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5-2-96

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

MAY 2 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Sulfentrazone.** Issues to be Presented to the HED Metabolism Committee on 5/20/96. Barcode D225222. CBTS# 17154

FROM: G.F. Kramer, Ph.D., Chemist
Tolerance Petition Team I
Chemistry Branch I, Tolerance Support
Health Effects Division (7509C)

THRU: E. Zager, Acting Branch Chief
Chemistry Branch I, Tolerance Support
Health Effects Division (7509C)

TO: HED Metabolism Committee Members[1]

FMC has submitted an application for permanent tolerances for the combined residues of the herbicide sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]methanesulfonamide) and its major metabolite 3-hydroxymethyl sulfentrazone (N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl] methanesulfonamide). The end use products, Authority 75DF Herbicide and Authority 4F Herbicide, are proposed to be registered for use on soybeans. To cover use on the primary crop, the petitioner has proposed the following tolerances (expressed as parent plus the metabolite 3-hydroxymethyl sulfentrazone):

Soybean Seed	--	0.05 ppm

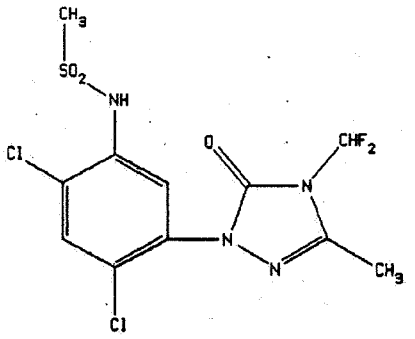
For residues in rotational crops (inadvertent residues), the petitioner has proposed the following tolerances (expressed as parent plus the metabolites 3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone [N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]methanesulfonamide]):

Wheat Forage	--	0.10 ppm

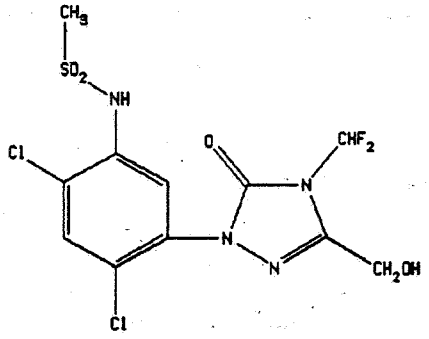
[1]Richard Loranger, Michael Metzger, Alberto Protzel, Karl Baetcke, William Burnam, Mike Ioannou, Byong-Han Chin, Randy Perfetti.

Wheat Straw	--	0.10 ppm
Wheat Grain	--	0.10 ppm
Corn Fodder	--	0.20 ppm
Corn Forage	--	0.20 ppm
Corn Grain	--	0.10 ppm
Rice Straw	--	0.20 ppm
Rice Grain	--	0.10 ppm

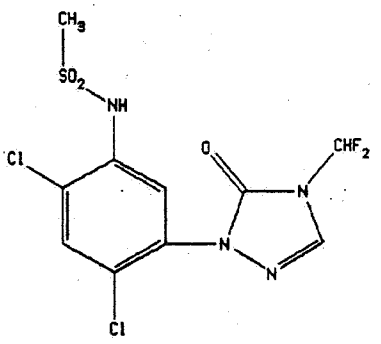
The structures of sulfentrazone and its metabolites are shown below:



Sulfentrazone



3-Hydroxymethyl Sulfentrazone



3-Desmethyl Sulfentrazone

Proposed Use.

Sulfentrazone is applied preemergence, at-plant or preplant soil incorporated. The maximum application rate is 0.375 lbs. ai/A and only one application may be made per season.

The label contains the following rotational crop restrictions: winter wheat, 4 months; spring wheat, 9 months; field corn, 10

months; and rice, 12 months.

Enforcement Method.

For plant RACs, the registrant has submitted a proposed analytical enforcement method which measures the parent and its metabolites (3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone) in a single chromatographic separation using GC with ECD. The limit of quantitation (LOQ) for each compound is 0.025 ppm. This method has undergone a successful Petition Method Validation for soybeans only.

Nature of the Residue.

Soybeans: Sulfentrazone, radiochemically labelled in the aromatic ring (phenyl-UL-^{14}C) or in the triazole ring (carbonyl-^{14}C) was applied to outdoor plots in a single preemergence broadcast application at a rate of 0.5 lbs. ai/A (1.3X). The plants were grown to maturity and harvested for seed and hay. Immature plants were also harvested for forage. The maximum residues observed in forage were 1.057 ppm; in hay, 1.073 ppm; and in seed, 0.171 ppm (Table 1). Metabolites were resolved on HPLC and compared with reference standards of sulfentrazone and possible metabolites (see fig. 1 for chemical structures). The major metabolites are 3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone, accounting for 38-50% and 13% of the TRR in forage, 9-23% and 26-27% of the TRR in hay and 30-35% and 4% of the TRR in seed, respectively. Other metabolites identified include sulfentrazone carboxylic acid, desmethylsulfonyl sulfentrazone, desdifluoromethyl desmethyl sulfentrazone, desdifluoromethyl sulfentrazone and methyl triazole.

Table 2- TRR in soybean RACs as a result of application of phenyl- or triazole-labelled sulfentrazone at a rate of 0.5 lbs. ai/A.

RAC	PHI (days)	Label	TRR (ppm)
Forage	63	Phenyl	1.057
		Triazole	1.028
Hay	114	Phenyl	1.073
		Triazole	1.006
Seed	145	Phenyl	0.084
		Triazole	0.171

Table 3- Summary of metabolite identification/characterization in soybean RACs.

Metabolite	Forage				Hay				Seed			
	Phenyl-labelled		Triazole-labelled		Phenyl-labelled		Triazole-labelled		Phenyl-labelled		Triazole-labelled	
	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR
Sulfentrazone	0.012	1.2	0.011	1.1	0.050	4.7	0.045	4.5	0.012	13.8	0.004	2.5
SCA	0.002	0.1	0.007	0.7	0.000	0.0	0.031	3.1	0.001	1.0	0.001	0.5
HMS	0.533	50.4	0.396	38.4	0.245	22.8	0.095	9.4	0.025	29.7	0.060	35.0
DMS	0.141	13.3	0.132	12.8	0.275	25.7	0.269	26.7	0.004	3.9	0.006	3.6
DMSS	0.008	0.8	0.006	0.5	0.011	1.0	0.009	0.9	0.001	1.2	0.001	0.6
DDS	0.061	5.8	0.076	7.4	0.065	6.0	0.076	7.6	0.005	5.9	0.009	5.2
DFMS	0.023	2.1	0.088	8.6	0.105	9.8	0.110	10.9	0.001	0.7	0.007	4.0
Methyl Triazole	ND	-	0.112	10.9	ND	-	0.029	2.9	ND	-	0.019	11.2

SCA = Sulfentrazone Carboxylic Acid
HMS = Hydroxy Methyl Sulfentrazone
DMS = Des-Methyl Sulfentrazone
DMSS = Des-MethylSulfonyl Sulfentrazone
DDS = Des-Difluoromethyl-Des-Methyl Sulfentrazone
DFMS = Des-difluoromethyl Sulfentrazone

Rotational Crops: In a confined crop rotation study, sulfentrazone, radiochemically labelled in the aromatic ring (phenyl-UL-^{14}C) or in the triazole ring (carbonyl-^{14}C), was applied to soil at a rate of 0.5 lbs. ai/A (1.3X) in a greenhouse. Crops (lettuce, radishes and barley) were seeded 30, 122, 245 and 364 days after treatment (DAT) of the soil with sulfentrazone. The highest residue levels were seen in barley straw (2.98-3.36 ppm at 30 DAT and 0.67-1.83 at 364 DAT) (Table 4). The identification of the residues is shown in Tables 5-7.

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Table 2- TRR in rotational crops as a result of application of phenyl- or triazole-labelled sulfentrazone to soil at a rate of 0.5 lbs. ai/A. The result are the average of two replicates.

DAT	Crop	RAC	Crop Age* (days)	Label Position (TRR, ppm)	
				Phenyl	Triazole
30	Radish	Top	50	0.716	0.868
		Root	50	0.312	0.343
	Lettuce	Leaf	50	0.651	0.440
	Barley	Forage	50	1.406	2.067
		Straw	243	2.984	3.362
		Grain	243	0.052	0.041
122	Radish	Top	72	0.099	0.132
		Root	72	0.066	0.063
	Lettuce	Leaf	72	0.194	0.110
	Barley	Forage	72	0.350	0.595
		Straw	214	2.725	4.264
		Grain	214	0.035	0.054
245	Radish	Top	74	0.176	0.162
		Root	74	0.044	0.047
	Lettuce	Leaf	74	0.044	0.034
	Barley	Forage	74	0.475	0.329
		Straw	154	1.060	1.705
		Grain	154	0.014	0.035
364	Radish	Top	62	0.042	0.143
		Root	62	0.058	0.139
	Lettuce	Leaf	62	0.115	0.030
	Barley	Forage	62	0.219	0.494
		Straw	236	0.673	1.831
		Grain	236	0.012	0.031

*Age of RAC when harvested

Table 5- Metabolite identification of radish residues. The results shown are the maximum observed in the phenyl- or triazole-labelled samples.

Metabolite	30 DAT		122 DAT		245 DAT		364 DAT	
	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR
Radish Tops								
HMS	0.266	37.2	0.032	32.8	0.091	51.6	0.020	48.5
DDS	0.262	36.6	0.029	29.7	0.032	18.3	0.006	4.2
SCA/DMS	0.034	4.1	0.004	3.6	0.018	10.0	0.005	11.5
Sulfentrazone	0.019	2.2	0.009	6.8	0.010	5.8	0.003	8.0
DMSS	0.010	1.2	0.002	2.3	0.001	0.3	0.003	2.4
MTz	0.137	15.8	0.016	11.9	0.017	10.2	0.028	19.9
Radish Root								
HMS	0.084	26.8	0.010	15.3	0.014	32.5	0.010	8.1
DDS	0.036	11.5	0.004	5.3	0.001	1.8	0.001	1.0
SCA/DMS	0.023	7.2	0.006	8.2	0.007	14.3	0.005	8.0
Sulfentrazone	0.040	11.5	0.008	12.2	0.006	14.1	0.003	3.7
DMSS	0.008	2.4	0.002	2.6	0.001	2.3	0.001	1.6
MTz	0.010	3.0	0.004	7.0	0.001	2.0	0.003	1.8

SCA = Sulfentrazone Carboxylic Acid
HMS = Hydroxy Methyl Sulfentrazone
DMS = Des-Methyl Sulfentrazone
DMSS = Des-MethylSulfonyl Sulfentrazone
DDS = Desmethyl Des(difluoromethyl) Sulfentrazone
MTz = Methyl Triazole

Table 6- Metabolite identification of lettuce leaf and barley forage residues. The results shown are the maximum observed in the phenyl- or triazole-labelled samples.

Metabolite	30 DAT		122 DAT		245 DAT		364 DAT	
	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR
Lettuce								
HMS	0.116	17.8	0.036	27.3	0.009	25.4	0.047	40.8
DDS	0.217	33.3	0.078	40.3	0.008	17.1	0.003	4.1
SCA/DMS	0.004	0.9	0.001	1.3	0.001	2.2	0.004	3.8
Sulfentrazone	0.037	6.3	0.011	5.7	0.002	4.5	0.005	4.1
DMSS	0.023	3.5	0.006	3.1	0.003	5.8	0.006	5.3
MTz	0.085	19.3	0.008	7.3	-		0.001	3.2

Metabolite	30 DAT		122 DAT		245 DAT		364 DAT	
	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR
Barley Forage								
HMS	0.303	19.3	0.069	16.6	0.136	28.7	0.111	28.4
DDS	0.364	25.9	0.144	35.7	0.039	8.2	0.029	5.9
SCA/DMS	0.439	31.2	0.088	15.6	0.140	29.6	0.084	29.1
Sulfentrazone	0.015	0.7	0.008	2.3	0.009	1.9	0.005	2.2
DMSS	0.079	5.6	0.018	3.5	0.014	3.0	0.007	3.4
MTz	0.515	24.9	0.100	16.9	0.090	27.4	0.084	17.1

SCA = Sulfentrazone Carboxylic Acid
HMS = Hydroxy Methyl Sulfentrazone
DMS = Des-Methyl Sulfentrazone
DMSS = Des-MethylSulfonyl Sulfentrazone
DDS = Desmethyl Des(difluoromethyl) Sulfentrazone
MTz = Methyl Triazole

Table 7- Metabolite identification of barley straw and grain residues. The results shown are the maximum observed in the phenyl- or triazole-labelled samples.

Metabolite	30 DAT		122 DAT		245 DAT		364 DAT	
	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR
Barley Straw								
HMS	0.959	32.2	0.774	24.6	0.186	17.5	0.170	14.7
DDS	0.045	1.5	0.037	0.9	0.075	7.1	0.054	6.5
SCA/DMS	0.862	28.9	0.773	27.7	0.300	28.3	0.224	23.4
Sulfentrazone	0.147	4.9	0.044	1.6	0.021	2.0	0.041	2.8
DMSS	0.167	5.6	0.102	2.8	0.039	3.4	0.019	2.9
MTz	0.827	24.6	0.927	21.7	0.090	5.3	0.063	3.5
Barley Grain								
HMS	0.010	19.1	0.006	14.6	0.002	16.8	NA	NA
SCA/DMS	0.010	19.9	0.006	14.4	0.003	22.0	NA	NA
Sulfentrazone	0.001	1.8	0.002	3.7	0.000	2.0	NA	NA
DMSS	0.001	2.7	0.001	2.8	0.001	6.4	NA	NA
MTz	0.001	3.1	0.008	14.0	0.008	23.6	NA	NA

[1] 30 DAT samples after acid hydrolysis, [2]Total of unknown HPLC peaks and unanalyzed fractions
-.= Not detected, NA = Not Analyzed

The nature of the residue in soybeans and rotational crops is understood (fig. 2, copied from p. 270 of MRID# 436565-01). Sulfentrazone is metabolized via four different pathways: 1) Oxidation of the 3-methyl group to form 3-hydroxymethyl sulfentrazone, followed by further oxidation to form sulfentrazone carboxylic acid which is decarboxylated to 3-desmethyl sulfentrazone. 2) Hydrolysis of the trifluoromethyl group to form desdifluoromethyl sulfentrazone which is oxidized and decarboxylated to form desdifluoromethyl desmethyl sulfentrazone. 3) Hydrolysis of the sulfonamide group to form desmethylsulfonyl sulfentrazone. and 4) Scission of the phenyl and triazole rings to produce methyl triazole. The corresponding phenyl metabolites are believed to remain bound.

Ruminants: In the ruminant metabolism study, [phenyl(U)-^{14}C]- and [triazole(carbonyl)-^{14}C]-sulfentrazone were administered orally to lactating goats at a rate of 4.9 ppm (phenyl) or 6.0 ppm (triazole). Of the administered radioactivity, 78-94% was recovered in urine. Another 4.5-7.4% was recovered in the feces and <0.04% was recovered in the milk, blood and tissues. The total recovery was over 85%. The TRR in tissues and milk is shown in Table 8. The greatest tissue residues were 0.013 ppm in kidney (phenyl). Sulfentrazone *per se* was the predominant component of the residue in kidney, accounting for 53.8% of the TRR. The metabolite 3-hydroxymethyl sulfentrazone (7.7% of the TRR) was also identified.

Table 8- TRR in goat milk and tissues following treatment with phenyl- or triazole-labelled sulfentrazone for 10 consecutive days.

Fraction	TRR (ppm)	
	Phenyl	Triazole
Liver	0.0068	0.0006
Kidney	0.0130	0.0010
Heart	0.0011	0.0001
Perirenal Fat	0.0004	<0.0001
Omental Fat	0.0007	0.0001
Longissimus Dorsi Muscle	0.0006	<0.0001
Semimembranous Muscle	0.0008	0.0004
Tricep Muscle	0.0003	<0.0001
Milk*	0.0011	0.0011

*Day 2 sample

Poultry: In the poultry metabolism study, [phenyl(U)-^{14}C]- and [triazole(carbonyl)-^{14}C]-sulfentrazone were administered orally to laying hens at a rate of 4.70 ppm (phenyl) or 4.73 ppm (triazole). Doses were administered once daily for 12 consecutive days. Of the administered radioactivity, 94-106% was recovered in excreta. The TRR in tissues and eggs is shown in Table 9. The greatest tissue residues were 0.030 ppm in kidney (phenyl). Sulfentrazone *per se* was the predominant component of the residue, accounting for 27-70% of the TRR (Table 10). The metabolites 3-hydroxymethyl sulfentrazone (18-33% of the TRR) and 3-desmethyl sulfentrazone (14% of the TRR in liver only) were also identified.

Table 9- Average TRR in hen excreta, eggs and tissues following treatment with phenyl- or triazole-labelled sulfentrazone for 12 consecutive days.

Fraction	TRR (ppm)	
	Phenyl	Triazole
Excreta	6.21	6.88
Egg White	0.011	0.012
Egg Yolk	0.008	0.007
Liver	0.014	0.007
Kidney	0.030	0.015
Gizzard	0.007	0.004
Fat	0.002	<0.002
Heart	0.007	0.001
Breast Muscle	<0.002	<0.002
Thigh Muscle	0.001	<0.002

Day 2 sample

Table 10- Metabolite identification in hen egg yolks, egg whites and liver

Metabolite	Phenyl		Triazole	
	ppm	% TRR	ppm	% TRR
Egg White				
Sulfentrazone	0.010	56.5	0.007	50.2
HMS	0.006	32.9	0.002	17.8
DMS	ND	-	ND	-

Metabolite	Phenyl		Triazole	
	ppm	% TRR	ppm	% TRR
Egg Yolk				
Sulfentrazone	0.010	70.4	NE	-
HMS	0.002	14.3	NE	-
DMS	ND	-	NE	-
Liver				
Sulfentrazone	0.003	26.8	NE	-
HMS	0.002	17.9	NE	-
DMS	0.002	13.5	NE	-

ND = Not Detected; NE = Not Extracted
HMS = Hydroxy Methyl Sulfentrazone
DMS = Des-Methyl Sulfentrazone

The metabolism of sulfentrazone in animals differs from that in plants as metabolism proceeds only by oxidation of the 3-methyl group to form 3-hydroxymethyl sulfentrazone, followed by further oxidation to form sulfentrazone carboxylic acid which is decarboxylated to 3-desmethyl sulfentrazone.

CBTS has concluded that tolerances are not required for residues in animal commodities from the proposed use on soybeans.

Magnitude of the Residue.

Soybeans: The registrant has submitted a total of 22 soybean residue trials. The maximum 3-hydroxymethyl sulfentrazone residue in soybeans was 0.022 ppm and residues of sulfentrazone *per se* were <0.005 ppm in all samples.

Rotational Crops: Rotational crop residue trials have been performed in wheat, corn and rice. The results are summarized in Table 11. Sulfentrazone was applied to the primary crop (soybeans) at a rate of 0.375-0.5 lbs. ai/A. (1-1.3X) and rotational crops were planted at the minimum plantback interval.

Table 11- Results of limited rotational crop field trials. Values of 0.005-0.025 ppm are above the LOD, but below the LOQ.

Crop	MAT[1]	RAC	Crop Age (Days)	Maximum Residue (ppm)			
				Sulfent.	DMS	HMS	Total
Wheat	4	Forage	61	0.016	0.046	0.052	0.114
		Grain	226	ND	ND	ND	ND
		Straw	266	0.068	0.081	0.029	0.178
Corn	9	Forage	114	0.019	0.054	0.007	0.080
		Grain	153	ND	ND	ND	ND
		Fodder	124	ND	0.020	ND	0.020
Rice	11	Straw	174	ND	0.094	0.037	0.131
		Grain	174	ND	0.025	0.052	0.077

[1]Months after treatment of soil with sulfentrazone when wheat was planted
ND = Not Detected; i.e., below the LOD (0.005 ppm).
HMS = Hydroxy Methyl Sulfentrazone
DMS = Des-Methyl Sulfentrazone

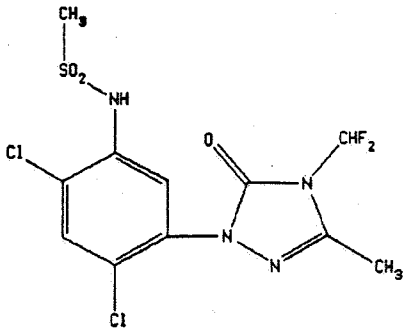
QUESTIONS TO THE METABOLISM COMMITTEE

1. Is there any scientific objection to establishing the soybean tolerance in terms of parent plus the metabolite 3-hydroxymethyl sulfentrazone or to establishing the rotational crop tolerances in terms of parent plus the metabolites 3-hydroxymethyl sulfentrazone and 3-desmethyl sulfentrazone? Is it appropriate to base the dietary risk assessment on these residues?

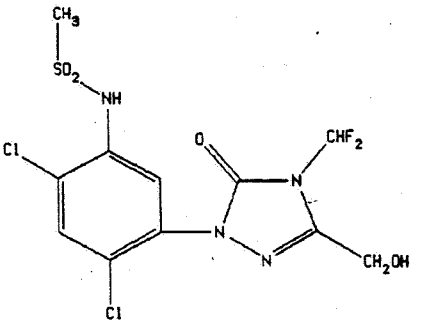
2. Are additional sulfentrazone metabolites at the levels reported of special toxicological concern? If so, which one(s)? Do they warrant inclusion in the tolerance regulation? Separate regulation? Inclusion in the dietary risk assessment? Additional metabolism studies? Toxicological studies?

cc: PP# 4F04407, S.F., Kramer, circ., R.F., HED Metabolism Committee File (R. Loranger), J. Rowe (Tox), S. Makris (Tox), D. Morgan/J. Miller (RD), D. McCall (RCAB)
RDI: R.A. Loranger (4/29/96), E. Zager (5/2/96)
G.F. Kramer:804V:CM#2:(703)305-5079:7509C

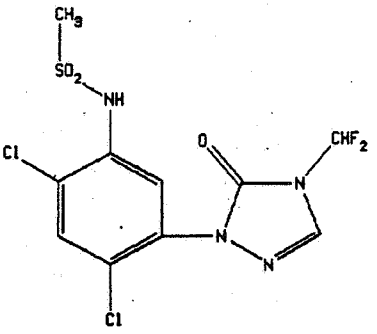
Figure 1- Structures of Sulfentrazone Metabolites Identified in Soybeans.



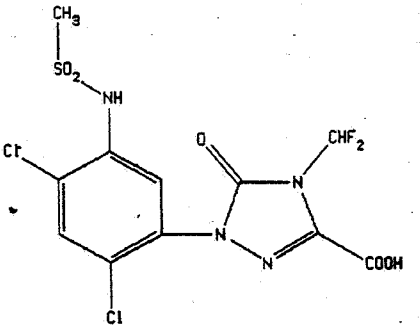
Sulfentrazone



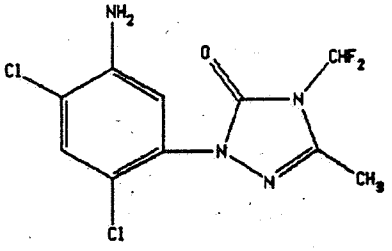
3-Hydroxymethyl Sulfentrazone



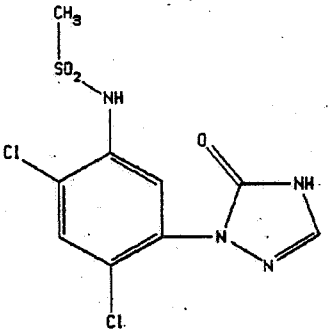
3-Desmethyl Sulfentrazone



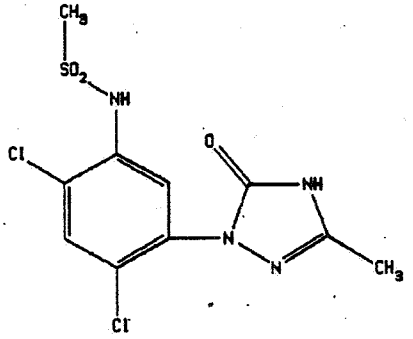
Sulfentrazone Carboxylic Acid



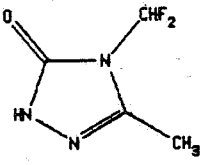
Desmethylsulfonyl Sulfentrazone



Desdifluoromethyl Desmethyl Sulfentrazone



Desdifluoromethyl Sulfentrazone



Methyl Triazole

Substantially Similar

Page 13 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
