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OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

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MEMORANDUM

Subject: **Mesosulfuron-methyl**. Meeting Report of the Metabolism Assessment Review Committee.

PC Code: 122009

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Health Effects Division (7509C)

# **SARC: Metabolism Assessment Summary**

Draft

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TXR Number: 0052410

Division: HED

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Methyl 2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate

Chemical Category:

Chemical Classification:

Meeting Date:

Conclusions

File

Attachment(s):

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# 1. INTRODUCTION

## Identification of Chemical

Mesosulfuron-methyl (AE F130060; PC Code 122009) is a new systemic herbicide developed by Aventis CropScience. Mesosulfuron-methyl is a sulfonyleurea which inhibits acetolactate synthase (ALS)/acetoxy acid synthase (AHAS). Mesosulfuron-methyl is absorbed through the foliage of treated weeds, rapidly inhibiting growth and causing yellowing to necrosis of the growing point and eventual plant death.

Aventis CropScience has proposed the establishment of permanent tolerances for residues of the herbicide mesosulfuron-methyl [methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[[(methylsulfonyl)amino]methyl]benzoate] in/on the following commodities:

Wheat, grain .....	0.03 ppm
Wheat, forage .....	0.60 ppm
Wheat, hay .....	0.06 ppm
Wheat, straw .....	0.30 ppm
Wheat, aspirated grain fractions .....	0.25 ppm*
Wheat, milled byproducts .....	0.03 ppm
Wheat, germ .....	0.10 ppm

\*Based on the processing study, the Agency will recommend that this tolerance be raised to 0.60 ppm.

Note: Upon submission of an acceptable livestock enforcement method, tolerances will be established in ruminant liver and kidney (or meat byproducts) at the demonstrated LOQ of the method.

The current petition represents the first food/feed registration application. No tolerances have been established for residues of mesosulfuron-methyl.

Chemical structure	
Common name	Mesosulfuron-methyl
Company experimental name	AE F130060 (Prior code number was HOE 130060)
IUPAC name	Methyl 2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate
CAS name	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[methylsulfonyl]amino]methyl]benzoate
CAS #	208465-21-8
End-use products/EP	OSPREY™ Herbicide (EPA Reg. No. 264-INE) for control of annual grasses and broadleaf weeds in winter wheat; SILVERADO™ Wild Oat Herbicide (EPA Reg. No. 264-INR) for control of wild oat and wild mustard in wheat, including durum.

### Issues Considered by the Committee

1. Does the committee agree that parent is the residue of concern for wheat commodities for the tolerance expression and dietary risk assessments?
2. Does the committee agree that parent is the residue of concern in rotational crops for the tolerance expression and dietary risk assessments?
3. Does the committee agree that parent is the residue of concern in ruminants and poultry for the tolerance expression and dietary risk assessments?
4. Does the committee think that any environmental degradates should be included in the risk assessment for drinking water?

## 2. MARC MEETING INFORMATION

### Decision

Chemical: MESOSULFURON-METHYL		
Meeting Date: 28-January-2004		
Table 2. Residues of Concern in Wheat, Livestock, Rotational Crops, and Water		
Matrix	For Risk Assessment	For Tolerance Expression
Wheat	Parent only	Parent only
Livestock (Ruminants and Poultry)	Parent only	Parent only
Rotational Crops	Parent only	Parent only
Water	Parent, AE F154851, AE F160459, and AE F160460	N/A

### Rationales:

**Wheat:** Metabolism studies conducted on wheat at 1.4X (pyrimidyl label) and 4.1X (phenyl label) indicated that the TRR in grain was very low (0.001 ppm). Parent was the major residue in wheat forage and hay; AE F160459 and AE F140584 were also present in forage at levels  $\geq 10\%$  TRR. The major residues in straw were AE F147447 and AE F 16059 but the levels were very low. Forage, hay, and straw are livestock feed items (with straw being a minor feed item), while grain is the only human food item. Field trials found parent in grain at maximum levels of 0.026 ppm (3.7X, spring wheat) and  $<0.01$  ppm (1.7X, winter wheat). Based on the low toxicity of the parent and the low level of exposure from food because of the low maximum application rate of 0.013 lb ai/A/season, the MARC concluded that parent only is the residue of concern for the tolerance expression and for risk assessment.

**Livestock:** TRR in the submitted dairy cow and poultry metabolism studies were low at exaggerated rates (13X for the dairy cow and 341X for poultry). Parent was the major metabolite in ruminant kidney, liver, and milk and in poultry liver and abdominal fat; in renal fat of ruminants, AE 0195141 and parent are the major residues. Based on the poultry metabolism study which was conducted at an exaggerated rate (341X), residues are not expected to occur in poultry tissues and eggs as a result of the proposed uses on wheat. Based on the low toxicity of the parent and the low level of exposure from livestock commodities, the MARC concluded that parent only is the residue of concern for the tolerance expression and for risk assessment.

**Rotational Crops:** The confined rotational crop study, conducted at 1X, indicated that TRRs are very low (<0.010 ppm) except for wheat straw. Identification of the TRR in straw indicated that parent was a minor component of the residue. However, based on the low toxicity of the parent and the low level of exposure, the MARC concluded that for the tolerance expression and risk assessment, parent only is the residue of concern.

**Drinking Water:** Environmental fate studies indicated that parent can be persistent in soils. Parent mesosulfuron-methyl does not bind strongly to soils and is expected to be mobile. Therefore, it has the potential to run off into surface water or leach to ground water. Laboratory studies indicated that biotransformation is the major route of degradation of mesosulfuron-methyl in the environment, while direct photolysis in water and photolysis on soil are not important degradation pathways for mesosulfuron-methyl. These data indicate that aerobic soil metabolism and aerobic and anaerobic aquatic metabolism can be major routes of degradation. The bridge-intact degradates AE F154851, AE F160459, and AE F160460 were found in all three studies (aerobic soil metabolism, aerobic and anaerobic aquatic metabolism), ranging from 5% to 20% of the applied dose. These degradates share a similar structure with the parent and, therefore, are considered to have toxicity and mobility which are similar to the parent. The MARC concluded that these metabolites (AE F154851, AE F160459, and AE F160460) should be included in the drinking water assessment. Other degradates can be excluded due to lower levels of exposure; they are less mobile than the parent and the application rates for the two end-use products are low. The MARC concluded that parent and the three degradates AE F154851, AE F160459, and AE F160460 are the residues of concern and should be included in the drinking water assessment.

**Members in Attendance:** Alberto Protzel, PV Shah, Abdallah Khasawinah, Yan Donovan, Norman Birchfield, Leonard Keifer, Christine Olinger, Bill Wassell.

**Members in Absentia:** Leung Cheng, John Doherty, Rick Loranger, Pauline Wagner.

**Alternate Members in Attendance:** David Soderberg.

**Non-members:** Nancy Dodd, Kelly O'Rourke, Judy Facey, Silvia Termes, Stephanie Syslo, Sarah Winfield.

### 3. BRIEFING MATERIALS

#### Residue Chemistry

#### Use Information

In conjunction with the current wheat tolerance petition, Aventis is seeking the registration of two end-use products (OSPREY™ Herbicide and SILVERADO™ Wild Oat Herbicide) containing mesosulfuron-methyl as the active ingredient. The two end-use products are classified as water-dispersible granular formulations and are to be applied postemergence as foliar sprays.

OSPREY™ Herbicide (4.5% ai) is for control of annual grasses and broadleaf weeds in winter wheat. For OSPREY™, one broadcast foliar spray application can be made with ground or aerial equipment at the maximum rate of 0.013 lb ai/A with PHIs of 30 days for forage and 55 days for grain and straw. The application can be made from wheat emergence up to the jointing stage of wheat.

SILVERADO™ Wild Oat Herbicide (2.0% ai) is for control of wild oat and wild mustard in wheat, including durum. For SILVERADO™, broadcast foliar spray applications can be made with ground or aerial equipment at the maximum proposed single application rate of 0.003 lb ai/A and the maximum proposed seasonal rate of 0.006 lb ai/A with PHIs of 30 days for forage and 55 days for grain and straw. Applications can be made from wheat emergence up to the jointing stage of wheat.



**Table 3.1. Summary of Directions for Use of Mesosulfuron-methyl.**

Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb a.i./A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb a.i./A)	PHI (days)	Use Directions and Limitations
Winter Wheat						

OSPREY™ Herbicide (EPA Reg. No. 264-1NE)	post-emergence up to the jointing stage of wheat; broadcast, foliar spray; ground or aerial equipment	0.009-0.013	1	0.013	forage: 30 grain: 55 straw: 55  Apply to young actively growing weeds in vigorously growing winter wheat. Apply from wheat emergence up to the jointing stage of wheat. Apply broadcast with ground equipment in at least 10 gals water per acre or with aerial equipment in a minimum of 5 gals water/A. Control the boom height (for ground applications) to maintain a distance above the crop canopy of 4 feet or less. Aerial application should be made at a maximum height of 10 feet above the crop.  An adjuvant is required; it must be tank mixed with OSPREY™.  Except in the Pacific Northwest, the adjuvant could be either a methylated seed oil (MSO) with ≥ 10% emulsifier at the rate of 1.5 pt/A in at least 10 gals spray solution or a "basic blend" type adjuvant at a rate of 0.8-1.6 pt/A. (A basic blend adjuvant is a formulated combination of a non-ionic surfactant or a methylated seed oil and a nitrogen source.) Substitute a nonionic surfactant (NIS) at a rate (concentration) of 0.5% v/v (2 qts per 100 gallons of spray solution) with ammonium nitrogen fertilizer for a methylated seed oil or a basic blend when using a tank mix partner that restricts the addition of a methylated seed oil surfactant (NIS) may be used at a rate (concentration) of 0.5% v/v (2 qts per 100 gallons of spray solution) with ammonium nitrogen fertilizer. For all geographic areas, at least 50% of the surfactant product must be active non-ionic surfactant.  Tank mix with the following specified herbicides, fungicides, and insecticides: Herbicides: Allyl®, Allyl® Extra, Buctril® Herbicide (or equivalent bromoxynil products), Bromate Advanced™ Herbicide (or equivalent bromoxynil products), Curtail™, Harmony® Extra, Harmony® GT, MCP esters, Peak®, Staraner™, Stinger™ and Finesse®; Fungicides: Stratego®, Tilt® or Topsin® 70W; Insecticides: Sevin® XLR Plus, Warrior® T or Mustang Max™.  The label prohibits the planting of rotational crops in fields treated with mesosulfuron-methyl for 7 days for wheat and barley, 30 days for sunflower, 90 days for cotton, dry beans, lentils, peas, peanuts, rice, and soybean, 12 months for corn, and 10 months for all other crops.  Do not apply to crops undersown with grass and legume species.  Do not apply when wind causes drift.  Do not apply through any type of irrigation system.  Do not use additives that lower the spray solution pH below 6.0. Best results are obtained at a spray solution pH of 6.0-8.0.  Do not make topdress applications of ammonium nitrogen fertilizer within 21 days following an OSPREY™ application.  Do not apply OSPREY™ Herbicide in tank mixture with malathion, mancozeb, di-syston, or methyl parathion as unacceptable phytotoxicity may occur.  OSPREY™ Herbicide may be applied to certain wheat varieties grown only in CA. The following CA wheat varieties exhibit tolerance to OSPREY™ Herbicide when applied at 4.75 oz/A: Bonus, Brooks, Dirkwin, Express, Yamhill, Madsen, Stephens, Summit, Weatherford, Yecora Rojo, and Kronos.  The restricted entry interval (REI) is 12 hours.
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Spring Wheat

<p><b>SILVERADO™</b> Wild Oat Herbicide (EPA Reg. No. 264-1NR)</p>	<p>post- emergence up to the jointing stage of wheat; broadcast, foliar spray; ground or aerial equipment</p>	<p>0.002- 0.003</p>	<p>not stated</p>	<p>0.006</p>	<p>forage: 30 grain: 55 straw: 55</p>	<p>Apply to young actively growing weeds in vigorously growing wheat, including durum. Apply from wheat emergence up to the jointing stage of wheat. Apply with ground equipment in 10-20 gals water/A or with aerial equipment in a minimum of 5 gals water/A. Control the boom height (for ground applications) to maintain a distance above the crop canopy of 4 feet or less. Aerial applications should be made at a maximum height of 10 feet above the crop. An adjuvant is required; it must be tank mixed with Silverado™. The adjuvant could be methylated seed oil (MSO) with ≥ 10% emulsifier at the rate of 1.5 pt/A in at least 10 gals spray solution, an MSO Basic Blend adjuvant (2% v/v in the spray solution) at a minimum rate of 1.5 pt/A in at least 10 gals spray solution, or a Basic Blend adjuvant (1% v/v in the spray solution) at 0.8-1.6 pt/A. (The Basic Blend is a formulated combination of a non-ionic surfactant or a methylated oil and a nitrogen source.) Tank mix with the following specified herbicides, fungicides, and insecticides: <u>Herbicides:</u> Allyl® Extra, Buctril® Herbicide (or equivalent bromoxynil products), Bronate Advanced™ Herbicide (or equivalent bromoxynil products), Curral™ M, Express™, Harmony® Extra, Harmony® GT, MCPA esters, Starane™, or Stinger™; <u>Fungicides:</u> Stratego®, Tilt® or Topsin® 70W; <u>Insecticides:</u> Sevin® XLR Plus, Warrior® T or Mustang Max™. The label prohibits the planting of rotational crops in fields treated with mesosulfuron-methyl for 7 days for wheat and barley, 30 days for sunflowers, 90 days for dry beans, lentils, peas, and soybeans, 10 months for sugar beets, potatoes, and canola, 12 months for corn, and 10 months for all other crops. Do not apply to crops undersown with grass and legume species. Do not apply when wind causes drift. Do not apply through any type of irrigation system. Do not use additives that lower the spray solution pH below 6.0. Best results are obtained at a spray solution pH of 6.0-8.0. Do not use liquid nitrogen fertilizer solutions such as 28-0-0 or 30-0-0 or 32-0-0 as the carrier when applying SILVERADO™. Do not apply SILVERADO™ in tank mixture with malathion, mancozeb, or methyl parathion as unacceptable phytotoxicity may occur. Varieties of wheat (including Durum) may differ in their response to herbicides. If no information is available, limit the initial use to a small area. The restricted entry interval (REI) is 12 hours.</p>
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The proposed use directions are adequate to allow RAB3 an assessment of whether the submitted residue data reflect the maximum residues likely to occur in wheat. Some label revisions will be recommended as follows:

For OSPREY™ Herbicide, a revised Section B/label is needed to propose a preharvest interval (PHI) for hay; the residue data would support a PHI of 60 days.

For SILVERADO™ Wild Oat Herbicide, a revised Section B/label is needed to add the statement "Do not make more than one application of SILVERADO™ Wild Oat Herbicide in one wheat growing season." This restriction is needed because the submitted residue data reflects one application. If the maximum single application rate is to remain at 0.003 lb ai/A, the maximum to be applied in one growing season (under "Precautions for Use") should be decreased from 4.5 oz/A to 2.25 oz/A. Also, a preharvest interval (PHI) for hay should be proposed; the residue data would support a PHI of 50 days.

Based on the results of submitted confined rotational crop studies, the petitioner is required to revise product labels for OSPREY™ Herbicide and SILVERADO™ Wild Oat Herbicide to specify a plantback interval of at least 30 days for barley. HED has no objection to longer crop rotation restrictions as specified on the labels. A plantback restriction is not needed for wheat.

## Physical/Chemical Properties

Parameter	Value	Reference
Melting point/range	189-192°C	45386213
pH	5.1 @ 25°C	45386220
Density	1.53 gm/cc at 23°C	45386214
Water solubility, g/L (20°C)	water (pH = 5.66) $2.14 \times 10^{-2} \pm 0.17 \times 10^{-2}$ buffer pH 4 $2.15 \times 10^{-3} \pm 0.14 \times 10^{-3}$ buffer pH 5 $7.24 \times 10^{-3} \pm 0.36 \times 10^{-3}$ buffer pH 7 $0.483 \pm 0.008$ buffer pH 9 $15.39 \pm 0.32$ buffer pH 10 13.80	45386215, 45386216
Solvent solubility, g/L (20°C)	isopropanol $9.6 \times 10^{-2}$ acetone 13.66 acetonitrile 8.37 n-hexane $<2.29 \times 10^{-4}$ methylene chloride 3.79 ethyl acetate 2.03 toluene $1.26 \times 10^{-2}$	45386215
Vapor pressure at 20°C	$3.5 \times 10^{-12}$ Pascal	45386217
Dissociation constant, pK <sub>a</sub> , at 20°C	$4.35 \pm 0.04$	45386218
Octanol/water partition coefficient	log P <sub>ow</sub> = 1.90 (pH 4); 1.39 (pH 5); -0.48 (pH 7); -2.06 (pH 9); -2.10 (pH 10)	45386219
UV/visible absorption spectrum	G <sup>2</sup>	

<sup>1</sup> D297240, Shyam Mathur, PhD, 1/15/04

<sup>2</sup> data gap

Overall Summary

**TABLE 3.3. Summary of Metabolites and Degradates.**

MATRICES		MAJOR METABOLITES/ DEGRADATES <sup>1</sup>	MINOR METABOLITES/ DEGRADATES <sup>2</sup>
<b>PLANT METABOLISM</b>			
wheat	forage	parent, AE F160459, AE F140584	AE F147447
	hay	parent	AE F160459
	straw	AE F147447, AE F160459	AE F140584, parent
	grain	TRR (0.001 ppm) was too low to identify.	
<b>LIVESTOCK METABOLISM</b>			
Ruminants	Muscle	TRR (0.003-0.004 ppm) was too low to identify.	
	Renal Fat	AE 0195141, parent	No minor metabolites were identified.
	Kidney	parent	AE F147447, AE F140584, AE 0195141
	Liver	parent	AE F140584, AE F147447
	Milk	parent	AE F140584, AE F160459
Poultry	Muscle	TRR (<0.002 ppm) was too low to identify.	
	Abdominal Fat	parent	tentatively identified: AE F140584/AE F147447
	Liver	parent	AE 0195141, AE F140584, AE F160459
	Egg Whites	Without quantitative data, the residues in the egg white extract were tentatively identified as unchanged parent and possibly AE F147447.	
	Egg Yolks	Without quantitative data, the residues in the egg yolk extract were tentatively identified as unchanged parent and several minor metabolites, namely AE F160459, AE F154851, and AE F140584. An unknown metabolite less polar than the parent was possibly present.	

MATRICES		MAJOR METABOLITES/ DEGRADATES <sup>1</sup>	MINOR METABOLITES/ DEGRADATES <sup>2</sup>
<b>ROTATIONAL CROPS</b>			
carrot	tops	TRR were all <0.010 ppm.	
	roots		
spinach	leaves		
wheat	grain		
wheat	straw	AE F147447	AE F092944, AE F140584, parent, AE F154851
<b>RATS</b>			
Rats	feces	parent	AE F140584, AE F160459, AE F147447, AE F154851, AE F151015, AE 0195141
	bile	parent <sup>3</sup>	AE F160459, AE F151015

<sup>1</sup> Major is defined as comprising >10% of the total radioactive residues in a plant or livestock metabolism study, or as >10% of the applied dose in an environmental fate study.

<sup>2</sup> Minor is defined as comprising <10% of the total radioactive residues in a plant or livestock metabolism study, or as <10% of the applied dose in an environmental fate study.

<sup>3</sup> Parent was the residue present at the highest level but it was present at only 3.8% in males and 5.2% in females, respectively.

Chemical structure		
Radiolabel position	C2 position of the pyrimidyl ring (used in a wheat metabolism study and in the confined rotational crop study)	Uniformly in the phenyl ring (used in wheat, ruminant, and poultry metabolism studies and in the confined rotational crop study)

## Summary of Metabolism Data - Crops

### *Wheat (MRIDs 45386510 and 45386511)*

Aventis has submitted the results of two studies investigating the metabolism of [pyrimidyl-2-<sup>14</sup>C]mesosulfuron-methyl and [phenyl-U-<sup>14</sup>C]mesosulfuron-methyl in wheat. The radiolabeled test substances were applied as water-dispersible granular formulations to wheat plants in the tillering stage and grown outdoors in stainless steel containers. For the pyrimidyl-label study, wheat plants were either treated once at 0.0089 lb ai/A (10 g ai/ha) or twice, with a one-day retreatment interval, at 0.0089 lb ai/A per application (10 g ai/ha per application) for a total of 0.0178 lb ai/A (20 g ai/ha; 1.4x the maximum proposed seasonal rate). For the phenyl-label study, wheat plants were either treated once at 0.0268 lb ai/A (30 g ai/ha) or twice, with a one-day retreatment interval, at 0.0268 lb ai/A per application (30 g ai/ha per application) for a total of 0.0535 lb ai/A (60 g ai/ha; 4.1x the maximum proposed seasonal rate). Both studies focused the residue characterization efforts on wheat samples treated twice because overall residues were higher than in those samples treated once. The formulations included the safener AE F107892 at a 1:3 ratio (1 part active substance to 3 parts safener) to reduce phytotoxic effects.

The total radioactive residues (TRR; expressed as mesosulfuron-methyl equivalents) in/on treated wheat matrices were generally low. In the pyrimidyl-label study reflecting two treatments, the TRR were 0.0187 ppm in forage, 0.0112 ppm in hay, 0.0188 ppm in straw, and 0.001 ppm in grain. In the phenyl-label study reflecting two treatments, the TRR were 0.0186 ppm in forage, 0.013 ppm in hay, 0.0457 ppm in straw, and 0.0012 ppm in grain.

Residues in/on wheat matrices were adequately extracted using aqueous acetonitrile, and the extract was repeatedly cleaned up prior to chromatographic analysis. In the pyrimidyl-label study, approximately 67%, 80%, and 87% of the TRRs were extractable in straw, hay, and forage, respectively. In the phenyl-label study, about 86% and 90% of the TRRs were extractable in straw and forage, respectively. The nonextractable residues which remained following repeated extraction with aqueous acetonitrile were 0.0019-0.0066 ppm. TRRs, which were low absolute values, were reported as 100% for wheat matrices, being calculated as the sum of percent extractable and percent non-extractable.

In the pyrimidyl-label study, approximately 45%, 62%, and 69% of the TRR were identified and characterized in straw, hay, and forage, respectively. The parent, mesosulfuron-methyl, was identified at 1.8% TRR in straw, 15.3% TRR in hay, and 23.4% TRR in forage. In addition to the parent, the metabolite AE F160459 was identified at 3.7-8.6% TRR. The remainder of extractable residues were characterized as polar residues consisting of at least eight components, none of which exceeded a residue level of 0.003 ppm.

In the phenyl-label study, approximately 71% and 76% of the TRR were identified and characterized in straw and forage, respectively. The parent, mesosulfuron-methyl, was identified at 3.0% TRR in straw and 22.9% TRR in forage. The following metabolites were additionally identified in straw and forage: AE F140584 (8.8-10.1% TRR), AE F160459 (12.6-14.0% TRR),



and AE F147447 (5.0%-18.1% TRR). The remainder of extractable residues were characterized as polar residues consisting of at least five components and unresolved peak fractions, none of which exceeded a residue level of 0.004 ppm.

In both the pyrimidyl-label study conducted at the total rate of 0.0178 lb ai/A and the phenyl-label study conducted at the total rate of 0.0535 lb ai/A, the parent and each identified metabolite were individually <0.010 ppm.

The metabolic route of mesosulfuron-methyl in wheat proceeds by cleavage of the parent between the two rings to yield AE F140584 and subsequent isothiazole ring formation to form AE F147447. In addition, hydrolysis of a methoxy group on the pyrimidine ring of the parent yields the hydroxy metabolite AE F160459.

TABLE 3.5. Use Pattern Information	
Chemical name	[pyrimidyl-2- <sup>14</sup> C]mesosulfuron-methyl and [phenyl-U- <sup>14</sup> C]mesosulfuron-methyl
Composition of spray mixture	Each radiolabeled test substance was applied with the safener AE F107892 at a 1:3 ratio (1 part active substance to 3 parts safener). The spray mixture was applied as a water-dispersible granular formulation.
Application method	Each formulated test substance was applied as a spray treatment using a graphic spray pistol (type: Walther Pilot 93 ND).
Application rates and number of applications	For the <u>pyrimidyl-label study</u> , two treatment rates were used: 1. Wheat plants grown in container 6 were spray treated once at 0.0089 lb ai/A (10 g ai/ha). 2. Wheat plants grown in container 3 were spray treated twice at 0.0089 lb ai/A per application (10 g ai/ha per application) for a total of 0.0178 lb ai/A (20 g ai/ha). The second application was made one day after the first application. For the <u>phenyl-label study</u> , two treatment rates were used: 1. Wheat plants grown in container 2 were spray treated once at 0.0268 lb ai/A (30 g ai/ha). 2. Wheat plants grown in container 5 were spray treated twice at 0.0268 lb ai/A per application (30 g ai/ha per application) for a total of 0.0535 lb ai/A (60 g ai/ha). The second application was made one day after the first application.
Timing of applications	For the <u>pyrimidyl-label study</u> , the test substance was applied when wheat plants were at the advanced tillering stage (stage 25-29 according to BBCH code) with plant height of ~20 cm. For the <u>phenyl-label study</u> , the test substance was applied when wheat plants were at the tillering stage (stage 23 according to BBCH code) with plant height of ~25 cm.
Preharvest Interval (PHI)	<u>Pyrimidyl-label study</u> 1. Leaves were collected on day-0 after the spray mixture has dried. 2. Forage was collected at PHIs of 35/36 days. 3. Hay was collected at a PHI of 49 days. 4. Mature grain and straw were collected at a PHI of 95 days. <u>Phenyl-label study</u> 1. Leaves were collected on day-0 after the spray mixture has dried. 2. Forage was collected at PHIs of 41/42 days. 3. Hay was collected at PHIs of 57/58 days. 4. Mature grain and straw were collected at a PHI of 103/104 days.

**TABLE 3.6. Summary of Characterization and Identification of Radioactive Residues in Wheat Matrices Following Two Spray Treatments of [Pyrimidyl-2-<sup>14</sup>C]Mesosulfuron-methyl for a Total of 0.0178 lb ai/A (20 g ai/ha; 1.4x the maximum proposed seasonal rate).**

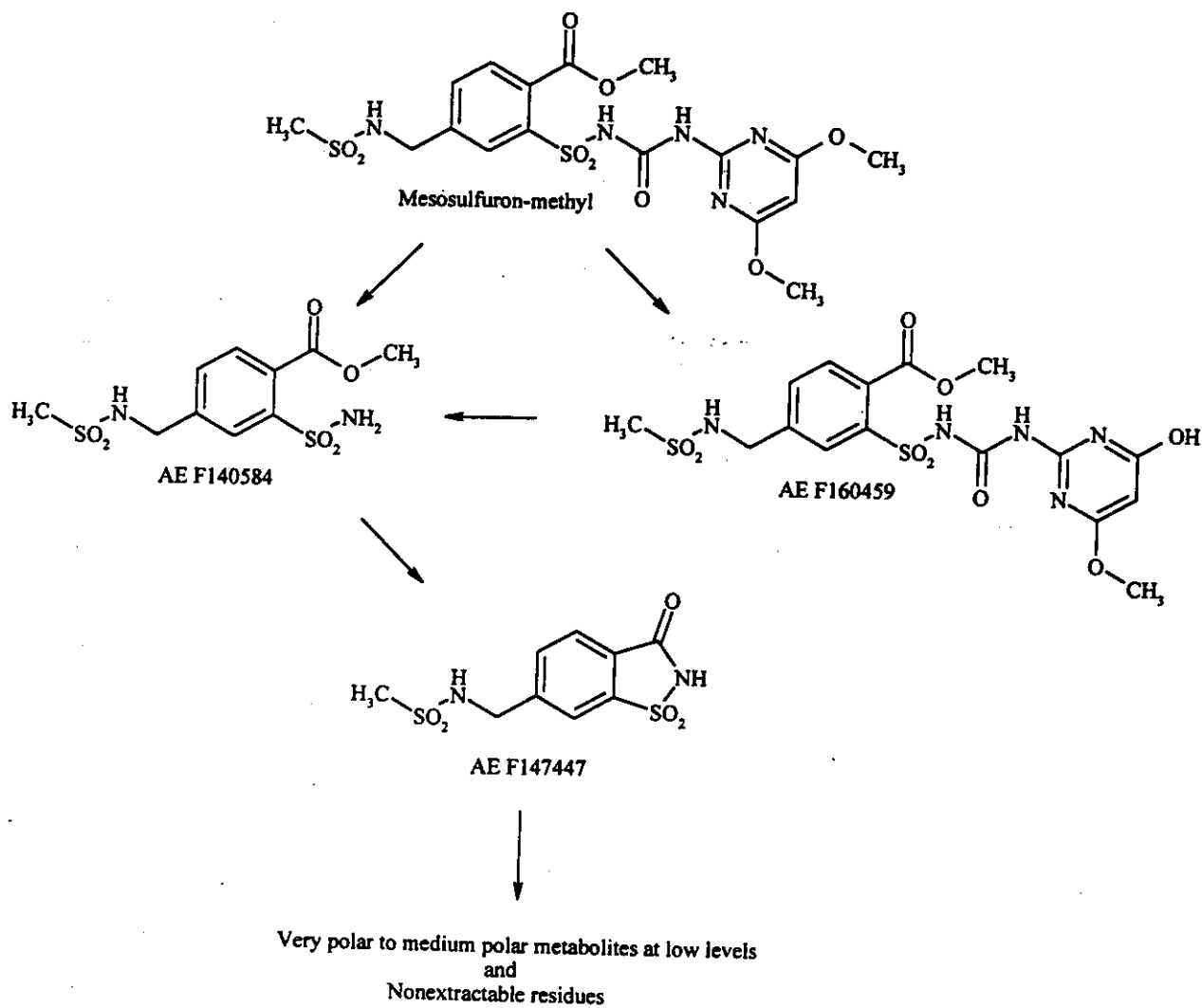
Compound	Straw		Hay		Forage	
	(TRR = 0.0188 ppm)		(TRR = 0.0112 ppm)		(TRR = 0.0187 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
<b>Identified:</b>						
Mesosulfuron-methyl	1.8	0.0003	15.3	0.0017	23.4	0.0044
AE F160459	8.6	0.0016	5.4	0.0006	3.7	0.0007
<b>Characterized:</b>						
Very polar HPLC peaks	27.8	0.0053	6.5	0.0007	10.2	0.0019
Polar HPLC peaks	5.4	0.0010	6.6	0.0008	4.1	0.0007
Medium polar HPLC peaks	1.2	0.0002	15.0	<0.0018	18.5	0.0034
Unresolved peaks	--	--	13.4	0.0015	8.6	0.0016
Total extractable	67.4	0.0127	80.3	0.0090	87.2	0.0163
Total identified	10.4	0.0019	20.7	0.0023	27.1	0.0051
Total characterized	34.4	0.0065	41.5	<0.0048	41.4	0.0076
Loss during work-up	23.0	0.0043	18.0	0.0020	18.6	0.0035
Total bound	32.6	0.0061	19.7	0.0022	12.8	0.0024

**TABLE 3.7. Summary of Characterization and Identification of Radioactive Residues in Wheat Matrices Following Two Spray Treatments of [Phenyl-U-<sup>14</sup>C]Mesosulfuron-methyl for a Total of 0.0535 lb ai/A (60 g ai/ha; 4.1x the proposed seasonal rate).**

Compound	Straw		Forage	
	(TRR = 0.0457 ppm)		(TRR = 0.0186 ppm)	
	% TRR	ppm	% TRR	ppm
<b>Identified:</b>				
Mesosulfuron-methyl	3.0	0.0014	22.9	0.0043
AE F140584	8.8	0.0040	10.1	0.0019
AE F160459	12.6	0.0058	14.0	0.0026
AE F147447	18.1	0.0083	5.0	0.0009
<b>Characterized:</b>				
Very polar HPLC peaks	8.9	0.0041	2.3	0.0004
Polar HPLC peaks	14.4	0.0066	19.8	0.0037
Medium polar HPLC peaks	5.2	0.0024	2.1	0.0004
<b>Total extractable</b>	<b>85.5</b>	<b>0.0390</b>	<b>89.9</b>	<b>0.0168</b>
<b>Total identified</b>	<b>42.4</b>	<b>0.0194</b>	<b>52.1</b>	<b>0.0097</b>
<b>Total characterized</b>	<b>28.5</b>	<b>0.0131</b>	<b>24.2</b>	<b>0.0045</b>
<b>Loss during work-up</b>	<b>14.6</b>	<b>0.0066</b>	<b>13.6</b>	<b>0.0025</b>
<b>Total bound</b>	<b>14.5</b>	<b>0.0066</b>	<b>10.1</b>	<b>0.0019</b>

FIGURE 3.1

Proposed Metabolic Pathway of Mesosulfuron-methyl in Wheat



**TABLE 3.8. Identification of Compounds from the Wheat Metabolism Study**

Common name/code	Chemical name	Chemical structure
Mesosulfuron-methyl/ AE F130060	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]-sulfonyl]-4-[[[(methylsulfonyl)-amino]methyl]benzoate (CAS)	
AE F160459	Methyl 2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate (IUPAC)	
AE F140584	Methyl 4-methanesulfonamidomethyl-2-sulfamoylbenzoate (IUPAC)	
AE F147447	6-Methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (IUPAC)	

## Summary of Metabolism Data - Livestock

### *Meat and Milk (MRID 45386513)*

Aventis has submitted the results of a study investigating the metabolism of [phenyl-U-<sup>14</sup>C]mesosulfuron-methyl in ruminants. A lactating dairy cow was orally dosed for five consecutive days with the radiolabeled test substance at 20.54 ppm in the diet. The feeding dose level is 13x the maximum theoretical dietary burden of 1.599 ppm for dairy cattle. During the dosing period, milk was collected twice daily. Approximately 22 hours after the final dosing period, the test animal was sacrificed, and samples of edible tissues were collected.

The total radioactive residues (TRR; expressed as mesosulfuron-methyl equivalents) were 0.002-0.004 ppm in milk, 0.031 ppm in liver, 0.058 ppm in kidney, 0.003-0.004 ppm in muscle, and 0.009-0.032 ppm in fat. The majority of the radioactive residues was extractable using organic solvents including 92.32% of the TRR in 120-hour milk, 81.70% of the TRR in liver, 82.86% of the TRR in kidney, and 95.58% of the TRR in renal fat. The major component of the identified residues was unchanged parent. In addition, the cleavage products AE F140584 and AE F147447 were identified. Finally, the alcohol metabolite AE 0195141 was detected as a minor component in kidney and a major component in fat. The identification and characterization of residues in the milk and edible tissues of the dairy cow is summarized below.

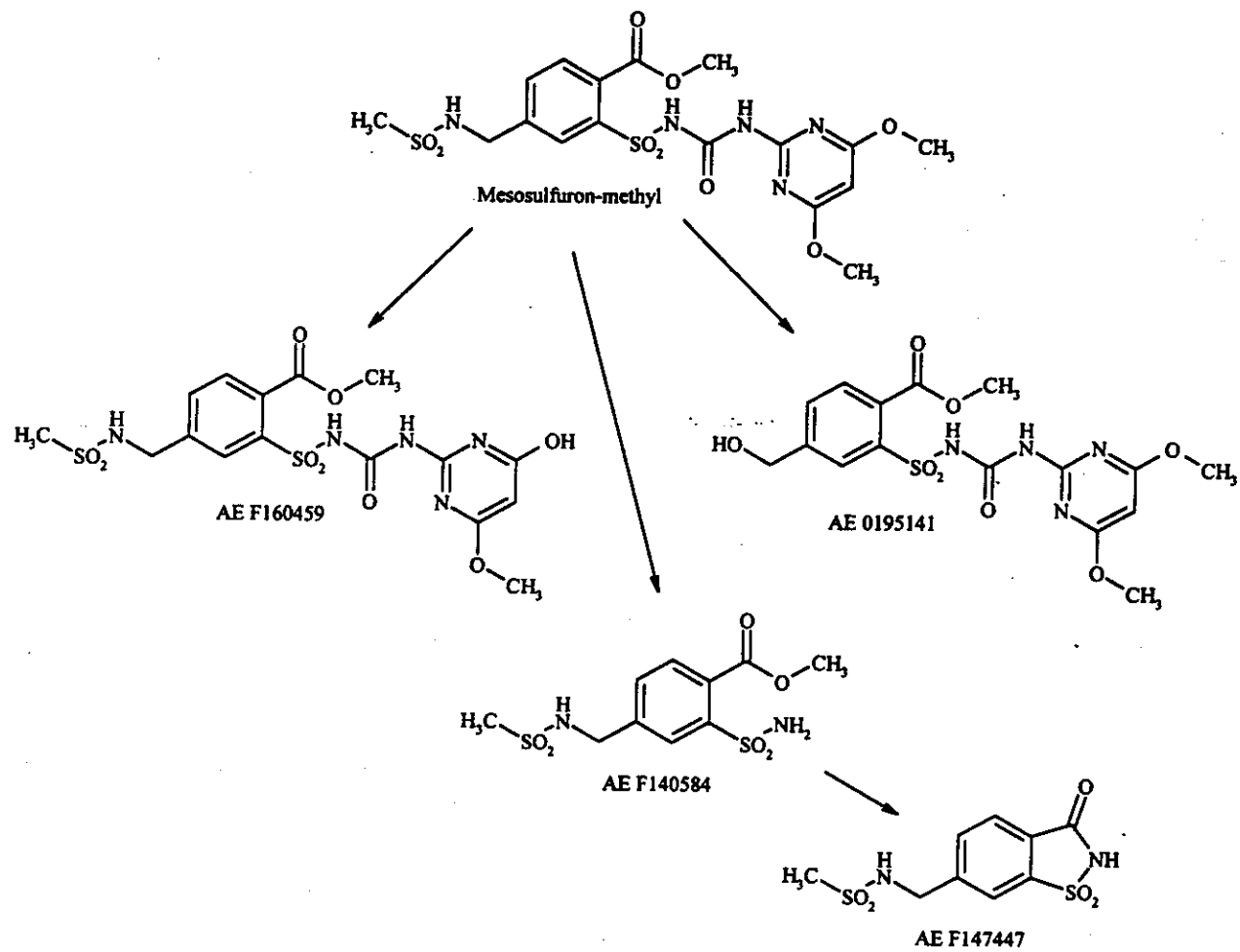
The metabolic route of mesosulfuron-methyl in ruminants proceeds by cleavage of the parent between the two rings to yield AE F140584 and subsequent isothiazole ring formation to form AE F147447. In addition, hydrolysis of a methoxy group on the pyrimidine ring of the parent yields the hydroxy metabolite AE F160459. Oxidative deamination of the parent forms the alcohol metabolite AE 0195141.

Treatment Type	Level of administered dose (mg/day)	Food consumption (kg/day)	Residue Intake in Diet (ppm)	Vehicle	Timing/Duration
Oral	221.56 ± 1.97	10.79 ± 1.01	20.54	capsule	One capsule per day for 5 consecutive days

**TABLE 3.10. Summary of Characterization and Identification of Radioactive Residues in Dairy Cow Matrices Following Dosing with [Phenyl-U-<sup>14</sup>C]Mesosulfuron-methyl at 20.54 ppm in the Diet (13x the Maximum Theoretical Dietary Burden)**

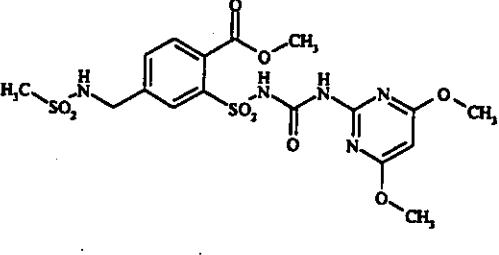
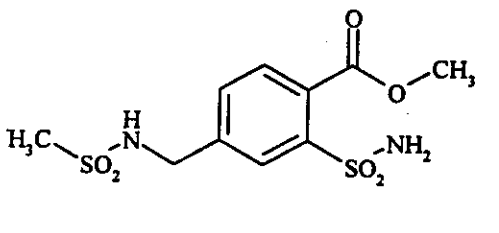
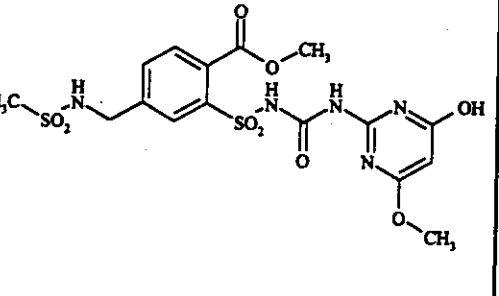
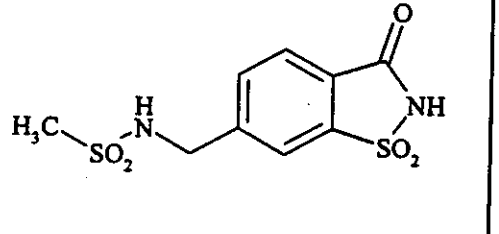
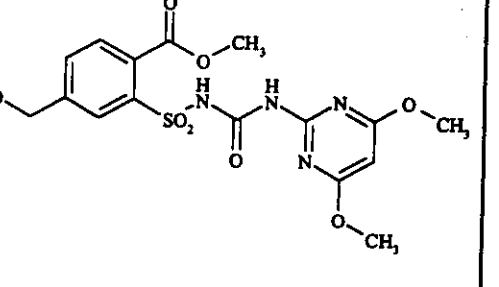
Compound	Milk, 120-Hr		Liver		Kidney		Renal fat	
	(TRR = 0.004 ppm)		(TRR = 0.031 ppm)		(TRR = 0.058 ppm)		(TRR = 0.032 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
<b>Identified residues</b>								
Mesosulfuron-methyl	23.12	0.001	52.60	0.017	41.15	0.024	20.02	0.006
AE F140584	--	--	8.22	0.003	5.23	0.003	--	--
AE F147447	--	--	3.79	0.001	6.31	0.004	--	--
AE 0195141	--	--	--	--	1.42	0.001	26.91	0.009
<b>Characterized residues</b>								
AE F140584/AE F160459	17.17	0.001	--	--	--	--	--	--
Polar compounds	6.93	<0.001	--	--	--	--	15.13	0.005
Unknown metabolites	7.64	<0.001	3.16	0.001	5.56	<0.003	16.28	0.005
<b>Total identified</b>	<b>23.12</b>	<b>0.001</b>	<b>64.61</b>	<b>0.021</b>	<b>54.11</b>	<b>0.032</b>	<b>46.93</b>	<b>0.015</b>
<b>Total characterized</b>	<b>31.74</b>	<b>&lt;0.003</b>	<b>3.16</b>	<b>0.001</b>	<b>5.56</b>	<b>&lt;0.003</b>	<b>31.41</b>	<b>0.010</b>
<b>Total extractable</b>	<b>92.32</b>	<b>0.004</b>	<b>81.70</b>	<b>0.026</b>	<b>82.86</b>	<b>0.049</b>	<b>95.58</b>	<b>0.031</b>
<b>Total bound</b>	<b>7.68</b>	<b>&lt;0.001</b>	<b>18.30</b>	<b>0.006</b>	<b>17.15</b>	<b>0.010</b>	<b>4.41</b>	<b>0.001</b>

**FIGURE 3.2. Proposed Metabolic Profile of Mesosulfuron-methyl in Milk and Edible Tissues of a Dairy Cow.**





**TABLE 3.11. Identification of Compounds from the Dairy Cow Metabolism Study.**

Common name/code	Chemical name	Chemical structure
Mesosulfuron-methyl/ AE F130060	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[[(methylsulfonyl)amino]methyl]benzoate (CAS)	
AE F140584	Methyl 4-methanesulfonamidomethyl-2-sulfamoylbenzoate (IUPAC)	
AE F160459	Methyl 2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate (IUPAC)	
AE F147447	6-Methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (IUPAC)	
AE 0195141	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-(hydroxymethyl)benzoate  This metabolite was identified by mass spectrometry. No metabolite standard was available for this metabolite.	

*Poultry and Eggs (MRID 45386512)*

Aventis has submitted the results of a study investigating the metabolism of [phenyl-U-<sup>14</sup>C]mesosulfuron-methyl in poultry. Laying hens were orally dosed for 14 consecutive days with the radiolabeled test substance at 10.24 ppm in the diet (341x the maximum theoretical dietary burden). During the dosing period, eggs were collected twice daily and sorted into egg whites and yolks. Approximately 22 hours after the final dosing period, the test animals were sacrificed, and samples of edible tissues (skin, skeletal muscle from the breast and thigh, liver, and subcutaneous and abdominal fat) were collected.

The total radioactive residues (TRR; expressed as mesosulfuron-methyl equivalents) in egg yolks were detectable within 24 hours of administration of the initial dose and rose steadily to reach a plateau by Day-10 of dosing at  $0.012 \pm 0.002$  ppm. The TRR in egg whites were very similar to those observed in egg yolks with a maximum TRR of  $0.011 \pm 0.004$  ppm reached by Day-8 of dosing. In edible tissues, the highest TRR was observed in liver at 0.023 ppm. The TRR in skin, fat, and muscle were an order of magnitude lower at 0.004, 0.002, and  $<0.002$  ppm, respectively.

The characterization/identification of radioactive residues in poultry matrices was performed on liver, abdominal fat, egg whites, and egg yolks. The majority of the radioactive residues was extractable using organic solvents including 79.14% of the TRR in liver, 85.22% of the TRR in abdominal fat, 69.81% of the TRR in egg whites, and 84.96% of the TRR in egg yolks.

The parent, mesosulfuron-methyl, was the major component identified in liver (21.52% TRR) and abdominal fat (~70% TRR). The metabolites AE F140584, AE F160459, and AE 0195141 were identified in liver as minor metabolites ( $\leq 6\%$  TRR each). No metabolites were conclusively identified in egg whites and yolks because the residue levels in the respective extracts were below the trigger value ( $\leq 0.01$  ppm). However, residues in the egg white extract were tentatively identified as unchanged parent and possibly AE F147447. Residues in the egg yolk extract were tentatively identified as parent and several minor metabolites, namely AE F160459, AE F154851, and AE F140584.

The metabolic route of mesosulfuron-methyl in poultry proceeds by cleavage of the parent between the two rings to yield AE F140584 and subsequent isothiazole ring formation to form AE F147447. In addition, hydrolysis of a methoxy group on the pyrimidine ring of the parent yields the hydroxy metabolite AE F160459. Oxidative deamination of the parent forms the alcohol metabolite AE 0195141.

Treatment Type	Level of administered dose (mg/day)	Food consumption (kg/day)	Daily Dose of Test Substance in the diet (ppm)	Vehicle	Timing/Duration
Oral	$1.4419 \pm 0.009$ (overall average)	0.1403 (overall average)	10.00 (target) 10.24 (actual mean)	Gelatin capsule	Once per day for 14 consecutive days

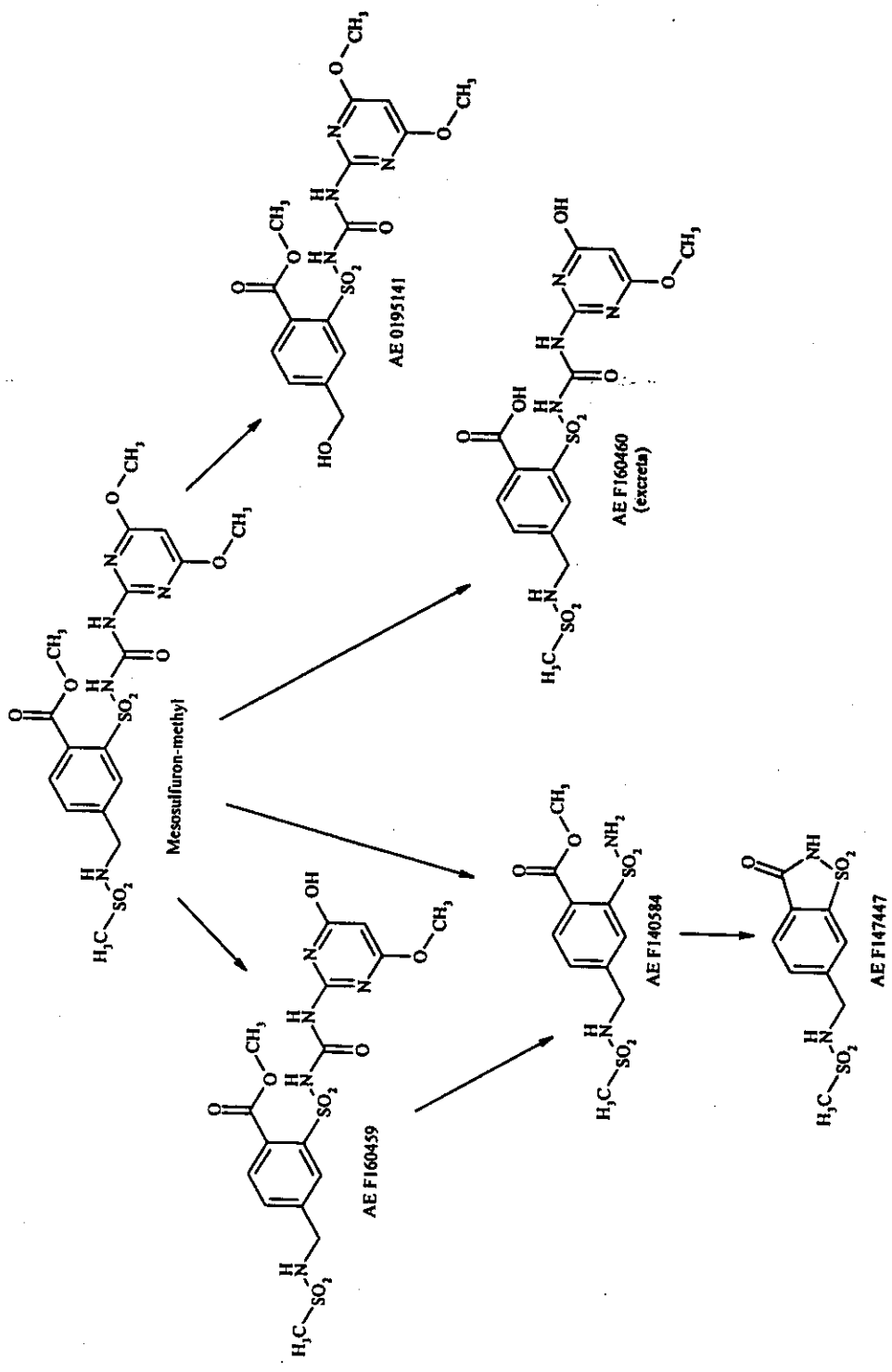
**TABLE 3.13. Summary of Characterization and Identification of Radioactive Residues in Poultry Matrices Following Dosing with [Phenyl-U-<sup>14</sup>C]Mesosulfuron-Methyl at 10.24 ppm in the Diet (341x the Maximum Theoretical Dietary Burden).**

Compound	Liver		Abdominal fat		Egg whites, Day 10		Egg yolks, Day 10	
	(TRR = 0.023 ppm)		(TRR = 0.002 ppm)		(TRR = 0.011 ppm)		(TRR = 0.012 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
<b>Identified residues</b>								
Mesosulfuron-methyl	21.52	0.005	~70.00	-0.001	--	--	--	--
AE F140584	2.59	<0.001	--	--	--	--	--	--
AE F160459	0.99	<0.001	--	--	--	--	--	--
AE 0195141	5.31	0.001	--	--	--	--	--	--
<b>Characterized residues (includes tentatively identified residues)</b>								
AE F130060/AE F140584	17.89	0.004	--	--	--	--	--	--
AE F140584/AE F147447	--	--	<5.00	<0.001	--	--	--	--
Polar compounds	4.65	0.001	--	--	--	--	--	--
Total identified	30.41	<0.008	~70.00	-0.001	--	--	--	--
Total characterized	22.54	0.005	<5.00	<0.001	58.78 <sup>1</sup>	0.006 <sup>1</sup>	99.07 <sup>2</sup>	0.012 <sup>2</sup>
Total extractable	79.14	0.018	85.22	0.002	69.81	0.008	84.96	0.010
Total bound	21.35	0.005	14.79	<0.001	33.41	0.004	16.16	0.002

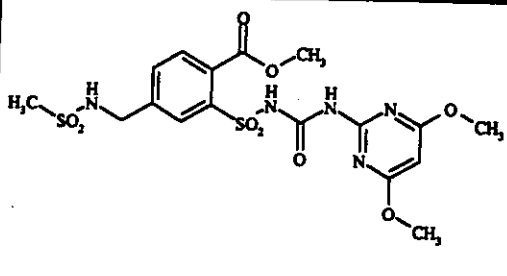
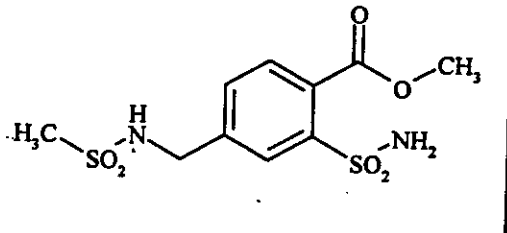
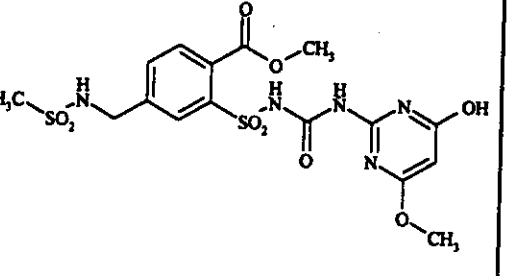
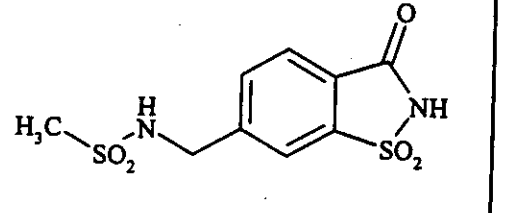
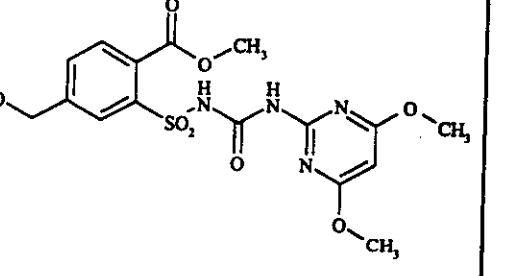
<sup>1</sup> Without quantitative data, the residues in the egg white extract were tentatively identified as unchanged parent and possibly AE F147447.

<sup>2</sup> Without quantitative data, the residues in the egg yolk extract were tentatively identified as unchanged parent and several minor metabolites, namely AE F160459, AE F154851, and AE F140584.

**FIGURE 3.3 Proposed Metabolic Profile of Mesosulfuron-methyl in Poultry and Eggs**



**TABLE 3.14. Identification of Compounds from the Hen Metabolism Study.**

Common name/code	Chemical name	Chemical structure
Mesosulfuron-methyl/ AE F130060	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[methylsulfonyl]amino]methyl]benzoate (CAS)	
AE F140584	Methyl-4-methanesulfonamidomethyl-2-sulfamoylbenzoate (IUPAC)	
AE F160459	Methyl-2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate (IUPAC)	
AE F147447	6-Methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (IUPAC)	
AE 0195141	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-(hydroxymethyl)benzoate  This metabolite was identified by mass spectrometry. No metabolite standard was available for this metabolite.	

Common name/code	Chemical name	Chemical structure
AE F154851	2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethyl benzoic acid (IUPAC)	

### Summary of Confined Rotational Crops Data

#### *Confined Rotational Crop Study (MRIDs 453865-04 to - 09)*

Aventis CropScience USA has submitted the results of confined rotational crop studies with [pyrimidyl-<sup>14</sup>C]mesosulfuron-methyl and [phenyl-<sup>14</sup>C]mesosulfuron-methyl. The radiolabeled test substances, formulated as water-dispersible granular formulations, were separately applied once to bare sandy loam soil at a nominal rate of 0.0134 lb ai/A (equivalent to 15 g ai/ha; 1.0x the maximum proposed seasonal rate). Following treatment, the treated soil was transferred to stainless steel containers, as the 5 cm top layer, and allowed to age under outdoor conditions at intervals of 31/32, 124/125, and 368/369 days. At the end of each interval, carrots (a root crop), spinach (a leafy vegetable crop), and wheat (a small grain crop) were sown and grown to maturity according to good agricultural practices.

Total radioactive residues (TRR) were all below 0.010 ppm in/on all harvested rotational crop matrices except in wheat straw. TRR were 0.0219, 0.0125, and 0.0144 ppm in pyrimidyl-labeled wheat straw from the 31/32, 124/125, and 368/369 plantback intervals (PBIs), respectively. TRRs were 0.0110, 0.0112, and 0.0088 ppm in phenyl-labeled wheat straw from 31/32, 124/125, and 368/369 PBIs, respectively.

The wheat straw samples from the 31/32-day rotation were subjected to further analytical work in order to elucidate the nature of the residue. Solvent extraction released about 66% and 87% TRR from pyrimidyl- and phenyl-labeled wheat straw, respectively; the nonextractable residues were 10-26% TRR (0.001-0.006 ppm). Residues in/on the organosoluble extracts of wheat straw were analyzed by HPLC. The parent, mesosulfuron-methyl, was identified in both the pyrimidyl- and phenyl-labeled wheat straw at 2.0-3.5% TRR (0.0004 ppm). The AE F147447 metabolite was the predominant residue (30.8% TRR, 0.0034 ppm) in phenyl-labeled wheat straw. AE F140584 and AE F154851 were additionally identified as minor metabolites each at ≤6% TRR (0.0003-0.0006 ppm) in phenyl-labeled wheat straw. The AE F092944 metabolite was identified as a minor residue (7.2% TRR, 0.0016 ppm) in pyrimidyl-labeled wheat straw. In

addition, up to 7 unknowns were characterized in wheat straw with each unknown detected at <8% TRR ( $\leq 0.0012$  ppm), except for one very polar unknown in the pyrimidyl-labeled straw which was present at 33.6% TRR (0.0074 ppm) and one very polar unknown in the phenyl-labeled straw which was present at 13.1% TRR (0.0014 ppm).

Based on identification of residues in wheat straw, the metabolic route of mesosulfuron-methyl in the rotational crop wheat proceeds by cleavage of the parent between the two rings to yield AE F140584 and subsequent isothiazole ring formation to form AE F147447. Cleavage of the parent between the two rings also yields AE F092944. Hydrolysis of the methyl ester on the phenyl ring to the carboxylic acid forms the acid metabolite AE F154851.

**TABLE 3.15. Total Radioactive Residues (TRR) in Rotational Crop Matrices Following Application of Mesosulfuron-methyl to the Soil at 0.0134 lb ai/A (1.0x the maximum proposed seasonal rate).**

Matrix	Plantback interval (days)	Pyrimidyl label (ppm)	Phenyl label (ppm)
Carrot, tops	31/32	0.0057	0.0043
	124/125	0.0047	0.0065
	368/369	0.0065	0.0025
Carrot, roots	31/32	0.0012	0.0011
	124/125	0.0004	0.0006
	368/369	0.0005	0.0004
Spinach	31/32 <sup>2</sup>	—	—
	124/125	0.0008	0.0008
	368/369	0.008	0.0008
Wheat, grain	31/32	0.0016	0.0005
	124/125	0.0011	0.0005
	368/369	0.0010	0.0004
Wheat, straw	31/32	0.0219	0.0110
	124/125	0.0125	0.0112
	368/369	0.0144	0.0088

<sup>1</sup> [Pyrimidyl-<sup>14</sup>C]mesosulfuron-methyl and [phenyl-<sup>14</sup>C]mesosulfuron-methyl were separately applied once to bare sandy loam soil at a nominal rate of 0.0134 lb ai/A (15 g ai/ha).

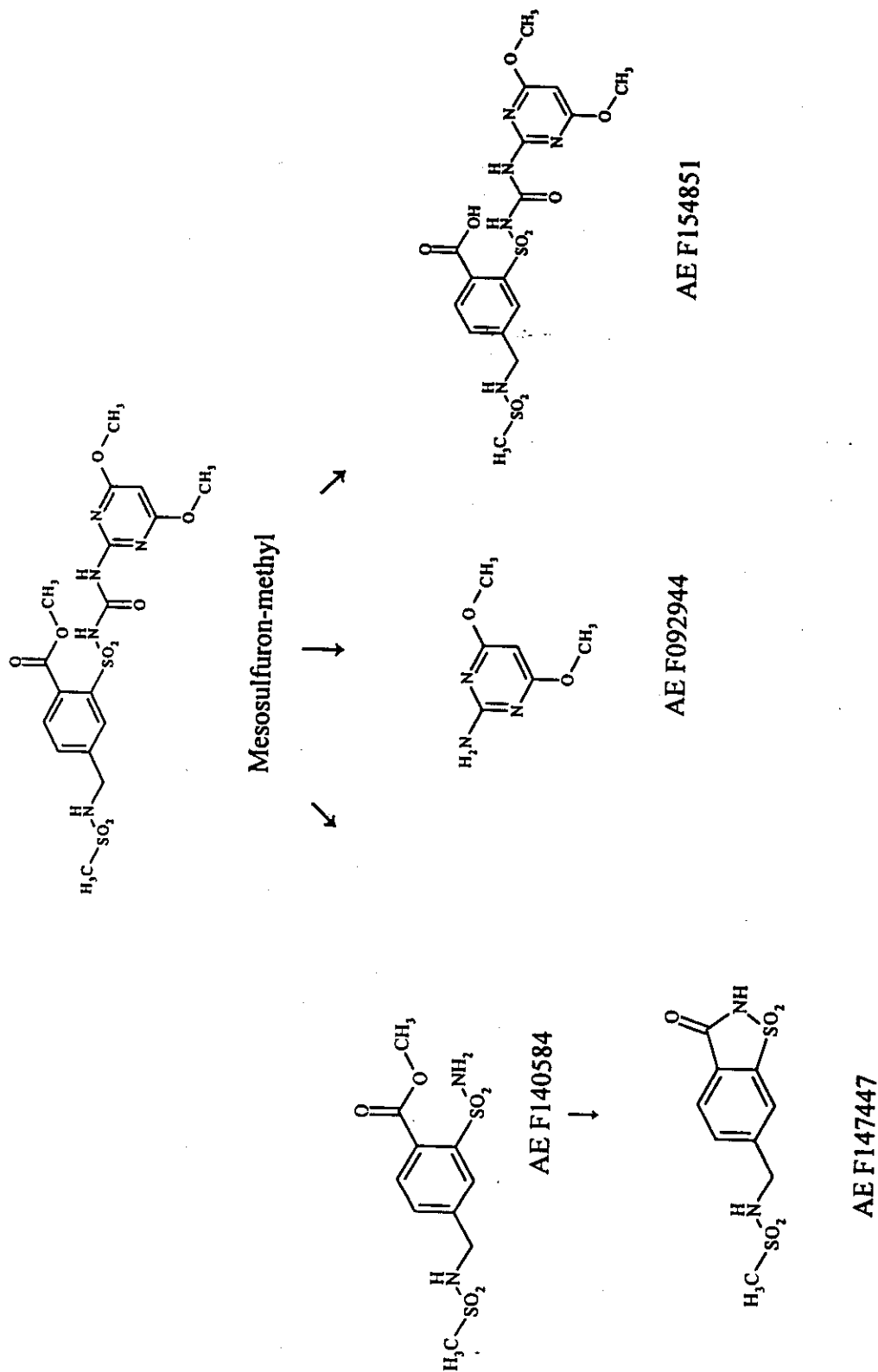
<sup>2</sup> Spinach could not be harvested from the 31- or 32-day plantback interval due to severe growth damage from the sensitivity of this crop to the active substance.

**TABLE 3.16. Summary of Characterization and Identification of Radioactive Residues in Rotational Crop Matrices Following Application of Radiolabeled Mesosulfuron-methyl to the Soil at a Nominal Rate of 0.0134 lb ai/A (1.0x the maximum proposed seasonal rate).**

Compound	Wheat, straw; Pyrimidyl-label (31-day PBI)		Wheat, straw; Phenyl-label (32-day PBI)	
	(TRR = 0.0219 ppm)		(TRR = 0.0110 ppm)	
	% TRR	ppm	% TRR	ppm
Mesosulfuron-methyl	2.0	0.0004	3.5	0.0004
AE F147447	--	--	30.8	0.0034
AE F140584	--	--	5.8	0.0006
AE F154851	--	--	2.3	0.0003
AE F092944	7.2	0.0016	--	--
Unknowns	49.5	0.0108	29.8	0.0033
Total identified	9.2	0.0020	42.4	0.0047
Total characterized	49.5	0.0108	29.8	0.0033
Total extractable	65.9	0.0144	86.5	0.0095
Total bound	25.5	0.0056	10.5	0.0012



**FIGURE 3.4. Proposed Metabolic Profile of Mesosulfuron-methyl in Rotational Wheat Straw**



**TABLE 3.17. Identification of Compounds from the Confined Rotational Crop Study**

Common name/code	Chemical name	Chemical structure
Mesosulfuron-methyl/ AE F130060	Methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[[(methylsulfonyl)amino]methyl]benzoate (CAS)	
AE F140584	Methyl 4-methanesulfonamidomethyl-2-sulfamoylbenzoate (IUPAC)	
AE F147447	6-Methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (IUPAC)	
AE F154851	2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethyl benzoic acid (IUPAC)	
AE F092944	2-amino-4,6-dimethoxypyrimidine (IUPAC)	

## Summary of Analytical Methods

### *Wheat Matrices (MRIDs 45386514 - 45386521)*

<b>Matrix</b>	wheat grain, forage, hay, straw, aspirated grain fractions, and processed commodities
<b>Method ID</b>	EM F08/99-0
<b>Type</b>	enforcement method
<b>Analytes (method detects)</b>	mesosulfuron-methyl (AE F130060)
<b>Instrumentation</b>	LC/MS/MS, monitoring transition ions m/z 504.2 to m/z 182.0 for mesosulfuron-methyl.
<b>Extraction</b>	<p>Cereal grain commodities are extracted (2x) with ACN:0.02 mol/L triethylamine (4:1, v:v), centrifuged, and filtered.</p> <p>The combined organic filtrates are partitioned with hexane and the hexane phase re-partitioned with ACN:0.02 mol/L triethylamine (4:1; v:v). The ACN:water phases are combined, and concentrated to aqueous by rotary evaporation. The concentrated aqueous phase is dissolved in 0.01 mol/L formic acid and partitioned (3x) with ethyl acetate. The combined ethyl acetate phases are reduced to dryness and residues redissolved in ACN:water (1:1, v:v).</p>
<b>ILV</b>	An independent laboratory validation [ILV] of the method was conducted to verify the reliability of Method No. EM F08/99-0 for the determination of mesosulfuron-methyl residues in wheat grain, shoot (forage), and straw. The values obtained are indicative that method EM F08/99-0 is reliable.
<b>Radiovalidation Extraction Efficiency</b>	See below.
<b>LOQ</b>	0.01 ppm for cereal grain 0.05 ppm for cereal straw and forage
<b>LOD</b>	Not specified, but the method notes that nondetectable residues were <30% of the LOQ.

Aventis has submitted (MRID 45386516) radiovalidation data from extraction efficiency studies with the proposed enforcement method. Aged radiolabeled wheat shoot (forage) and stubble samples from a wheat metabolism study ( $[^{14}\text{C}\text{-pyrimidyl}]$ -labeled mesosulfuron-methyl; MRID 45386510) were extracted using the procedures of the proposed enforcement method (LC/MS/MS method EM F08/99-0 with slight modifications; different aliquot volumes). Samples of wheat grain were not analyzed because of the very low residues (<LOQ). Total radioactive residues (TRR) were determined by summing the radioactivity in the extractable and nonextractable

residues, quantitated by LSC and combustion/LSC. Residues in the wheat extracts were below the LC/MS/MS method LOQ (<0.05 ppm) and could not be quantitated using the residue method.

The extraction efficiency data demonstrate that the residue analytical method adequately extracts aged residues of mesosulfuron-methyl from wheat shoot (forage) and straw/stubble; the results are reported below in Table 3.19. We note that the TRR of the samples used for extraction by the residue method were much lower than determined in the metabolism study, but that the %TRR extracted using the residue method was comparable to that extracted in the metabolism study. The petitioner has included concurrent method recovery data with the extraction efficiency studies to confirm the method LOQ; recoveries were 109-112% in forage and 109-123% in stubble fortified with mesosulfuron-methyl at 0.05 ppm. The determination of the residues was done using solvent standards.

**TABLE 3.19. Radiovalidation of the Enforcement Analytical Method Using Radiolabeled Samples from Wheat Metabolism Study.**

Matrix	Metabolism study		Residue Method <sup>1</sup>	
	% TRR	ppm	% TRR	ppm
<b>Wheat, shoot (forage, day 36)</b>	TRR = 0.019 ppm		TRR = 0.0097 ppm	
Radioactive residue in extractable fraction by LSC	87.2	0.0163	88	0.0046
Radioactive residue in final HPLC-solution (following cleanup) by LSC	-	-	76	0.004
Mesosulfuron-methyl	23.4	0.0044	cannot calculate <sup>2</sup>	<0.05
<b>Wheat, straw (day 95)</b>	TRR = 0.019 ppm		TRR = 0.0052 ppm (Wheat Stubble)	
Radioactive residue in extractable fraction by LSC	67.4	0.0127	66	0.0065
Radioactive residue in final HPLC-solution (following cleanup) by LSC	-	-	50	0.0049
Mesosulfuron-methyl	1.8	0.0003	cannot calculate <sup>2</sup>	<0.05

<sup>1</sup> Average of three separate extraction samples. Total radioactive residues (TRR) were determined by summing the radioactivity in the extractable and nonextractable residues, quantitated by LSC and combustion/LSC.

<sup>2</sup> Because the residues were below the LOQ in the final extract for both shoot and straw, no peaks were detected by LC/MS/MS.

### *Livestock Matrices (No MRID)*

No analytical methods for livestock commodities have been submitted.

As determined by HED's ChemSAC on 11/12/03, a livestock enforcement method for the parent compound in ruminant liver and kidney (or meat byproducts) must be submitted as a condition of registration. (Refer to "Summary of Magnitude of the Residue Studies - Livestock" for the rationale.)

### *Multiresidue Methods (MRID 45386524)*

Mesosulfuron-methyl was analyzed according to the FDA's Multiresidue Method Test guidelines in PAM, Vol. I, Appendix II (1/94). The results showed that multiresidue methods are not suitable for the analysis of mesosulfuron-methyl. Testing using Protocol A was not conducted because mesosulfuron-methyl is not an *N*-methylcarbamate and is not naturally fluorescent. Testing through Protocol B was not conducted because mesosulfuron-methyl is not an acid or phenol. Testing using Protocol C produced no GC responses with acceptable  $rr_t$  limits and sufficient sensitivity under the Level I and Level II conditions of Protocol C. Further testing through Protocols D, E, and F was not conducted because Protocol C was unsuccessful. Testing using Protocol G with a C-18 column equipped with a post-column photolysis/derivatization system with fluorescence detection exhibited a peak with poor shape and low sensitivity. These multiresidue data will be forwarded to FDA for further evaluation.

### **Summary of Magnitude of the Residue Studies – Crops**

#### *Wheat (MRIDs 45386529 and 45386530)*

##### Spring Wheat:

Aventis has submitted field trial data for spring wheat. Ten field trials were conducted in Regions 5 (MN, ND, and SD; 4 trials), 7 (MT, ND, NE, SD, and WY; 5 trials), and 11 (ID; 1 trial) during the 1998 growing season. At each field trial site, four separate plots were treated with either a tank mix of the 75% WDG formulation of mesosulfuron-methyl with safener AE F107892 or a tank mix of the 20% WDG formulation of iodosulfuron-methyl-sodium with safener AE F107892; the treatments for mesosulfuron-methyl are described below. Applications to all plots were made in 4.45-5.30 gal/A of water and most applications were made with a typical long chain alcohol surfactant (Synperonic A7).

**Table 3.20. Description of Treatments and Crop Parts Sampled/Analyzed**

Treatment	Description	Wheat RAC Sampled/Analyzed
B	Single broadcast application of a tank mix of the 75% WDG formulation of mesosulfuron-methyl at ~0.022 lb ai/A with the 10% EC formulation of the safener AE F107892 at ~0.067 lb ai/A, made to wheat at the Zadok 30 growth stage (just prior to first node emergence).	Forage and hay (residue decline study)
D	Single broadcast application of a tank mix of the 75% WDG formulation of mesosulfuron-methyl at ~0.022 lb ai/A with the 10% EC formulation of the safener AE F107892 at ~0.067 lb ai/A, made to wheat 55 days prior to harvest.	Mature straw and grain

The maximum residues of mesosulfuron-methyl in/on spring wheat forage harvested 4-24 days following treatment regime B were 0.4708 ppm. All residues of mesosulfuron-methyl in/on wheat hay harvested 14-50 days following treatment regime B were less than the method LOQ (<0.05 ppm). The maximum residues of mesosulfuron-methyl in/on wheat straw and grain harvested 54-57 days following treatment regime D were 0.1389 and 0.0264 ppm, respectively. Although residue decline data were generated using treatment regime B, no discernible trend could be made because all treated wheat samples bore residues below the method LOQs.

Residues of mesosulfuron-methyl in/on wheat forage, hay, straw, and grain were quantitated using the US HPLC/MS/MS data gathering method (RAM CK/03/00). The validated LOQs were 0.01 ppm for wheat grain and 0.05 ppm for wheat forage, hay, and straw. This method is adequate for data collection based on acceptable concurrent method recovery data.

**TABLE 3.21. Summary of Residue Data from Spring Wheat Field Trials with Mesosulfuron-methyl at -0.022 lb ai/A (3.7x).**

Commodity	Treat. Regime <sup>1</sup>	Total Applic. Rate; mesosulfuron-methyl + safener (lb ai/A)	PHI (days)	Analyte	Residue Levels (ppm) <sup>2</sup>					
					n	Min.	Max.	HAFT <sup>3</sup>	Mean	SD <sup>4</sup>
Wheat forage	B	0.020-0.024 + 0.059-0.070	4-24	Mesosulfuron-methyl	20	<0.05	0.47	0.38	<0.083	0.10
Wheat hay	B	0.020-0.024 + 0.059-0.070	14-50	Mesosulfuron-methyl	20	<0.05	<0.05	<0.05	<0.05	NA <sup>5</sup>
Wheat straw	D	0.021-0.024 + 0.064-0.070	54-57	Mesosulfuron-methyl	18	<0.05	0.14	0.13	<0.059	0.026
Wheat grain	D	0.021-0.024 + 0.064-0.070	54-57	Mesosulfuron-methyl	18	<0.01	0.026	0.025	<0.012	0.0048

<sup>1</sup> Treatment Regimes:

B = single broadcast application of a tank mix of mesosulfuron-methyl (AE F130060) and the safener AE F107892 made at Zadok 30.

D = single broadcast application of a tank mix of mesosulfuron-methyl (AE F130060) and the safener AE F107892 made at 55 days prior to harvest.

<sup>2</sup> Data from the residue decline study were included at the PHI closest to 30 days for forage and 50 days for hay.

<sup>3</sup> HAFT = Highest Average Field Trial.

<sup>4</sup> SD = Standard Deviation.

<sup>5</sup> NA = Not Applicable.

### Winter Wheat:

Aventis has submitted field trial data for winter wheat. Fourteen field trials were conducted in Regions 2 (NC; 1 trial), 4 (AR; 1 trial), 5 (KS, MO, and ND; 3 trials), 6 (TX; 2 trials), 8 (CO, KS, OK, and TX; 6 trials), and 11 (WA; 1 trial) during the 1999 growing season. At each field trial site, four separate plots were treated with either a tank mix of the 75% WDG formulation of mesosulfuron-methyl with safener AE F107892 or a tank mix of the 20% WDG formulation of iodosulfuron-methyl-sodium with safener AE F107892; the treatments for mesosulfuron-methyl are described below. Applications to all plots were made in 9.42-10.60 gal/A of water and included a typical long chain alcohol surfactant (Synperonic A7).

<b>Treatment</b>	<b>Description</b>	<b>Wheat RAC Sampled/Analyzed</b>
B	Single broadcast application of a tank mix of the 75% WDG formulation of mesosulfuron-methyl at ~0.022 lb ai/A with the 10% EC formulation of the safener AE F107892 at ~0.067 lb ai/A, made to wheat at the Zadok 30 growth stage (just prior to first node emergence).	Forage, hay, and grain
D	Single broadcast application of a tank mix of the 75% WDG formulation of mesosulfuron-methyl at ~0.022 lb ai/A with the 10% EC formulation of the safener AE F107892 at ~0.067 lb ai/A, made to wheat 55 days prior to harvest.	Mature straw and grain

The maximum residues of mesosulfuron-methyl in/on winter wheat forage harvested 9-68 days following treatment regime B were 0.55 ppm. All residues of mesosulfuron-methyl in/on wheat hay harvested 37-92 days following treatment regime B were less than the method LOQ (<0.01 ppm). The maximum residues of mesosulfuron-methyl in/on wheat straw harvested 54-57 days following treatment regime D were 0.25 ppm. Residues of mesosulfuron-methyl were less than the method LOQ (<0.01 ppm) in/on all wheat grain samples harvested 81-134 days following treatment regime B and 54-57 days following treatment regime D. Although residue decline data were generated using treatment regimes B and D, no discernible trend could be made because all treated wheat samples bore residues at or below the method LOQs.

Residues of mesosulfuron-methyl in/on wheat forage, hay, straw, and grain were quantitated using the US HPLC/MS/MS data gathering method (RAM CK/03/00). The validated LOQs were 0.01 ppm for all wheat matrices. This method is adequate for data collection based on acceptable concurrent method recovery data.



**TABLE 3.23. Summary of Residue Data from Winter Wheat Field Trials with Mesosulfuron-methyl at ~0.022 lb ai/A (1.7x).**

Commodity	Treat. Regime <sup>1</sup>	Total Applic. Rate of mesosulfuron-methyl + safener (lb ai/A)	PHI (days)	Analyte	Residue Levels (ppm)					
					n <sup>2</sup>	Min.	Max.	HAFT <sup>3</sup>	Mean <sup>4</sup>	SD <sup>5</sup>
Wheat forage	B	0.021-0.023 + 0.065-0.069	9-36	Mesosulfuron-methyl	26	<0.01	0.55	0.47	<0.065	0.13
Wheat hay	B	0.021-0.023 + 0.065-0.069	37-66	Mesosulfuron-methyl	22	<0.01	<0.01	<0.01	<0.01	NA <sup>6</sup>
Wheat straw	D	0.021-0.023 + 0.065-0.070	54-57	Mesosulfuron-methyl	28	<0.01	0.25	0.22	<0.03	0.06
Wheat grain	D	0.021-0.023 + 0.065-0.070	54-57	Mesosulfuron-methyl	28	<0.01	<0.01	<0.01	<0.01	NA

<sup>1</sup> Treatment Regimes:

B = single broadcast application of a tank mix of mesosulfuron-methyl (AE F130060) and the safener AE F107892 made at Zadok 30 growth stage (just prior to first node emergence).

D = single broadcast application of a tank mix of mesosulfuron-methyl (AE F130060) and the safener AE F107892 made at 55 days prior to harvest.

<sup>2</sup> Fourteen field trials with 2 samples each equals 28 samples for straw and grain. For hay, three studies at PHIs of 77, 92, and 83 days were excluded. For forage, one study at a 68-day PHI was excluded. The highest value for forage was found at an 11-day PHI; decline of residues with time has not been demonstrated so the early PHI studies were included. For each of the two decline field trials, the one PHI closest to 30 days for forage or 55 days for grain, hay, or straw was used.

<sup>3</sup> HAFT = Highest Average Field Trial.

<sup>4</sup> Values of "<0.01" ppm were included in the mean calculation as 0.01 ppm.

<sup>5</sup> SD = Standard Deviation.

<sup>6</sup> NA = Not Applicable.

### *Wheat Processed Commodities (MRID 45386531)*

A wheat processing study on mesosulfuron-methyl was submitted. To generate samples for the processing study, a winter wheat field trial was conducted in WA (Region 11). Wheat grain samples were harvested 54 days following a single broadcast application of the 75% WDG formulation at 0.070 lb ai/A; the test formulation was tank mixed with safener AE F107892 at 0.205 lb ai/A. Using simulated commercial procedures, the harvested grain samples were processed into flour, middlings, shorts, germ, and bran. In addition, a sample of wheat aspirated grain fractions (AGFs) was generated.

Residues of mesosulfuron-methyl ranged from nondetectable (<0.01) to 0.0107 ppm in/on wheat grain prior to processing. Following processing, mesosulfuron-methyl residues were nondetectable (<0.01 ppm) in flour and middlings, 0.0117-0.0150 ppm in bran, <0.01-0.0139 ppm in shorts, 0.0425-0.0482 ppm in germ, and 0.1645-0.2696 ppm in AGFs.

The wheat processing data indicates that mesosulfuron-methyl residues may: (i) concentrate slightly in wheat bran and shorts (average processing factors: 1.3x for bran and 1.2x for shorts); (ii) concentrate in wheat germ and AGFs (average processing factors of 4.3x for germ and 21.6x for AGFs); and (iii) do not concentrate in wheat flour and middlings (<0.01 ppm; average processing factor of 1.0x) processed from wheat grain treated with the 75% WDG formulation of mesosulfuron-methyl tank mixed with safener AE F107892. The reported concentration factors do not exceed the theoretical concentration factors. According to Table 3 of OPPTS 860.1520, the theoretical concentration factors are 7.7x for bran, 1.4x for flour, and 8.3x for shorts.

Samples of wheat grain, AGFs, flour, middlings, shorts, germ, and bran were quantitated for residues of mesosulfuron-methyl using the US LC/MS/MS data gathering method (RAM CK/03/00). The validated limit of quantitation (LOQ) was 0.01 ppm for all wheat matrices. Overall, this method is adequate for data collection based on acceptable concurrent method recovery data; the average recovery over all matrices was 76% although six individual recoveries were below 70% (57-69%).

**Table 3.24. Residue Data from Wheat Processing Study with Mesosulfuron-methyl.**

RAC	Processed Commodity	Total Rate (lb ai/A)	PHI (days)	Residues (ppm) <sup>1</sup>	Processing Factor <sup>2</sup>
Wheat grain	Grain (RAC)	0.07	54	<0.01, 0.0105, 0.0107 (0.0104)	--
	Flour			<0.01, <0.01, <0.01	1.0x, 1.0x, 1.0x (1.0x)
	Bran			0.0117, 0.0148, 0.0150	1.1x, 1.4x, 1.4x (1.3x)
	Shorts			<0.01, 0.0137, 0.0139	1.0x, 1.3x, 1.3x (1.2x)
	Middlings			<0.01, <0.01, <0.01	1.0x, 1.0x, 1.0x (1.0x)
	Germ			0.0425, 0.0430, 0.0482	4.1x, 4.1x, 4.6x (4.3x)
Aspirated grain fractions (AGFs)	AGFs (RAC)			0.1645, 0.2400, 0.2696	15.8x, 23.1x, 25.9x (21.6x)

<sup>1</sup> Average residues are reported in parentheses for the grain RAC.

<sup>2</sup> Calculated by the study reviewer using the average residues in the grain RAC samples from the processor; average processing factors are reported in parentheses.

### Summary of Magnitude of the Residue Studies – Livestock

Wheat grain, forage, hay, straw, aspirated grain fractions, and milled byproducts are feed items of beef and dairy cattle. Wheat grain and milled byproducts could be fed to poultry and swine. The maximum theoretical dietary burden of mesosulfuron-methyl to livestock is presented in Table 3.25.

**Table 3.25. Calculation of Maximum Theoretical Dietary Burdens of Mesosulfuron-Methyl to Livestock.**

Feed Commodity	% Dry Matter <sup>1</sup>	% Diet <sup>1</sup>	Proposed or Recommended Tolerance, ppm	Dietary Contribution, ppm <sup>2</sup>
<b>Beef Cattle</b>				
Wheat, forage	25	25	0.60	0.600
Wheat, straw	88	10	0.30	0.034
Wheat, hay	88	25	0.06	0.017
Wheat, aspirated grain fractions	85	20	0.60	0.141
Wheat, grain	89	20	0.03	0.007
Total Burden		100		0.799
<b>Dairy Cattle</b>				
Wheat, forage	25	60	0.60	1.44
Wheat, straw	88	10	0.30	0.034
Wheat, hay	88	10	0.06	0.007
Wheat, aspirated grain fractions	85	20	0.60	0.141
Total Burden		100		1.622
<b>Poultry</b>				
Wheat, grain	NA	80	0.03	0.024
Wheat, milled byproducts	NA	20	0.03	0.006
Total Burden		100		0.030
<b>Swine</b>				
Wheat, grain	NA	80	0.03	0.024
Wheat, milled byproducts	NA	20	0.03	0.006
Total Burden		100		0.030

<sup>1</sup> Table 1 (OPPTS Guideline 860.1000).

<sup>2</sup> Contribution = [tolerance / % DM (if cattle)] x % diet). Poultry and swine diets are not corrected for % dry matter.

Livestock feeding studies were not submitted as part of this petition. Instead, the petitioner submitted a waiver (MRID 45386528) for the conduct of ruminant and poultry feeding studies based on the results of submitted livestock metabolism studies.

Predicted residues in milk and dairy cattle tissues:

Following oral dosing of a lactating dairy cow with [phenyl-U-<sup>14</sup>C]mesosulfuron-methyl for five consecutive days at 20.54 ppm in the diet (13x the maximum theoretical dietary burden), the TRR were 0.002-0.004 ppm in milk, 0.031 ppm in liver, 0.058 ppm in kidney, 0.003-0.004 ppm in muscle, and 0.009-0.032 ppm in fat. The parent, mesosulfuron-methyl, was the major residue component identified in 120-hr milk (23.12% TRR; 0.001 ppm), liver (52.60% TRR; 0.017 ppm),

kidney (41.15% TRR; 0.024 ppm), and renal fat (20.02% TRR; 0.006 ppm). In addition, the metabolites AE F140584, AE F147447, and AE 0195141 were identified.

Predicted residues in eggs and poultry tissues:

Following oral dosing of laying hens with [phenyl- $^{14}\text{C}$ ]mesosulfuron-methyl for 14 consecutive days at 10.24 ppm in the diet (341x the maximum theoretical dietary burden), the TRR were detectable within 24 hours of administration of the initial dose and rose steadily to reach a plateau by Day-10 of dosing at  $0.012 \pm 0.002$  ppm. The TRR in egg whites were very similar to those observed in egg yolks with a maximum TRR of  $0.011 \pm 0.004$  ppm reached by Day-8 of dosing. In edible tissues, the highest TRR was observed in liver at 0.023 ppm. The TRR in skin, fat, and muscle were an order of magnitude lower at 0.004, 0.002, and  $<0.002$  ppm, respectively. The parent, mesosulfuron-methyl, was the major component identified in liver (21.52% TRR; 0.005 ppm) and abdominal fat (70% TRR; 0.001 ppm). Assuming again that a linear relationship exists between dosing level and residues, the predicted level of mesosulfuron-methyl and its relevant metabolites in eggs and poultry tissues would be well below 0.01 ppm at 1.0x the dietary burden.

*Conclusions.*

Ruminants: In response to a registrant request for a waiver of a ruminant feeding study, the ChemSAC decided in a meeting on 11/12/03 that ruminant feeding studies should not be required. Based on a ruminant metabolism study conducted at an exaggerated rate (13x), any secondary residues in ruminant commodities are expected to be below the likely LOQ of the enforcement method (0.05 ppm). Since a method is not available to enforce tolerances in livestock commodities, the ChemSAC does not recommend that livestock tolerances be established at this time. However, as a condition of registration, submission of a livestock enforcement method for the parent compound should be required. Upon submission of an acceptable livestock enforcement method, tolerances will be established in ruminant liver and kidney (or meat byproducts) at the demonstrated LOQ of that method. In the meantime, the dietary risk assessment should include exposure to mesosulfuron-methyl in ruminant meat byproducts at the likely LOQ of the method (0.05 ppm). The bases for this decision were the following: (i) as the dietary burden calculations were theoretical maxima and since wheat commodities comprise 80% of the beef cattle diet and 90% of the dairy cattle diet, they are quite exaggerated; (ii) based on other sulfonylurea compounds, the parent compound is expected to be the only residue of concern and it is not expected to accumulate in livestock commodities; (iii) the parent compound was found at very low levels in ruminant commodities as a result of a ruminant metabolism study at an exaggerated rate; and (iv) Codex has not established livestock tolerances for mesosulfuron-methyl.

Swine: Tolerances for swine commodities a result of the proposed uses on wheat are not required. Based on the ruminant metabolism study which was conducted at an exaggerated rate (685x), there is no reasonable expectation that residues of mesosulfuron-methyl will occur in swine

commodities as a result of the proposed uses on wheat. The proposed uses on wheat fall under 40 CFR §180.6(a)(3) with regard to secondary residues in swine commodities.

Poultry: Tolerances for poultry commodities a result of the proposed uses on wheat and poultry feeding studies are not required. Based on the poultry metabolism study which was conducted at an exaggerated rate (341x), there is no reasonable expectation that residues of mesosulfuron-methyl will occur in poultry tissues and eggs as a result of the proposed uses on wheat. The proposed uses on wheat fall under 40 CFR §180.6(a)(3) with regard to secondary residues in poultry commodities.

#### **International Considerations**

There are currently no Codex, Canadian, or Mexican MRL's or tolerances for mesosulfuron-methyl on wheat. Therefore, international harmonization is not an issue at this time.

## Toxicology

### HAZARD CHARACTERIZATION

Mesosulfuron-methyl is a non-irritant chemical, with a low acute toxicity (toxicity category III or IV) via the oral (IV), dermal (IV), or inhalation (III) routes of exposure. Mesosulfuron-methyl is not a skin irritant (IV) and irritation that occurred in the eye (III) cleared up 48 hours after exposure.

Subacute and subchronic studies showed no effects to primary target organs when exposed to mesosulfuron-methyl.

There was no evidence of increased susceptibility of the young animals following exposure to mesosulfuron-methyl in either rat and rabbit developmental toxicity studies or the two-generation reproduction study in rats in the data base.

There was no evidence of mesosulfuron-methyl-induced neurotoxicity. No neurotoxicity or neuropathology was seen in either the acute or sub-chronic toxicity studies.

In the chronic toxicity study in dogs (MRID 45386330), 3/6 male dogs had minimal to slight, and minimal, increased mucus secretion in the cardiac and fundic sections of the stomach at the highest dose level (HDT). In one of these animals the increased secretion was accompanied by chronic superficial gastritis. There were no treatment-related histopathological changes in females at HDT, or in male and female dogs at the lower dose levels.

Mesosulfuron-methyl has no carcinogenic potential, as indicated in both the rat and the mouse carcinogenicity studies. It is "not likely a human carcinogen" based on the lack of evidence of carcinogenicity in both the rat and the mouse.

Mesosulfuron-methyl has no mutagenicity potential, based on several *in vivo* and *in vitro* studies.

Rat metabolism studies indicated the mesosulfuron-methyl onset of absorption was quick, but the quantity absorbed was low. The feces was the major route of excretion in both sexes (parent and metabolite AE F140584). The highest tissue residue levels were found in the plasma, blood, and liver. Metabolism of mesosulfuron-methyl involved amidases (breakdown of the sulfonyleurea-bridge), hydroxylation, demethylation and hydrolysis.

## Toxicological Endpoints

**Table 3.26. Summary of Toxicology Dose and Endpoints for Mesosulfuron-methyl**

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary: All Population	An endpoint attributable to a single dose was identified in the database.		
Chronic Dietary: All populations	NOAEL= 155 mg/kg/day UF = 100 Chronic RfD = 1.55 mg/kg/day	FQPA SF = 1X cPAD = <u>chronic RfD</u> FQPA SF = 1.55 mg/kg/day	Chronic oral toxicity study in dogs. LOAEL = 574 mg/kg/day [M] based on increased mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) of male dogs.
Incidental Oral: Short and Intermediate-Term	No residential uses are proposed for mesosulfuron-methyl.		
Dermal Exposure: Short, Intermediate and Long-Term	No hazard identified. Quantification of dermal risk is not required since there is no dermal, systemic, neuro or developmental toxicity.		
Inhalation Exposure: Short, Intermediate and Long-Term	Oral NOAEL= 155 mg/kg/day (100% Oral Absorption Factor)	Residential LOC for MOE = NA  Occupational LOC for MOE = 100	Chronic oral toxicity study in dogs. LOAEL = 574 mg/kg/day [M] based on increased mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) of male dogs.
Cancer (oral, dermal, inhalation)	"Not likely to be carcinogenic to a humans" based on the lack of evidence of carcinogenicity in the rats and mice.		

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

## 1. Acute Reference Dose (aRfD) - All Populations

An effect of concern attributable to a single exposure (dose) was not identified from the oral toxicity studies including developmental toxicity studies in rats and rabbits.

## 2. Chronic Reference Dose (cRfD)

Study Selected: Chronic Oral Toxicity Study in Dogs §870.4100b

MRID No.: 45386330

Executive Summary: In a chronic toxicity study (MRID 45386330) 6 Beagle dogs/sex/dose were exposed to AE F130060 (mesosulfuron-methyl; 95.3 -95.7 % a.i.; Lot/Batch #: not reported) in the diet at concentrations of 0, 400, 4000, or 16,000 ppm (equivalent to 0, 14.7, 155, and 574 mg/kg/day in males and 0, 15.3, 169, and 646 mg/kg/day in females, respectively) for up to 12 months.

Mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmoscopic findings, hematology, clinical chemistry, urinalysis, and organ weights for both sexes at all doses were unaffected by treatment.

At the high dose level (16,000 ppm) 3/6 males had minimal to slight, and minimal, increased mucus secretion in the cardiac and fundic sections of the stomach. In one of these animals the increased secretion was accompanied by chronic superficial gastritis. There were no treatment-related histopathological changes in females at 16,000 ppm, or in male and female dogs at the lower dose levels.

Therefore, the LOAEL is 16,000 ppm (equivalent to 574 mg/kg/day in males), based on the increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs (HDT) and chronic superficial gastritis (1/6). The NOAEL is 4000 ppm (equivalent to 155 mg/kg/day in males).

This study is classified acceptable/guideline and satisfies the guideline requirements [OPPTS 870.4100, OECD 452] for a chronic study in dogs.

Dose and Endpoint for Establishing cRfD: A NOAEL of 4000 ppm (155 mg/kg/day [M]). The LOAEL was 16,000 ppm (equivalent to 574mg/kg/day [M]), based on increased mucus secretion in the cardiac and fundic sections of the stomach and chronic superficial gastritis (1/6) in males.

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variations).



Comments about Study/Endpoint/Uncertainty Factor: This study duration and route of exposure is appropriate for this risk assessment.

$$\text{Chronic RfD} = \frac{155 \text{ mg/kg/day (NOAEL)}}{100} = 1.55 \text{ mg/kg/day}$$

3. Classification of Carcinogenic Potential

In accordance with the 1999 Draft Carcinogen Risk Assessment Guidelines (July 1999), the HIARC classified mesosulfuron-methyl as "not likely a human carcinogen" based on the lack of evidence of carcinogenicity in the rat and the mouse.

4. Mutagenicity

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to mesosulfuron-methyl.

5. Neurotoxicity

The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to mesosulfuron-methyl. Acute and subchronic neurotoxicity studies were not performed. No sign of neurotoxicity was observed in the entire database for mesosulfuron-methyl.

6. Developmental Toxicity

A. Determination of Susceptibility

The data available for evaluation suggest that there is no evidence of increased quantitative or qualitative susceptibility of the offspring after *in utero* or post-natal exposure. Neither acceptable Developmental Toxicity Study in rats or rabbits (MRIDs 45386401 and 45430404) revealed enhanced susceptibility of the fetus after *in utero* exposure. Similarly, the results of the Two Generation Reproduction Toxicity Study (MRIDs 45430405) did not indicate an enhanced susceptibility to the test article *in utero* or during post-natal exposure.

B. Degree of Concern Analysis and Residual Uncertainties

There are no concerns or residual uncertainties for pre and or post natal toxicity.

C. Proposed Hazard-based Special FQPA Safety Factor(s):

Based on the above- described data, no special FQPA safety factor is needed (i.e., 1X) since there are no residual uncertainties for pre and/or post natal toxicity.

**NOTE:** The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment of each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

## **Rat Metabolism**

### ***Metabolism studies in rats***

**EXECUTIVE SUMMARY:** In the eight (8) rat metabolism studies (MRIDs 45386407-45386415), [<sup>14</sup>C]-AE F130060 in 2% starch mucilage was administered to Wistar rats by gavage. In a preliminary study, [2-pyrimidyl-<sup>14</sup>C]-AE F130060 (mesosulfuron-methyl; Batch No.: Z 26003-0; radiochemical purity of 96.9%) was administered to 2 Wistar rats/sex as a single gavage dose at 10 or 1000 mg/kg nominal. In the main studies, [phenyl-U-<sup>14</sup>C]-AE F130060 (mesosulfuron-methyl; Batch Nos.: Z 27019-1, Z 28008-1, Z 27038-0, and Z 27063-1; radiochemical purity of ≥96.9%) was administered to 4 Wistar rats/sex as a single gavage dose at 10 or 1000 mg/kg nominal. [Phenyl-U-<sup>14</sup>C]-AE F130060 was also administered once daily for seven days to 3/sex/interval rats at 250 mg/kg nominal. Pharmacokinetic analyses of the absorption and distribution were performed, including blood kinetics and analysis of bile, along with identification of the metabolites in the excreta and bile.

Overall recovery of the radioactive dose was 98-103%, predominantly recovered in the feces within 24 hours (80-97% dose). The onset of absorption was quick (detected in the blood 15 minutes post-dose), but the quantity absorbed was low. At 72 hours post-dose (or 168 hours following the final dose of the repeated study), urinary excretion accounted for 1-4% (except 13-14% in the 10 mg/kg animals), and radioactivity in the bile of the 10 mg/kg animals was only 7-9% dose by 12 hours post-dose. The 10 mg/kg rats had slightly more radioactivity in urine and slightly less radioactivity in feces compared to the 1000 mg/kg rats. Bioaccumulation was not observed, and radioactivity in tissues was <0.1% dose in all animals at each study termination. Concentrations of radioactivity were highest in the plasma, blood, and liver. In the repeated dose study, concentrations in all tissues (except residual carcass) were generally higher (often 3-5 fold) in males at 3 hours post-dose than in females. Concentrations of radioactivity in blood were generally 2-3 fold higher in males than females. Increasing the dose 100 fold increased blood radioactivity by approximately 8.7 fold in males and 5.6 fold in females. No excretion of radioactivity in expired air was observed in the preliminary study. For all animals, the elimination half-lives were as follows: blood (8-13 h), feces (4-5 h), urine (7-11 h), and bile (6-9 h).

Parent and 6 metabolites were identified in excreta, as were 2 metabolites in bile. Parent and identified metabolites in excreta accounted for 88-103% dose in animals receiving a single dose at 10, 250, or 1000 mg/kg. Unidentified compounds accounted for <1.3% dose. The predominant compound identified in both urine and feces of all animals was the parent, 81-97%. The primary metabolite was AE F140584 which was found at 2-5% dose in animals receiving a single dose at

10, 250, or 1000 mg/kg, with the exception of 1000 mg/kg females (14% dose). Other metabolites (AE F160459, AE F147447, AE F154851, AE F151015, and AE 0195141) were found at <1.5% dose. The amount of metabolite (% daily dose) present in the repeated dose study demonstrated a similar profile to animals treated with a single dose. The parent was also the predominant compound identified in the bile, accounting for 4-5% dose. AE F160459 and AE F151015 were also identified in the bile, but each accounted for <0.1% dose. The parent was degraded primarily through the breakdown of the sulfonamide-bridge, O-demethylation, cleavage of the methanesulfonamidomethyl side chain, and hydrolysis of the methyl ester. Amidases, esterases, and cytochrome P450 monooxygenases may have been involved in the metabolism.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OPP 85-1] in rats.

**Table 3.27. Metabolite profile (% dose) in excreta of rats treated with <sup>14</sup>C-AE F130060. <sup>a</sup>**

Compound	10 mg/kg (Single dose) <sup>b</sup>		1000 mg/kg (Single dose) <sup>c</sup>	
	Males	Females	Males	Females
Parent	96.81	91.85	89.42	81.65
AE F140584	2.16	3.37	4.21	13.52
AE F160459	1.02	1.48	0.02	0.01
AE F147447	0.77	1.06	0.02	0.01
AE F154851	0.09	0.44	ND	ND
AE F151015	0.6	0.03	ND	ND
AE 0195141	1.25	0.65	0.04	0.01
<b>Total identified</b>	<b>103</b>	<b>99</b>	<b>94</b>	<b>95</b>
<b>Total unidentified</b>	<b>1.22</b>	<b>1.02</b>	<b>ND</b>	<b>ND</b>
<b>Total accounted for <sup>d</sup></b>	<b>104</b>	<b>100</b>	<b>94</b>	<b>95</b>

a Data were obtained from MRIDs 45386411 (n=4; pages 36-37) and 45386413 (n=4; page 33).

b Sum of pooled samples collected from 0-72 hours post-dose

c Sum of pooled samples collected from 0-24 hours (males) or 6-24 hours (females) post-dose

d Unanalyzed radioactivity from feces was not reported for each group, but may have ranged from approximately 1.45-4.87% dose, based on the selected values that were reported. Because exact values were not reported, only the total identified and unidentified were summed under *total accounted for*.

ND Less than the limit of quantitation

**Table 3.28. Metabolite profile (% total dose) in excreta of rats treated once a day for 7 days with 250 mg/kg [Phenyl-U-<sup>14</sup>C] AE F130060. <sup>a</sup>**

Compound	0-24 hours after initial dose (% initial dose)		0-48 hours after final dose <sup>b</sup>			
	Males	Females	(% total dose)		(% daily dose) <sup>c</sup>	
			Males	Females	Males	Females
Parent	87.66	81.48	14.13	15.84	98.91	110.88
AE F140584	4.9	5.49	0.53	0.08	3.71	0.56
AE F160459	0.05	0.12	ND	ND	ND	ND
AE F147447	0.07	0.08	0.01	0.01	0.07	0.07
AE F154851	ND	ND	ND	ND	ND	ND
AE F151015	0.13	0.09	0.03	ND	0.21	ND
AE 0195141	0.2	0.23	0.03	0.02	0.21	0.14
<b>Total identified</b>	<b>93</b>	<b>88</b>	<b>15</b>	<b>16</b>	<b>103</b>	<b>112</b>
<b>Total unidentified</b>	<b>0.96</b>	<b>0.71</b>	<b>0.12</b>	<b>0.07</b>	<b>0.84</b>	<b>0.49</b>
<b>Total accounted for<sup>d</sup></b>	<b>94</b>	<b>89</b>	<b>15</b>	<b>16</b>	<b>104</b>	<b>112</b>

a Data were obtained from MRID 45386415 (n=3; pages 37-39).

b Results are reported for the 12-24 hour interval following the final dose for metabolites in urine (only interval reported; the Sponsor stated that other collection intervals were not analyzed due to the low amount of radioactivity) and for 0-48 hour interval for feces.

c Approximated by the reviewers by multiplying the % of total dose by 7.

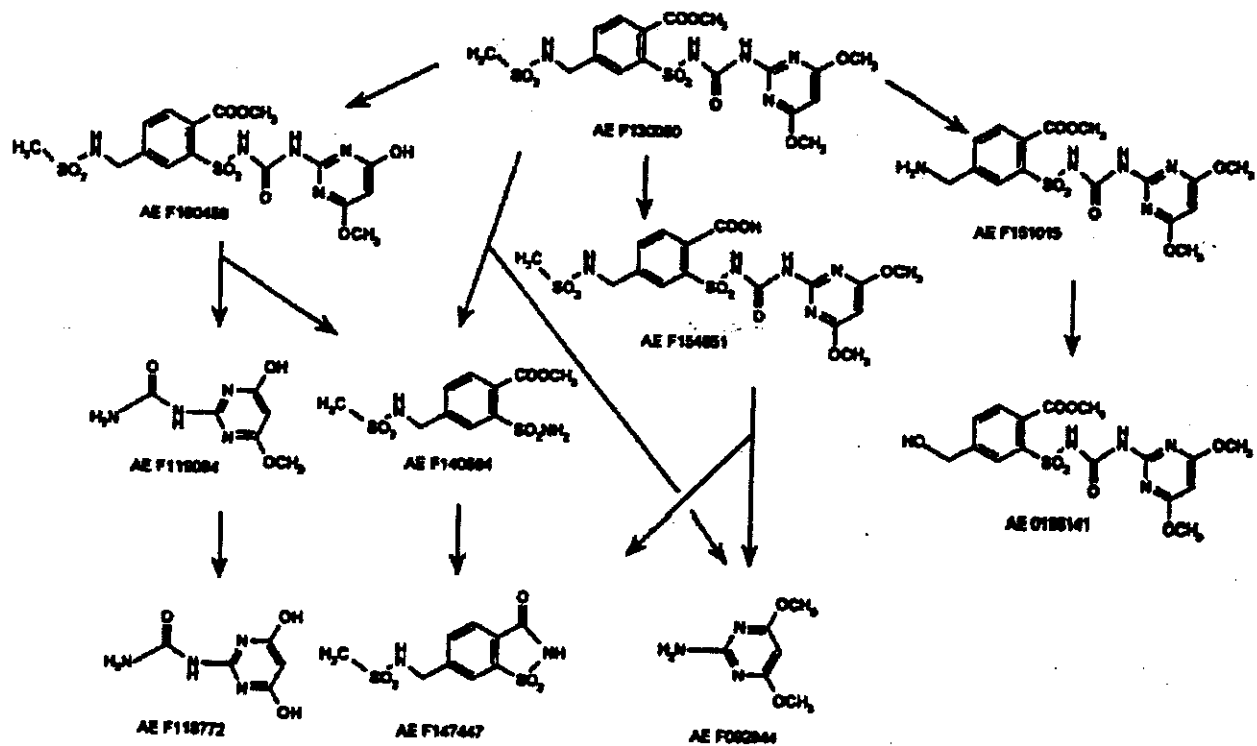
d Unanalyzed radioactivity from feces was not reported for each group, but may have ranged from approximately 1.45-4.87% dose, based on the selected values that were reported. Because exact values were not reported, only the total identified and unidentified were summed under *total accounted for*.

**Table 3.29. Metabolite profile (% total dose) in bile (0-12 h post-dose) of rats treated with 10 mg/kg <sup>14</sup>C-AE F130060. <sup>a</sup>**

Compound	Males	Females
Parent	3.81	5.15
AE F160459	0.02	0.04
AE F151015	0.09	0.03
<b>Total identified</b>	<b>3.92</b>	<b>5.22</b>
<b>Total unidentified</b>	<b>0.09</b>	<b>0.03</b>

a Data were obtained from MRID 45386411 (n=4; pages 38).

**Figure 3.5.** The proposed pathways for biotransformation of AE F130060 (mesosulfuron-methyl) in orally dosed rats (MRIDs 45386407-45386415).



AE F119084, AE F118772 and AE F092844 were detected in the study CM96/130 with [2-<sup>14</sup>C-pyrimidyl]-AE F130060 (Ref. 2).  
The arrows do not only represent one step of enzymatic reaction but mean complex metabolic transformations leading to the compounds shown.

## Environmental Fate

The common name of this pesticide is mesosulfuron-methyl ("mesosulfuron"). It belongs to the sulfonyleurea family of herbicides. Its herbicidal mode of action is inhibition of acetolactate synthase ("ALS-Inhibitor"). This enzyme is involved in the synthesis of branched amino acids in plants (e.g., valine, leucine). The uses under consideration are Winter wheat and Spring wheat, including durum. There are two proposed end-use products.

## Environmental Persistence

Biotransformation is the major route of degradation of mesosulfuron in the environment. Mesosulfuron is stable towards abiotic hydrolysis at pH 7 and 9 (half-lives  $\gg$  30 days), but it is faster under acidic conditions and higher temperatures. Direct photolysis in water and photolysis on soil are not important degradation pathways for mesosulfuron.

Considering the widespread, anticipated use areas of variable soil characteristics, climates and agricultural practices (e.g., differences in timing of planting for Winter and Spring wheat), variability in persistence in soil is expected. The kinetics of degradation of mesosulfuron in water, soil, water-sediment systems and in the field are summarized in the table below. However, the aerobic soil metabolism studies suggest that mesosulfuron has the potential to be persistent in soils (Refer to Table 3.30).

**Table 3.30. Persistence of Mesosulfuron in the Environment**

Media	Half-lives	Comments
<u>Abiotic media:</u> a. Hydrolysis b. Direct photolysis in water	<u>At 25° C</u> a. 3.5 d (pH 4); > 200 days (pH 7 and 9) b. $\gg$ 30 days	The rate of abiotic hydrolysis is pH and temperature dependent. In neutral and alkaline media, hydrolysis is significant only at temperatures above 40° C.
<u>Soil:</u> a. Photolysis on soil b. Aerobic soils	a. Photolysis on soil is not an important degradation pathway. b. <u>At 20° C</u> , the half-life of mesosulfuron ranged from 8 to 68 days, depending on the soil. <u>At 10° C</u> , the half-life of mesosulfuron ranged from 81 to 154 days.	Degradation in soils is mediated by microorganisms and exposure to sunlight does not appear to affect the rate of degradation.  Physical and chemical properties of the soils, microbial population, and temperature affect the rate of microbial degradation. From the aerobic soil metabolism studies, it can be concluded that mesosulfuron may be persistent enough to leach and/or reach surface water by direct runoff.
<u>Water-sediment systems:</u> a. Anaerobic conditions b. Aerobic conditions	a. 7 to 12 days in the water phase and in the whole system b. 14 to 57 days	The water phase in these studies is not abiotic.
Field Dissipation	11 days in FL; 15 days in IL; 17 days in CA	The EFED does not currently use data from field dissipation studies as input parameters to estimate exposure concentrations in water resources.

## Expected Mobility

Mesosulfuron, like all of the members of the sulfonylurea family of herbicides, exhibits weak binding to soils, as reflected by the low sorption coefficients. In batch-equilibrium adsorption/desorption studies conducted with 9 soils, the mean Koc was 93 and the median 48. Mesosulfuron, like other sulfonylurea herbicides, predominates in the water phase and not in the sediment.

Mesosulfuron has low potential to volatilize from soil or water or to bioaccumulate in fish.

## Environmental Metabolites

All of the degradates identified in the environmental fate studies retain the 4-methanesulfonamido group of the phenyl ring. Thus, all of the degradates containing the phenyl ring are unique to mesosulfuron. Degradates containing only the pyrimidinyl ring are not unique to mesosulfuron and have been identified for other sulfonylurea herbicides containing the 4,6-dimethoxypyrimidinyl group<sup>1</sup>. Three major degradation mechanisms are involved in environmental media, although more than one of the mechanisms may be operational:

- a. Cleavage of the sulfonylurea bridge to generate single ring products
- b. Methyl ethyl hydrolysis
- c. Demethoxyfication of the 4,6 methoxy groups in the pyrimidinyl ring.

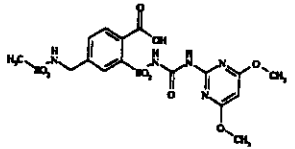
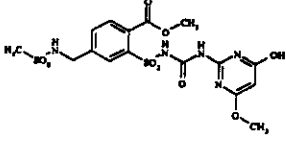
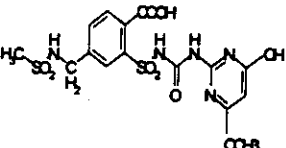
The dissipation behavior in aerobic soils was variable. That is, the aerobic soil metabolism studies showed variability in the type of degradate, maximum degradate concentration and time of maximum amount for the different soils and temperatures. This variability was also encountered in the water-sediment systems. Half-lives of degradates were not determined experimentally, but for some degradates, the half-lives were estimated using a multi-compartment pharmacokinetics model (TopFit 2.2).

The maximum degradate concentrations reported here correspond to the maximum found in any of the metabolism studies at 20° C incubation temperature.

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<sup>1</sup> Examples of sulfonylurea herbicides containing the 4,6-dimethoxypyrimidinyl group are bensulfuron, foramsulfuron, halosulfuron, nicosulfuron, rimsulfuron, sulfosulfuron, and trifloxysulfuron.

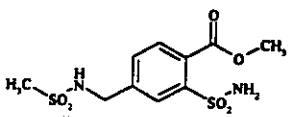
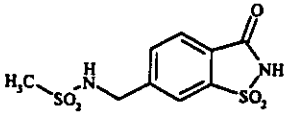
Table 3.31. Summary of Environmental Fate Studies for Mesosulfuron- Bridge Intact Degradates

Degradate (name and structure)	Maximum Degradate Concentration (% of applied) and Time (days) to Maximum Concentration in Study:			Degradates Analyzed in Study:		
	Soil Photo.	Aerobic Soil	Anaerobic. Aquatic	Aerobic Aquatic	Field Diss.	Ground Water and Surface Water
<p><b>AE F154851</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>16% (45 d)</p> <p><u>Estimated Half-life:</u> 8-210 d; Mean 61 d</p>	<p>9% total system; 7% in water phase</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>&lt; 5% at all times</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>
<p><b>AE F160459</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>&lt; 5% at all times</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>18- 20% total system; 15- 16% water phase (7 d)</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>18% in water at 112 d; &lt; 5% in sediment at all times</p> <p><u>Estimated Half-life:</u> Whole system, 21-115 days</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>
<p><b>AE F160460</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>7% (30 days)</p> <p><u>Estimated Half-life:</u> 8-74 days; Mean 41 days</p>	<p>16% total system; 15% in water phase (14 d)</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>&lt; 6% at all times</p> <p><u>Estimated Half-life:</u> 27- 21 d (whole system)</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>

Adsorption Coefficients (as Koc): AE F154851 50- 119 (mobile); No data for AE F160459 and AE F160460. However, note that these two degradates predominate in the water phase (see anaerobic aquatic metabolism)

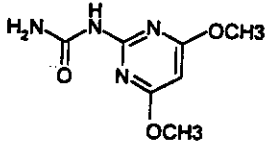
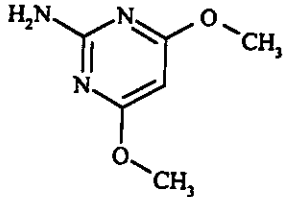
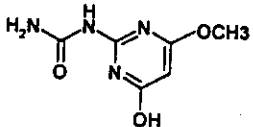


Table 3.32. Summary of Environmental Fate Studies for Mesosulfuron- Bridge-Cleavage Degradates (Phenyl ring). Unique to mesosulfuron

Degradate (name and structure)	Maximum Degradate Concentration (% of applied) and Time (days) to Maximum Concentration in Study:				Degradates Analyzed in Study:	
	Soil Photo.	Aerobic Soil	Anaerobic Aquatic	Aerobic Aquatic	Field Diss.	Ground Water and Surface Water
<p><b>AE F140584</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>5% (28 d)</p> <p><u>Estimated Half-life:</u> 196 d</p>	<p>1 to 2.4%</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Not detected</p> <p><u>Estimated Half-life:</u> Not applicable</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>
<p><b>AE F147447</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>7 % (284 d)</p> <p><u>Estimated Half-life:</u> 27 d</p>	<p>4% in total system; 3.6% in water (168 d)</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>13% water (224- 365 d); &lt; 3% in sediment at all times. This degradate was detected in only one system</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>

**Adsorption Coefficients (as Koc):** No data submitted. However, data submitted for other sulfonylurea herbicides containing an ester group at the 2-position of the phenyl ring suggest that they are potentially mobile. **AE F147447** is a saccharin analogue. Saccharin and saccharin analogues have been documented for other sulfonylurea herbicides

Table 3.33. Summary of Environmental Fate Studies for Mesosulfuron- Bridge-cleavage Degradates (Pyrimidinyl ring). In common with other sulfonylurea herbicides

Degradate (name and structure)	Maximum Degradate Concentration (% of applied) and Time (days) to Maximum Concentration in Study:				Degradates Analyzed in Study:	
	Soil Photo.	Aerobic Soil	Anaerobic. Aquatic	Aerobic Aquatic	Field Diss.	Ground Water and Surface Water
<p><b>AE F099095</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>29% (15 d)</p> <p><u>Estimated Half-life:</u> 15-96 d; Mean 52 d</p>	<p>Not detected</p>	<p>&lt; 1% at all times</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>
<p><b>AE F092944</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>10% (62 d)</p> <p><u>Estimated Half-life:</u> 4-18 d; Mean 10 d</p>	<p>7% total system; 5% in water</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>&lt; 3% at all times</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>
<p><b>AE F119094</b></p> 	<p>See aerobic soil</p> <p>See comment on soil photolysis of parent</p>	<p>Not detected</p>	<p>Not detected</p>	<p>&lt; 3% at all times</p> <p><u>Estimated Half-life:</u> Not estimated</p>	<p>Unclear</p>	<p>Mesosulfuron is a new chemical. No ground water (leaching) nor monitoring studies are available for parent or metabolites. The same applies to surface water.</p>

Adsorption Coefficients (as Koc): AE F099095 206 to 3856 Mobile to moderately mobile; AE F092944 and AE F119094. From data for other sulfonylurea herbicides, these degradates exhibit moderate mobility.

**cc: Nancy Dodd, Judy Facey, Silvia Termes**

**Template Version September 2003**