding the adequacy of the revised analytical enforcement method for plants is pending upon successful completion of a PMV by the ACL.

Analytical standards for sulfosulfuron are currently available in the National Pesticide Standards Repository; however, analytical standards for the ethyl sulfone chemophore metabolite of sulfosulfuron are not available (personal communication, Dynamac with D. Wright, 07-JUN-2006). **This is a deficiency.** Analytical reference standards of the ethyl sulfone metabolite should be supplied, and supplies for the analytical standards for sulfosulfuron and its ethyl sulfone metabolite should be replenished as requested by the Repository.

#### *Multiresidue Method*

The results of Multiresidue testing of sulfosulfuron and its sulfonamide metabolite CP 147937 have been forwarded to FDA (Memo, S. Chun, 30-Sep-1997; DP#: 239417). Sulfosulfuron and its sulfonamide metabolite were tested through Protocols A and C. Because of inadequate sensitivity, sulfosulfuron and sulfonamide metabolite were not tested through all of Protocol A or through Protocols D, E, and F. Sulfosulfuron appears to degrade under conditions in Protocol C. Therefore, no recoveries were obtained for sulfosulfuron and its metabolite using Protocol A and C.

#### *International Harmonization*

There are no established or proposed Codex or Mexican maximum residue limits (MRLs) for residues of sulfosulfuron in grasses or wheat. There are no established Canadian MRLs for residues of sulfosulfuron in grasses; a Canadian MRL has been established for sulfosulfuron residues in wheat. Therefore, there are no harmonization issues with respect to the proposed uses on grasses.

### **4.3 Environmental Degradation**

In soils and water, the major degradation products of sulfosulfuron are the sulfonamide and aminopyrimidine moieties due to cleavage of the sulfonylurea bond. Hydrolytic cleavage appears to be the major mechanism involved. The rate of formation of the sulfonamide and aminopyrimidine reflected the decline in concentration of sulfosulfuron. Depending on the pH of the system, a majority of parent sulfosulfuron may be transformed to these degradation products. See Appendix B for structures of sulfosulfuron and its degradation products.

In soil metabolism studies, in addition to the sulfonamide and aminopyrimidine products, two minor transformation products (<10% of applied radioactivity) were also identified: sulfosulfuron desmethyl (2.58%), and sulfosulfuron guanidine (1.74%).

The compounds listed above would be the most likely sulfosulfuron degradates to be present in surface and ground waters. Other degradates were formed in soil and water photolysis studies.

However, photodegradation (especially on soils) is not expected to be a major dissipation mechanism. Major photodegradation products (15% - 30%) include aminopyrimidine, sulfonamide, sulfamic acid, N'-hydroxy-urea, ethyl sulfone, oxamic acid, and sulfonic acid. Minor degradates (4-9%) include urea and cyanamide.

#### 4.4 Drinking Water Residue Profile

The drinking water values used in this dietary risk assessment were provided by EFED (Memo, J. Wolf, *et al.*, 24-MAY-2007; DP#: 327364) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM food categories "water, direct, all sources" and "water, indirect, all sources." Monitoring data are not available for sulfosulfuron in surface water or ground water. Concentrations in surface and ground water were estimated using modeling based on an aerial application scenario to grass forage, fodder and hay (crop group 17; which represents the highest use rate with annual application rate of 0.125 lbs ai/A/year). EFED used the Tier 1 model FQPA Index Reservoir Screening Tool (FIRST) to calculate surface water EDWCs and the Tier-1 model Screening Concentration in Ground Water (SCI-GROW) to calculate ground water estimated drinking water concentrations (EDWCs) for sulfosulfuron and its ethyl sulfone metabolites [including 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine-3-sulfonic acid (sulfonic acid), 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine-3-sulfonamide (sulfonamide), 2-(ethylsulfonyl)-imidazo[1,2-a]pyridine (sulfone)]. The models and their descriptions are available at the EPA internet site: <http://www.epa.gov/oppefed1/models/water/>.

The surface water concentrations were adjusted by the percent crop area (PCA) of 0.87. Tier I surface water EDWCs for sulfosulfuron were 10.4 ppb (acute) and 1.12 ppb (chronic). The Tier I groundwater EDWC for sulfosulfuron was 2.6 ppb. The groundwater number was used in the dietary assessment, since this number was higher than the surface water number (*i.e.*, more conservative).

#### 4.5 Dietary Exposure and Risk

A chronic dietary (food and drinking water) exposure and risk assessment was conducted using DEEM-FCID™, Version 2.03, which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The chronic dietary assessment assumed 100% crop treated (CT) for all commodities, DEEM-FCID™ (ver 7.78) default processing factors, and tolerance-level residues. EDWCs, provided by EFED, were included in the current assessment as well. HED is concerned when dietary risk exceeds 100% of the PAD. For the chronic dietary assessment, the resulting food + water exposure estimates were not of concern to HED (<1.0% of the cPAD).

An acute-dietary assessment was not conducted for sulfosulfuron because an endpoint of concern attributable to a single dose was not identified. A cancer dietary assessment was not conducted because sulfosulfuron was classified as "not likely to be carcinogenic" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. The

current endpoint selected for chronic RfD is considered protective of cancer and non-cancer effects.

#### 4.5.1 Chronic Dietary Exposure/Risk

As stated above, for chronic assessments HED is concerned when dietary risk exceeds 100% of the cPAD and for cancer assessments HED is concerned when the lifetime risk for the general U.S. population exceeds one in a million. The chronic analysis was performed using DEEM-FCID™ (ver. 2.03). The DEEM-FCID™ analysis estimates the dietary exposure of the U.S. population and various population subgroups. The results reported in Table 4.5.2 are for the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50+ years old. The resulting food + water exposure estimates were not of concern to HED (<1.0% cPAD).

<b>Table 4.5.2. Summary of Chronic Dietary Exposure and Risk for Sulfosulfuron.</b>			
<b>Population Subgroup</b>	<b>cPAD (mg/kg/day)</b>	<b>Exposure (mg/kg/day)</b>	<b>% cPAD</b>
General U.S. Population	0.24	0.000260	<1.0
All Infants (< 1 year old)		0.000465	<1.0
Children 1-2 years old		0.000981	<1.0
Children 3-5 years old		0.000711	<1.0
Children 6-12 years old		0.000440	<1.0
Youth 13-19 years old		0.000222	<1.0
Females 13-49 years old		0.000173	<1.0
Adults 20-49 years old		0.000175	<1.0
Adults 50+ years old		0.000168	<1.0

#### 5.0 RESIDENTIAL EXPOSURE/RISK

Residential exposure is not expected for the new proposed uses. However, a sulfosulfuron product, Outrider®, is registered for use on turf.

Residential homeowners are not expected to handle sulfosulfuron directly. However, sulfosulfuron is applied by professional commercial operators to lawn areas (such as apartment complexes, parks, schools, recreational areas and public areas) where residents would come into contact with sulfosulfuron residues. Therefore, as part of a previous risk assessment for this herbicide, post-application exposure and risk to residents (adults and children) was assessed.

In the 1998 risk assessment (Memo, S. Chun, et al., 02-NOV-1998; DP#: 245035), a cancer risk assessment was performed for adults contacting treated lawns. However, the HED CARC reclassified sulfosulfuron as “not likely to be carcinogenic” at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract (electronic



communication, P.V. Shah to S. Levy, 27-FEB-2008); therefore, quantification of cancer risk was not conducted based on this use pattern.

## 5.1 Residential Risk for Children

Post-application inhalation exposure is considered to be negligible. However, non-dietary, incidental ingestion of residues from treated turfgrass and ingestion of contaminated soil are possible.

To address the short-term residential risk to children from incidental oral exposure, HED used the NOAEL of 24 mg/kg/day from the combined chronic toxicity/carcinogenicity study in rats. This NOAEL is considered conservative and health protective for this assessment because it represents the lowest NOAEL in the most sensitive species (the basis for the cRfD).

The HED standard operating procedures (SOPs) for Residential Exposure Assessments (Draft, December 18, 1997) were used as a guideline for performing the residential post-application assessment (with amendments, 2001). Children's hand-to-mouth, object-to-mouth (turfgrass) and soil ingestion were assessed. For details on the assessment, see HED's 1998 risk assessment (Memo, S. Chun, *et al.*, D245035, 11/02/1998).

Children's estimated risk from oral hand-to-mouth activities on treated lawns is estimated to result in a short-term MOE of 1,700.

Children's estimated risk from oral object-to-mouth (turfgrass) from treated lawns is estimated to result in a short-term MOE of 6,800

Children's estimated risk from incidental ingestion of soil from treated lawns is estimated to result in a short-term MOE of 510,000.

Since short-term MOEs are above 100, HED does not have a concern. Chronic or long-term exposure is not expected.

While considered unlikely, if a toddler were to experience exposure from all of these sources at the same time, the combined incidental oral exposure would be 0.018 mg/kg/day. This combined exposure results in an estimated MOE of 1,400, which is not a concern.

## 5.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for sulfosulfuron. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State

Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical-by-chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database 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<sup>®</sup> computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

## 6.0 AGGREGATE RISK

Endpoints for risk assessment through exposure via acute and cancer dietary were not identified; therefore, aggregate risk assessments for these scenarios were not required. Additionally, no hazard via the dermal or inhalation routes was identified (for any duration). Short-term aggregate exposure is expected for adults resulting from dietary exposure (food and water), and for children resulting from dietary (food and water) and incidental oral exposure (from residential turf). Further, no aggregate intermediate-term assessment is required because intermediate-term incidental oral exposure is not expected based on the use pattern (30-day application interval).

### 6.1 Short-term Aggregate Risk

Due to the potential for post-application exposure from lawn uses of sulfosulfuron, short term aggregate risks were assessed. The short-term aggregate risk takes into account the exposure from potential residential sources in addition to average dietary residues from food and drinking water. The short-term aggregate risk assessment was performed for children only, since non-dietary incidental oral exposure is not expected for other population subgroups (youth, adults). As can be seen in Table 6.2 below, short-term aggregate risk for children results in a MOE of 1300 and is, therefore, not of concern to HED.

Population	Oral Exposure for Children Only					
	NOAEL (mg/kg/day)	LOC <sup>1</sup>	Max Allowable Exposure <sup>2</sup> (mg/kg/day)	Average Food & Water Exposure (mg/kg/day)	Residential Exposure <sup>3</sup> (mg/kg/day)	Aggregate MOE (food and residential) <sup>4</sup>
Children, 1-2 years old	24	100	0.24	0.000981	0.018	1300

<sup>1</sup> The LOC is 100, based on the standard 10X inter-species and 10X intra-species UFs totaling 100.

<sup>2</sup> Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.

<sup>3</sup> Residential Exposure = [Oral Exposure]. Taken from the 2004 HED risk assessment ((DP D304483, M. Clock-Rust, *et al.*, 10/07/2004), Table 5, oral exposure.

<sup>4</sup> Aggregate MOE = [NOAEL/(Avg. Food & Water Exposure + Residential Exposure)].

## 6.2 Chronic Aggregate Risk

The chronic aggregate risk assessment considered exposure from food and water (chronic residential exposure is not anticipated); therefore, the dietary exposure analysis presented in Section 4.5.1 represents chronic aggregate risk for sulfosulfuron. The analysis was an unrefined chronic dietary assessment assuming tolerance level residues, 100% crop treated, and DEEM (ver. 7.76) default processing factors. As can be seen in Table 4.5.2, the DEEM-FCID chronic exposure estimates were <1.0% cPAD for all populations subgroups, and are therefore not of concern to HED.

## 7.0 CUMULATIVE RISK

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

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

## 8.0 OCCUPATIONAL EXPOSURE/RISK

A summary of proposed and existing use pattern for sulfosulfuron is presented in Table 8.0 below.

Product	Formulation	Use Sites	Application Rates	Application Equipment	Area or Amount Treated	Timing of Application and Restrictions
Maverick Herbicide (EPA Reg# 524-500)	WDG	winter and spring wheat	0.03 lb ai/A	aerial groundboom	1200 A 200 A	Applied either pre- or post-emergence on winter wheat; apply only postemergence for spring wheat; 1 app per season for winter or spring wheat; PHI: 30 days for wheat for hay; 55 days for wheat for grain or straw
		Bermudagrass and Bahiagrass pastures	0.09 lb ai/A	aerial groundboom	350 A 80A	Apply from early spring through fall; not to exceed 0.125 lb ai/A/yr; max of 2 app per year
Forestry conifer release		0.094 lb ai/A OR 0.00094 lb ai/gal for handheld equipment	aerial groundboom backpack low pressure handwand	1200 A 200 A 40 gallons 40 gallons	Apply during spring or early summer	
		noncrop areas (roadsides, utility rights-of-way, airports, fallow areas, ditch banks, dry ditches, dry canals, fencerows, industrial sites, lumberyards, manufacturing sites, petroleum tank farms, pumping installations, railroads, storage areas, utility substations, warehouse areas)	0.09 lb ai/A (0.009 lb ai/gal) OR 0.0005 lb ai/gal for handheld equipment	aerial groundboom rights-of-way backpack low pressure handwand		350 A 80 A 1000 gallons 40 gallons 40 gallons
Outrider Herbicide (EPA Reg# 524-500)						

Based upon the proposed use pattern, HED expects the most highly exposed occupational pesticide handlers are likely to be:

Mixer/Loader:

(1) Mixing/Loading Dry Flowables for Aerial Applications (Pesticide Handlers Exposure Database; PHED);

Applicators:

(2) Applying Sprays via Rights-of-Way Equipment (PHED);

Mixer/Loader/Applicator:

(3) Mixing/Loading/Applying Wettable Powders with Low-Pressure Handwand (used as a surrogate); and

(4) Mixing/Loading/Applying Liquids with a Backpack Sprayer (used as a surrogate).

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED Surrogate Guide (August, 1998). For application via low-pressure

handwand and backpack sprayer, there are no data available for assessing exposure to WDG/dry-flowable (DF) formulations. For these scenarios, it is assumed that WDG/DF formulations would have lower exposures than the same scenarios using liquids or wettable powders. In other words, the dermal and inhalation risks for WDG/DF formulations would likely be lower than the estimated dermal and inhalation risks for liquids and wettable powders.

For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for “baseline”; that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves, as well as for “baseline” and the use of protective gloves or other PPE as might be necessary. The proposed product labels involved in this assessment direct applicators and other handlers to wear a long-sleeved shirt and long pants, socks, and shoes.

No short-, or intermediate-term dermal or inhalation endpoints were chosen; therefore, short- and intermediate-term assessments were not conducted. Additionally, long-term exposure for the proposed uses is not expected. Cancer risk estimates were not calculated as sulfosulfuron was classified by the CARC as “not likely to be carcinogenic” (CARC report pending, electronic communication, P.V. Shah to S. Levy, 27-FEB-2008). Furthermore, the cancer effects were seen only after a prolonged exposure at very high doses; therefore, quantification of cancer risk is not conducted based on this use pattern.

## **8.1 Restricted-Entry Level (REI)**

Sulfosulfuron is classified in Toxicity Category IV for acute dermal, acute oral, acute inhalation and primary skin irritation. It is classified in Toxicity Category III for primary eye irritation and it is not a dermal sensitizer. Therefore, the Worker Protection Standard (WPS) interim REI (12 hours) is adequate to protect agricultural workers from postapplication exposures to sulfosulfuron. The proposed end-use product labels list an REI of 12 hours.

## **9.0 DATA NEEDS/LABEL CHANGES**

### **9.1 Chemistry**

- **Revised Section B.** The petitioner should amend the proposed supplemental label for grasses by removing directions for use of a nonionic surfactant, or provide residue data that includes use of a nonionic surfactant. In addition, the supplemental labeling should be revised to reflect the information contained in Section B of the petition materials concerning the maximum number of applications per season (two) and the timing of applications (from early spring through the fall).

- **Revised Section F.** The petitioner should submit a revised Section F reflecting the HED-recommended tolerance levels and correct commodity definitions as specified in Table 4.2.1.2.
- **PMV of plant method.** The plant LC/MS/MS method was sent to the ACL for a PMV. The final decision regarding the adequacy of the revised analytical enforcement method for plants is pending upon successful completion of a PMV by the ACL.
- **Analytical standards for the ethyl sulfone chemophore metabolite of sulfosulfuron** are not available in the National Pesticide Standards Repository. Analytical reference standards of the ethyl sulfone metabolite should be supplied, and supplies for the analytical standards for sulfosulfuron and its ethyl sulfone metabolite should be replenished as requested by the Repository.

#### **Appendix A: Toxicology Assessment**

#### **Appendix B: Sulfosulfuron and Metabolite Structures**

RDI: G.F. Kramer (28-FEB-2008)  
S. Levy:S-10953:PY1:(703)305-0783:7590P

## Appendix A: Toxicology Assessment

### A.1 Toxicology Data Requirements

The toxicology requirements (40 CFR 158.340) for the sulfosulfuron food use are shown below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

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) .....	yes	yes
870.4100b Chronic Toxicity (nonrodent) .....	-	-
870.4200a Oncogenicity (rat) .....	-	-
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	yes
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	-

## A.2 Toxicity Profiles

<b>Table A.2.1. Acute Toxicity Profile – Sulfosulfuron.</b>				
<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID(s)</b>	<b>Results</b>	<b>Toxicity Category</b>
870.1100	Acute oral rat	44295737	LD <sub>50</sub> >5,000 mg/kg	IV
870.1200	Acute dermal rat	44295739	LD <sub>50</sub> >5,000 mg/kg	III
870.1300	Acute inhalation rat	44295745	No mortality at 3.0 mg/L	IV
870.2400	Acute eye irritation rabbit	44295741	Moderately irritating	III
870.2500	Acute dermal irritation rabbit	44295743	Not an irritant	IV
870.2600	Skin sensitization guinea pig	44295747	Not a sensitizer	N/A

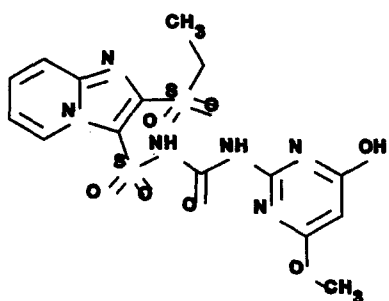


<b>Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Sulfosulfuron.</b>			
<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
870.3100	90-Day oral toxicity rat	44295750 (1995) Acceptable 0, 20, 200, 2000, 6000 or 20000 ppm M: 0, 1.2, 12.1, 123.2, 370.3 or 1277.5 mg/kg/d F: 0, 1.5, 14.6, 144.3, 447.5 or 1489.1 mg/kg/d	NOAEL = 370.3 mg/kg/day LOAEL = 1277.5 mg/kg/day based on decreased body weight/litter weight gain in males, possible decreased weight gain in pregnant females during gestation days 14-21, and possible renal lesions related to formation of calculi.
870.3150	90-Day oral toxicity dog	44295751 (1996) Acceptable 0, 30, 100, 300 or 1000 mg/kg/d	NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on lesions in the urinary bladder in females occurring subsequent to urinary formation/urolithiasis and on abnormal urinary crystals in males and females.
870.3200	21/28-Day dermal toxicity (species)	44295752 (1994) Acceptable/guideline 0, 100, 300 or 1000 mg/kg/d 5d/wk for 4 wks	NOAEL > 1000 mg/kg/day LOAEL was not determined.
870.3700a	Prenatal developmental in rat	44295756 (1994) Acceptable/guideline 0, 100, 300 or 1000 mg/kg/d; days 6-15.	<b>Maternal</b> NOAEL > 1000 mg/kg/day LOAEL was not determined. <b>Developmental</b> NOAEL > 1000 mg/kg/day LOAEL was not determined.
870.3700b	Prenatal developmental in rabbit	44295757 ( ) Acceptable/guideline 0, 50, 250 or 1000 mg/kg/d; days 7-19.	<b>Maternal</b> NOAEL > 1000 mg/kg/day LOAEL was not determined. <b>Developmental</b> NOAEL > 1000 mg/kg/day LOAEL was not determined.
870.3800	Reproduction and fertility effects rat	44295758 Acceptable 0, 50, 500, 5000 or 20,000 ppm M (P): 0, 31.6, 312.1 and 1318.2 mg/kg/d F (P): 0, 3.6, 36.2, 363.2 or 1454.1 mg/kg/d M (F1a): 0, 3.1, 31.1, 315.8 and 1378.8 mg/kg/d F (F1a): 0, 3.7, 37.7, 377.8 and 1598.0 mg/kg/d	<b>Parental/Systemic</b> NOAEL = 312.8 mg/kg/day LOAEL = 1312.8 mg/kg/day based on decreased parental body weight gain during premating, gestation and lactation. <b>Reproductive</b> NOAEL ≥ 1312.8 mg/kg/day LOAEL ≥ 1312.8 mg/kg/day <b>Offspring</b> NOAEL = 312.1 mg/kg/day LOAEL = 1312.8 mg/kg/day based on decreased body weight gain in postweaning adolescent rats.
870.4100b	Chronic toxicity dog	44295754 (1997) Acceptable 0, 5, 20, 100 or 500 mg/kg d-	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on the presence of abnormal urinary crystals and bladder pathology secondary to formation of urinary tract calculi in males.

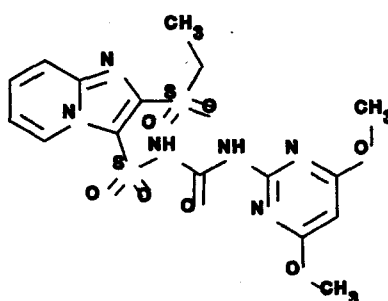
<b>Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Sulfosulfuron.</b>			
<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
870.4200	Carcinogenicity rat	44295759 (1997) Acceptable 0, 50, 500, 5000 or 20000 ppm M: 0, 2.4, 24.4, 244.2 or 1178.3 mg/kg/d (20000 ppm male group terminated at day 259 due to excessive mortality) F: 0, 3.1, 30.4, 314.1 or 1296.5 mg/kg/d	NOAEL = 24.4 mg/kg/day LOAEL = 244.2 mg/kg/day based on increased incidence of urinary tract gross/microscopic lesions, mineralization in several tissues (males), abnormal urine crystals and possible albumin (males, termination). <b>At the high dose, urinary bladder transitional cell carcinoma and papilloma were observed in females (1/50 each vs. 0/controls) and were considered treatment-related.</b>
870.4300	Carcinogenicity mouse	44295755 (1997) Acceptable 0, 30, 700, 3000 or 7000 ppm M: 0, 4.0, 93.4, 393.6 or 943.5 mg/kg/d F: 0, 6.5, 153.0, 634.9 or 1388.2 mg/kg/d	NOAEL (M) = 93.4 mg/kg/day LOAEL (M) = 393.6 mg/kg/day based on gross and microscopic effects related to urinary calculus formation in the urinary bladder of males. <b>The incidence of benign mesenchymal tumors of the urinary bladder was increased in males in the high dose (5/60) compared to controls (0/60).</b>
Gene Mutation 870.5100	<i>Salmonella typhimurium</i> ; <i>E. coli</i> / mammalian activation gene mutation assay	44295760 (1995) Acceptable 312, 624, 1250, 2500 or 5000 µg/mL	Negative for inducing reverse gene mutations with <i>Salmonella typhimurium</i> strains TA1535, TA1537, TA98, TA 100 or TA102 exposed in either the presence or absence of mammalian metabolic activation at doses up to 5,000 µg/plate. Cytotoxicity observed at ≥ 1,500 µg/plate.
Cytogenetics 870.5300	<i>In Vitro</i> mammalian cells in culture gene mutation assay in Chinese hamster ovary cells	44295761 (1995) Acceptable 624-5000 µg/mL	Negative for inducing forward gene mutations at the HGPRT locus in Chinese hamster ovary (CHO) cells exposed in either the presence or absence of S9 activation up to 5,000 µg/mL. Doses caused cytotoxicity at 5,000 µg/mL in the absence of S9 but not in the presence of S9; however, MON 37500 was insoluble at or above 2,500 µg/mL.
Other Effects 870.5375	<i>In vitro</i> mammalian chromosome aberration	44280201 (1996) Acceptable/guideline 1000, 1250, 2000, 2500, 3000 or 5000 µg/mL	Positive under non-activated conditions; however, precipitation occurred Negative under activated conditions.

<b>Table A.2.2. Subchronic, Chronic and Other Toxicity Profile – Sulfosulfuron.</b>			
<b>Guideline No.</b>	<b>Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
Other Effects 870.5375	<i>In vitro</i> mammalian chromosome aberration	44295762 (1996) Acceptable 100, 250, 500, 750 or 1000 µg/mL	Negative for inducing structural chromosome damage in Cultured Human Lymphocytes exposed at levels up to 1,000 µg/mL in either the presence or absence of S9 and harvested either at 18 or 42 hrs posttreatment. Cytotoxicity (decreased mitotic indices) were observed at 1,000 µg/mL with and without S9. MON 37500 was precipitated at 1,000 µg/mL.
Other Effects 870.5395	<i>In vitro</i> mammalian micronucleus assay	44295763, 4429564 (1995) Acceptable 0, 1250, 2500 or 5000 mg/mL	Negative for inducing micronuclei in polychromatic erythrocytes from male or female CD-1 mice at dose levels up to 5,000 mg/kg. Although no indication of cytotoxicity was observed, a pharmacokinetic study demonstrated that MON 37500 reached the bone marrow in male CD-1 mice at 2 and 8 hrs following an oral gavage dose of 2,000 mg/kg.
870.6200a	Acute neurotoxicity screening battery	44295749 (1997) Acceptable 0, 125, 500 or 2000 mg/kg/d	NOAEL > 2000 mg/kg/day LOAEL > 2000 mg/kg/day.
870.6200b	Subchronic neurotoxicity screening battery	44295753 (1997) Acceptable 0, 200, 2000 or 20000 ppm M: 0, 12, 122 or 1211 mg/kg/d F: 0, 14, 141 or 1467 mg/kg/d	NOAEL = 1211 mg/kg/day LOAEL > 1211 mg/kg/day.
870.7485	Metabolism and pharmacokinetics rat	44295765 (1998) Acceptable Single oral dose of 10 or 1000 mg/kg Repeated oral dose of 10 mg/kg (14 doses, followed by 1 unlabeled dose) Single iv dose of 10 mg/kg	90% of radioactivity excreted over 72 hrs. Between 77-87% excreted in the urine, 5-13% in the feces at low dose. At high dose, 55-63% excreted in the feces and 32-33% excreted in the urine. Biliary excretion accounted for 5-9% of an iv dose. Urinary excretion followed a biexponential pattern with half-life of 2.2-5.8 hrs initial phase and 21.4-56.7 hrs terminal phase. Minimal radioactivity was retained in the tissues (>0.07%). Expiration of <sup>14</sup> CO <sub>2</sub> was insignificant. Parent was excreted mostly unchanged. Metabolism occurred via ring hydroxylation or demethylation. Major metabolites were desmethyl MON 37500 (3.5%), 5-hydroxy MON 37500 (1.9%), and sulfonamide (2.9%). Other minor metabolites were also present.

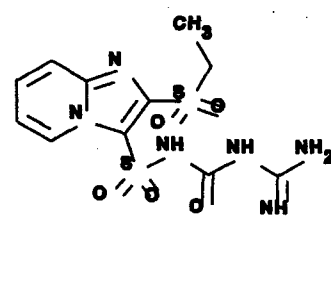
**Appendix B. Structures, Chemical and Common Names of Sulfosulfuron and Selected Degradation Products.**



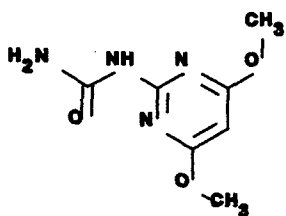
**37500 Deemethyl**



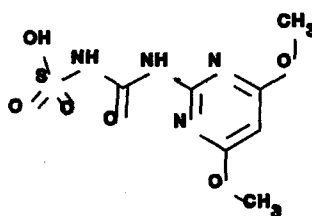
**MON 37500 (Parent)**



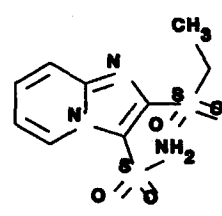
**37500 Guanidine**



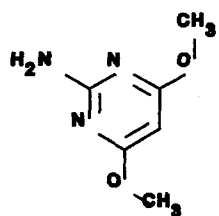
**37500 Urea**



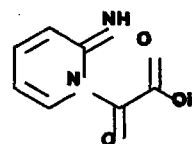
**37500 Sulfamic acid**



**37500 Sulfonamide**



**37500 Aminopyridine**



**37500 Oxamic acid**



13544

# R158148

**Chemical:** Sulfosulfuron

**PC Code:**  
085601

**HED File Code:** 14000 Risk Reviews

**Memo Date:** 2/28/2008

**File ID:** DPD327363

DPD304483

DPD237683

DPD245035

DPD328450

DPD327364

DPD349704

DPD249043

DPD332807

DPD239417

**Accession #:** 000-00-0124

**HED Records Reference Center**  
3/31/2008