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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 4 March 2004

SUBJECT: Human Health Risk Assessment for Mesosulfuron-methyl to Support Request for New Active Ingredient Uses on Wheat

DP Barcode: D298764
PC Code: 122009
Trade Names: Silverado™ and Osprey™
EPA Reg #s: 264-INR and 264-INE

Petition #: PP#1F06298
Class: Herbicide

TO: Tobi Colvin-Snyder/Jim Tompkins, PM Team #25
Herbicide Branch
Registration Division (7505C)

FROM: Kelly M. O'Rourke, Biologist/Risk Assessor
Nancy Dodd, Chemist
Judy Facey, Toxicologist
Ayaad Assaad, Toxicologist
Sarah Winfield, Environmental Protection Specialist
Registration Action Branch 3
Health Effects Division (7509C)

THRU: Steve Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of the new systemic herbicide mesosulfuron-methyl [methyl 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[(methylsulfonyl)amino]methyl]benzoate] in/on wheat.

Table of Contents

Tables

Page

Appendix

INTRODUCTION

The Health Effects Division (HED) has conducted a human health risk assessment for the new systemic herbicidal active ingredient, mesosulfuron-methyl, for the purpose of making a tolerance and registration eligibility decision to establish the use (wheat) requested by the petitioner, Bayer CropScience LP (formerly Aventis CropScience).

The formulated end use products evaluated in this assessment are labeled under the trade names Silverado™ and Osprey™. In this memorandum, the name mesosulfuron-methyl will be used for the active ingredient (ai) in these products. The formulations of mesosulfuron-methyl evaluated in this assessment are water-dispersible granules (i.e., Silverado™ 2.0% ai and Osprey™ 4.5% ai).

A summary of the findings and an assessment of human health risk resulting from the uses of mesosulfuron-methyl are provided in this document. The residue chemistry reviews and dietary exposure assessment were provided by Nancy Dodd. The occupational/residential assessment was performed by Sarah Winfield. Judy Facey and Ayaad Assaad performed the toxicology assessment, and Kelly O'Rourke conducted the risk assessment. The drinking water exposure assessment was performed by Silvia Termes of the Environmental Fate & Effects Division (EFED).

Recommendation for Tolerances

Provided the data needs pertaining to revised Section Bs/labels (860.1200) and a revised Section F (860.1550) are met as specified in Section 8.1 of this risk assessment, there are no residue chemistry data gaps that would preclude the establishment of the following permanent tolerances for residues of mesosulfuron-methyl. HED recommends for *conditional* registration for mesosulfuron-methyl on wheat based upon the need for an EPA method validation, a livestock enforcement method, and storage stability data (see Section 8.1 for details):

Sponsor	Crop Matrix	Tolerance (ppm)
Bayer Crop Science	grain, aspirated fractions	0.60 ppm
(formerly Aventis CropScience)	wheat, grain	0.03 ppm
	wheat, forage	0.60 ppm
	wheat, hay	0.06 ppm
	wheat, straw	0.30 ppm
	wheat, germ	0.10 ppm

Upon submission of an acceptable livestock enforcement method, the petitioner must propose tolerances in ruminant liver and kidney (or meat byproducts) at the demonstrated LOQ of that method.

HED recommends that conversion of conditional registration to unconditional registration be considered for wheat upon submission of the requested data.

1.0 EXECUTIVE SUMMARY

Bayer CropScience LP (formerly Aventis CropScience) has requested the establishment of permanent tolerances for residues of the new systemic herbicide mesosulfuron-methyl [methyl 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[(methylsulfonyl)amino]methyl]benzoate] in/on wheat.

Mesosulfuron-methyl (AE F130060) is a new systemic herbicide proposed for use on wheat. It is a pyrimidinylsulfonylurea which inhibits acetolactate synthase (ALS)/acetohydroxy acid synthase (AHAS); it is absorbed through the foliage of treated weeds, rapidly inhibiting growth and causing yellowing to necrosis of the growing point and eventual plant death. Mesosulfuron-methyl belongs to the pesticide class known as sulfonylureas. Other sulfonylureas registered in the US for use on wheat are chlorsulfuron, metsulfuron methyl, prosulfuron, sulfosulfuron, triasulfuron, tribenuron methyl, and thifensulfuron methyl. There are presently no established tolerances for residues of mesosulfuron-methyl in/on plant and livestock commodities.

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for residues of mesosulfuron-methyl in/on plant or animal commodities.

Proposed Uses

Bayer CropScience has proposed use of two water-dispersible granular formulations on wheat: OSPREY™ Herbicide (4.5% ai) for control of annual grasses and broadleaf weeds in winter wheat and SILVERADO™ Wild Oat Herbicide (2.0% ai) for control of wild oat and wild mustard in wheat, including durum. 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. 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. Based on the residue data, HED will request that the number of applications for SILVERADO™ be limited to one per growing season. For both labels, applications can be made from wheat emergence up to the jointing stage of wheat.

Tolerances have been proposed for residues of mesosulfuron-methyl in/on wheat commodities. The HED Metabolism Assessment Review Committee (MARC) determined in a meeting on 1/28/04 that the residue of concern in wheat is mesosulfuron-methyl. No significant residues of mesosulfuron-methyl are expected to occur in rotational crops. No livestock tolerances have been proposed; however, residues in the kidney, liver, and/or meat byproducts of cattle, goats, and sheep have been included in the risk assessment at the expected limit of quantitation (LOQ) of the requested livestock commodity method (0.05 ppm). Tolerances for these livestock commodities will be established when an adequate livestock enforcement method is submitted.

Hazard Assessment

On January 20, 2004, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for mesosulfuron-methyl with regard to the toxicology database, and the toxicological endpoint selections, for the dietary and residential/occupational exposure assessments. The toxicology database supports the establishment of permanent tolerances for residues of mesosulfuron-methyl in/on the raw agricultural commodities (RACs) resulting from the proposed uses.

The acute toxicity data indicate that mesosulfuron-methyl has low acute oral, dermal, and inhalation toxicity. It was not found to be a skin irritant, and irritation that occurred in the eye cleared up 48 hours after exposure. There is no indication that mesosulfuron-methyl is a dermal sensitizer; however the sensitization study is currently considered unacceptable because the submitted positive control study was not conducted within 6 months of the sensitization study (i.e., they were approximately 9 months apart).

There are no primary target organs identified that were associated with exposure to mesosulfuron-methyl. Increased mucus secretion in the cardiac and fundic sections of the stomach (at the highest dose in 3 out of 6 animals), and chronic superficial gastristis (at the highest dose in 1 out of 6 animals) were noted in the chronic toxicity study in dogs.

There was no evidence of developmental or reproductive toxicity. The data demonstrate no increased sensitivity of rats or rabbits to *in utero* or early postnatal exposure to mesosulfuron-methyl. Based on several negative *in vivo* and *in vitro* studies, mesosulfuron-methyl has no mutagenicity potential. Carcinogenicity studies in rats and mice did not show increased incidence of spontaneous tumor formation. Mesosulfuron-methyl is classified as "not likely to be carcinogenic to humans". There was no evidence of neurotoxicity in the acute, subchronic, or chronic toxicity studies.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

As mentioned previously, the HED HIARC met on January 20, 2004 to evaluate the potential for increased susceptibility of infants and children from exposure to mesosulfuron-methyl according to the February 2002 Office of Pesticide Programs (OPP) 10X guidance document. The special FQPA SF was reduced to 1X based on toxicological considerations by the HIARC, the lack of evidence of increased quantitative/qualitative susceptibility in the available acceptable guideline studies, and the lack of residual uncertainties for pre- and/or post-natal toxicity. Additionally, the dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children, and there are currently no residential uses.

Based on available data, a suitable endpoint for acute dietary risk assessment was not identified because no effects were observed in oral toxicity studies (including developmental studies) which could be attributed to a single-dose exposure. Therefore, an acute dietary risk assessment was not performed.

For assessing chronic dietary risk, the HIARC selected a **chronic reference dose (cRfD) of 1.55 mg/kg/day** by applying an uncertainty factor (UF) of 100 to the NOAEL (no-observable-adverse-effect level) of 155 mg/kg/day from the chronic toxicity study in the dog. The systemic toxicity LOAEL (lowest-observable-adverse-effect level) is 574 mg/kg/day based on increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs and chronic superficial gastritis. Because the FQPA safety factor was removed (i.e., reduced to 1X), the chronic population-adjusted dose (cPAD) also equals 1.55 mg/kg/day.

There are no proposed residential uses; therefore, endpoints were not selected for incidental oral exposure.

Quantification of dermal risk is not required for this route of exposure due to the lack of dermal, systemic, neurological, or developmental toxicity concerns. Therefore, a dermal risk assessment was not performed.

In the absence of a route-specific inhalation study, the endpoint from an oral study (i.e., the chronic dog study) was chosen for inhalation risk assessment. The NOAEL of 155 mg/kg/day was chosen, based on increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs and chronic superficial gastritis at 574 mg/kg/day (LOAEL). The HIARC recommended that absorption via inhalation should be assumed to be equivalent to oral absorption (i.e., 100% of the oral dose).

Dietary Exposure Estimates from Food Sources

An acute dietary assessment was not conducted for mesosulfuron-methyl because an endpoint of concern attributable to a single dose was not identified.

A Tier I chronic dietary exposure analysis was performed using both the DEEM-FCID™ and Lifeline™ models. This Tier I analysis used tolerance level residues, default (1x) processing factors, and 100% crop treated data, with no refinements. The results of the Lifeline™ analysis are fully consistent with the DEEM-FCID™ results. Exposures from both the DEEM-FCID™ and Lifeline™ analyses were **<1% of the cPAD for the general US population and <1% of the cPAD for all population subgroups** included in the analysis, which are below HED's level of concern. The results of this dietary exposure analysis should be viewed as very conservative (health protective). The use of anticipated residues, empirical processing factors, and projected market share data would refine HED's exposure and risk estimates.

A cancer dietary assessment was not conducted because mesosulfuron-methyl was classified as "not likely to be carcinogenic to humans".

Dietary Exposure Estimates from Drinking Water Sources

Data concerning the environmental fate of mesosulfuron-methyl were presented to the MARC for a determination of the residues of concern in water. The MARC concluded that mesosulfuron-methyl and the metabolites designated as AE F154851, AE F160459, and AE F160460 should be included in the drinking water assessment.

EFED provided a water assessment for mesosulfuron-methyl. The water assessment was designed to assess concentrations of the parent compound and metabolites (mesosulfuron-methyl plus AE F154851, AE F160459, and AE F160460) because the degradates were found in the aerobic soil and the aquatic metabolism studies, partition predominantly into the water phase, are similar in structure to the parent and, therefore, are believed to have similar toxicity and mobility compared to the parent. A cumulative residue approach was employed to provide conservative estimated concentrations in water for mesosulfuron-methyl and its degradation products. This approach was taken because of limited environmental fate data for the degradation products. The Tier I annual average (chronic) estimated drinking water concentration (EDWC) of total residues in surface water (from FIRST modeling) is 0.15 µg/L. The Tier I EDWC for total residues in ground water (from SCI-GROW modeling) is 0.015 µg/L.

Residential Exposure and Risk Estimates

Mesosulfuron-methyl is not intended for use in public or residential settings. Therefore, residential exposure is not expected (neither handler nor postapplication), and no residential risk assessment was performed.

Aggregate Exposure and Risk Assessment/Characterization

An acute dietary risk assessment was not conducted because no acute oral endpoint was identified by the HIARC; therefore, an acute aggregate risk assessment was not necessary. Short- and intermediate-term aggregate risk assessments were not performed because residential exposure, which is combined with the dietary exposure for aggregate assessments, is not expected.

Chronic risk estimates resulting from aggregate (food + water) exposure to mesosulfuron-methyl are below HED's level of concern. Surface and ground water EDWCs were used to compare against back-calculated Drinking Water Levels of Comparison (DWLOCs) for the aggregate assessment. For the chronic scenario, the DWLOCs are 54,000 µg/L for the U.S. population and 16,000 µg/L for the most highly exposed subpopulation (all Children subgroups). The chronic EDWCs (highest 0.15 µg/L) are less than the Agency's DWLOCs for mesosulfuron-methyl residues in drinking water as a contribution to chronic aggregate exposure. HED thus concludes with reasonable certainty that residues of mesosulfuron-methyl in drinking water will not contribute significantly to the aggregate chronic human health risk, and that the chronic aggregate exposure from mesosulfuron-methyl residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the Chronic PAD) for chronic dietary aggregate exposure by *any* population subgroup. This risk assessment is considered high confidence, very conservative, and very protective of human health.

Occupational Exposure and Risk Estimates

There is a potential for occupational exposure to mesosulfuron-methyl during mixing, loading, application, and postapplication activities. Because no dermal endpoints were identified by HIARC, the occupational risk assessment was based on inhalation exposure only. Short-term and intermediate-term risks were assessed. Long-term exposures are not expected for handlers of mesosulfuron-methyl for the proposed use pattern.

MOEs for occupational handler inhalation exposure range from 900,000 (mixer/loader: open mixing water-dispersible granules for aerial application) to 10,000,000 (aerial application of liquid: closed cockpit). **All occupational handler MOEs are greater than HED's target MOE of 100, and therefore, are not of concern.** The minimum level of personal protective equipment (PPE) for handlers is based on the acute toxicity for the end-use products. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

Occupational postapplication dermal exposure is possible following treatment of crops with mesosulfuron-methyl. However, because no appropriate dermal endpoints were identified for this exposure potential, a risk assessment was not conducted. Postapplication inhalation exposure is expected to be negligible; therefore, a risk assessment for this route was also not performed. Per the Worker Protection Standard, a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III or IV. The REIs indicated on the proposed Silverado™ and Osprey™ labels are both 12 hours, and thus are in compliance with the WPS.

Recommendation for Tolerances

Provided the data needs pertaining to revised Section Bs/labels (860.1200) and a revised Section F (860.1550) are met as specified in Section 8.1 of this risk assessment, there are no residue chemistry data gaps that would preclude the establishment of the following permanent tolerances for residues of mesosulfuron-methyl. HED recommends for *conditional* registration for mesosulfuron-methyl on wheat based upon the need for an EPA method validation, a livestock enforcement method, and storage stability data (see Section 8.1 for details):

Sponsor	Crop Matrix	Tolerance (ppm)
Bayer Crop Science	grain, aspirated fractions	0.60 ppm
	wheat, grain	0.03 ppm
	wheat, forage	0.60 ppm
	wheat, hay	0.06 ppm
	wheat, straw	0.30 ppm
	wheat, germ	0.10 ppm

Upon submission of an acceptable livestock enforcement method, the petitioner must propose tolerances in ruminant liver and kidney (or meat byproducts) at the demonstrated LOQ of that method. **HED recommends that conversion of conditional registration to unconditional registration be considered for wheat upon submission of the requested data.**

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Chemical Identity and Structure

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

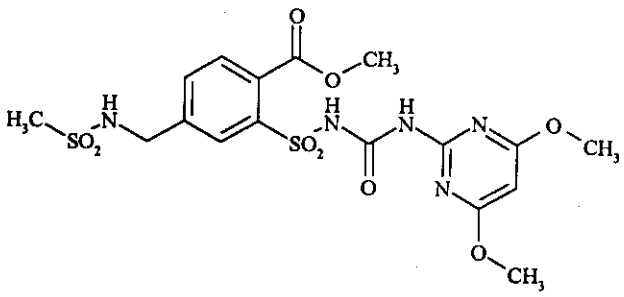
CAS Name: Methyl 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-[[(methylsulfonyl)amino]methyl]benzoate

CAS Registry: 208465-21-8

Chemical Class: Herbicide

Empirical Formula: $C_{17}H_{21}N_5O_9S_2$

Molecular Structure:



Mesosulfuron-methyl

Table 1. Physical and Chemical Properties of Mesosulfuron-methyl Technical

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 ± 0.008 buffer pH 9 15.39 ± 0.32 buffer pH 10 13.80	45386215, 45386216
Solvent solubility, g/L (20°C)	isopropanol 9.6×10^{-2} acetone 13.66 acetonitrile 8.37 n-hexane $<2.29 \times 10^{-4}$ methylene chloride 3.79 ethyl acetate 2.03 toluene 1.26×10^{-2}	45386215
Vapor pressure at 20°C	3.5×10^{-12} Pascal	45386217
Dissociation constant, pK_a, at 20°C	4.35 ± 0.04	45386218
Octanol/water partition coefficient	log $P_{o/w}$ = 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	data gap	

[1] D297240, Shyam Mathur, PhD, 1/15/04

There are no isomeric forms of mesosulfuron-methyl.

The petitioner has not discussed whether there are impurities of known toxicological concern (e.g., nitrosamines, dioxins, etc.) in mesosulfuron-methyl technical (memo, Shyam Mathur, PhD, 1/15/04).

2.3 Physical/Chemical Properties Characterization

Technical mesosulfuron-methyl is a solid powder formulated as a water-dispersible granule. The technical is close to insoluble in water at low pH (pH 4-7); solubility in water increases to slightly soluble at higher pH (pH 9-10). It is close to insoluble to slightly soluble in organic solvents. The vapor pressure is very low.

3.0 HAZARD CHARACTERIZATION

References:

Mesosulfuron-methyl: PC Code: 122009. Report of the Hazard Identification Assessment Review Committee, J. Facey, 3/4/2004. (Attachment 1)

The existing toxicological database for mesosulfuron-methyl supports the establishment of permanent tolerances for residues of mesosulfuron-methyl in/on the RACs resulting from the proposed uses. The HIARC requested that a 21/28-day inhalation study, and a 21/28-day dermal toxicity study be conducted to better characterize route-specific hazard. However, at a subsequent meeting which took place on March 3, 2004, HED's Risk Assessment Review Committee (RARC) recommended that the requirement for these studies should be waived. For the dermal study, this recommendation was based on the fact that, qualitatively, the oral endpoint, assuming 100% dermal absorption, when compared to the highest occupational dermal exposure potential, would not indicate a dermal risk concern. The waiver recommendation was made for the inhalation study because the possible concern for portal of entry effects is greatly diminished given the low exposure potential, and that the lowest calculated inhalation MOE was 900,000 (compared to a target of 100).

3.1 Hazard Profile

The overall toxicity profile for mesosulfuron-methyl is summarized in Tables 2 and 3. The acute toxicity data indicate that mesosulfuron-methyl has low acute oral, dermal, and inhalation toxicity. It was not found to be a skin irritant, and irritation that occurred in the eye cleared up 48 hours after exposure. There is no indication that mesosulfuron-methyl is a dermal sensitizer; however the sensitization study is currently considered unacceptable because the submitted positive control study was not conducted within 6 months of the sensitization study (i.e., they were approximately 9 months apart).

Table 2. Acute Toxicity of Mesosulfuron-methyl - Technical

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral toxicity	45386321	LD_{50} > 5000 mg/kg [M/F]	IV
870.1200	Acute dermal toxicity	45386322	LD_{50} > 5000 mg/kg [M/F]	IV
870.1300	Acute inhalation toxicity	45386323	LC_{50} > 1.33 mg/kg [M/F]	III
870.2400	Acute eye irritation	45386324	Conjunctival irritation at 24 hrs in 1/3 which cleared by 48 hrs.	III
870.2500	Acute dermal irritation	45386325	Non Irritant	IV
870.2600	Skin sensitization	45386326	Unacceptable	Negative [1]

[1] There was no indication that the material is a dermal sensitizer; however, the study is unacceptable because the submitted positive control study was not conducted within 6 months (i.e., they were approximately 9 months apart).

Subchronic toxicity

There were no primary target organs or toxicity identified from exposure to mesosulfuron-methyl in the subchronic mice, rat or dog studies.

Chronic toxicity

While there are no primary target organs from exposure to mesosulfuron-methyl, increased mucus secretion in the cardiac and fundic sections of the stomach (at the highest dose in 3 out of 6 animals), and chronic superficial gastristis (at the highest dose in 1 out of 6 animals) were noted in the chronic toxicity study in dogs.

Developmental and Reproduction

There was no observed toxicity, and no evidence of increased susceptibility of the young animals following exposure to mesosulfuron-methyl in any of the developmental toxicity studies or the 2-generation reproduction study in the database.

Neurotoxicity

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

Carcinogenicity

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

Mutagenicity

Mesosulfuron-methyl does not appear to have mutagenicity potential, based on several negative *in vivo* and *in vitro* studies.

Metabolism

Rat metabolism studies indicated that the onset of absorption of mesosulfuron-methyl from oral dosing was quick, but the quantity absorbed was low. The feces were 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 sulfonylurea-bridge), hydroxylation, demethylation and hydrolysis.

Table 3. Toxicity Profile of Mesosulfuron-methyl Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity in rats	45386327 (1999) Acceptable/guideline 0, 240, 1200, 6000, 12000 ppm M: 0, 17.5, 88.6, 435, 908mg/kg/day F: 0,19.1, 96.1, 475, 977 mg/kg/day	NOAEL = 908/977 [M/F] mg/kg/day LOAEL = not observed.
870.3100 90-Day oral toxicity in mice	45386328 (1999) Acceptable/guideline 0, 140, 1000, 7000 ppm M: 0, 25.5, 176.1, 1238.3 mg/kg/day F:0, 32.3, 206.1, 1603.4 mg/kg/day	NOAEL = 1238.3/ 1603.4 [M/F] mg/kg/day LOAEL = not observed.
870.3150 90-Day oral toxicity in dogs	45386329 (2000) Acceptable/guideline 0, 750, 3750, 7500 ppm M: 0, 63, 348, 648 mg/kg/day F:0, 75, 348, 734 mg/kg/day	NOAEL = 648/ 734 [M/F] mg/kg/day LOAEL = not observed.
870.3200 21/28-Day dermal toxicity	Study not available.	Study not available.
870.3250 90-Day dermal toxicity	Study not available.	Study not available.
870.3465 90-Day inhalation toxicity	Study not available.	Study not available.
870.3700a Prenatal developmental in rats	45430404 (1999) Acceptable/guideline 0, 100, 315, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not observed

Table 3. Toxicity Profile of Mesosulfuron-methyl Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Prenatal developmental in rabbits	45386401 (1998) Acceptable/guideline 0, 100, 315, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not observed
870.3800 Reproduction and fertility effects in rats	45430405 (2000) Acceptable/guideline 0,160, 1600, 16000 ppm M: 0, 11.7, 115.3, 1175.2 mg/kg/day F: 0, 13.5, 132.6, 1387.6 mg/kg/day	**Parental/Systemic** NOAEL = 1175.2/ 1387.6 [M/F] mg/kg/day LOAEL = not observed **Reproductive** NOAEL = 1175.2/ 1387.6 [M/F] mg/kg/day LOAEL = not observed **Offspring** NOAEL = 1175.2/ 1387.6 [M/F] mg/kg/day LOAEL = not observed
870.4100a Chronic toxicity in rats	45430402 (2000) Acceptable/guideline 0, 160, 1600, 16000 ppm M: 0, 7.46, 73.8, 764 mg/kg/day F: 0, 9.39, 94.7, 952 mg/kg/day	NOAEL = 764/ 952 [M/F] mg/kg/day LOAEL = not observed.
870.4100b Chronic toxicity in dogs	45386330 (2000) Acceptable/guideline 0, 400, 4000, 16000 ppm M: 0, 14.7, 155, 574, mg/kg/day F: 0, 15.3, 169, 646 mg/kg/day	NOAEL = 155 [M] mg/kg/day LOAEL = 574 [M] mg/kg/day based on increased mucus secretion in the cardiac and fundic sections of the stomach of the males dogs (HDT) and chronic superficial gastritis (1/6).
870.4200 Carcinogenicity rats	45430402 (2000) Acceptable/guideline 0, 160, 1600, 16000 ppm M: 0, 7.46, 73.8, 764 mg/kg/day F: 0, 9.39, 94.7, 952 mg/kg/day	NOAEL = 764/ 952 [M/F] mg/kg/day LOAEL = not observed. **(no) evidence of carcinogenicity**
870.4300 Carcinogenicity mice	45430403 (2000) Acceptable/guideline 0, 80, 800, 8000 ppm M: 0, 10.6, 102.8, 1069.4 mg/kg/day F: 0, 13.9, 129.8, 1355.6 mg/kg/day	NOAEL = 1069.4/ 1355.6 [M/F] mg/kg/day LOAEL = not observed. **(no) evidence of carcinogenicity**
Gene Mutation 870.5100 Bacterial reverse mutation assay	45386402 (1996) Acceptable/ guideline (a.i.)	Negative ± S9 up to cytotoxic 5000 µg/ml plate
Gene Mutation 870.5300 Mammalian cell culture	45386404 (1998) Acceptable/ guideline (a.i.)	Negative ± S9 up to cytotoxic 2500 µg/ml and precipitation 250 µg/ml

Table 3. Toxicity Profile of Mesosulfuron-methyl Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5375 Chromosomal aberrations	45386403 (1998) Acceptable/ guideline (a.i.)	Negative ± S9 precipitation ≥ 100 μg/ml
Cytogenetics 870.5395 Micronucleus test on mouse	45386406 (1998) Acceptable/ guideline (a.i.)	Negative at the highest dose tested (limit dose) 2000 mg/kg.
Other Effects 870.5550 Unscheduled DNA	45386405 (1998) Acceptable/ guideline (a.i.)	Negative ± S9 precipitation ≥ 100 μg/mL
870.6200a Acute neurotoxicity screening battery	Study not available.	Study not available.
870.6200b Subchronic neurotoxicity screening battery	Study not available.	Study not available.
870.6300 Developmental neurotoxicity	Study not available.	Study not available.
870.7485 Metabolism and pharmacokinetics	45386407- 45386415 (1997- 2000) Acceptable/guideline Dose:10 or 1000 mg/kg [phenyl- U-^{14}C]- AE F130060	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% of the 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% of the dose in all animals at each study termination.
870.7600 Dermal penetration	45386416 (2000) Unacceptable/ guideline Doses: 0.0075 cm ai/cm2 or 0.3 mg ai/cm2	
Special studies	Study not available.	Study not available.

3.2 FQPA Considerations

On January 20, 2004, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to mesosulfuron methyl according to the February 2002 OPP 10X guidance document. There are no concerns or residual uncertainties for prenatal toxicity. On this basis the HIARC concluded that a special FQPA Safety Factor of 1X be applied. The mesosulfuron-methyl risk assessment team evaluated the quality of the exposure data, and based on these data, agreed that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- There is no evidence of increased quantitative/qualitative susceptibility in the available acceptable guideline studies;
- There are no residual uncertainties for pre- and/or post-natal toxicity;
- Clear NOAELs have been identified for the effects of concern;
- No adverse effects were noted at the highest dose tested in the acceptable guideline developmental toxicity and reproduction studies in rats, and developmental toxicity study in rabbits;
- Dietary exposure estimates from food and drinking water are based on Tier 1 assessments and do not underestimate exposure/risk; and
- There are no proposed residential uses.

3.3 Dose-Response Assessment

On January 20, 2004, the HIARC evaluated the toxicology database for mesosulfuron-methyl with regard to the acute and chronic reference doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational exposure/ risk assessments. The doses and toxicological endpoints selected for various exposure scenarios are discussed below and summarized in Table 4.

Acute Dietary Endpoint: No suitable study was identified in the toxicology database for the category of Females 13-50 years old, or for the category of General Population, because no effects were observed which could be attributed to a single-dose exposure.

Chronic Dietary Endpoint: The cRfD of 1.55 mg/kg/day is based on a NOAEL of 155 mg/kg/day; an uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variations - the special FQPA Safety Factor was removed) was applied. The systemic LOAEL (574 mg/kg/day) is based on increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs (HDT) and chronic superficial gastritis (1/6) in a chronic oral toxicity study in dogs.

Carcinogenicity: Characterized as "not likely to be carcinogenic to humans" based on the lack of increased tumor incidence in the rat and the mouse carcinogenicity studies.

Incidental Oral: Because there are no proposed residential uses, endpoints were not selected for incidental oral exposure.

Dermal Endpoint: Quantification of dermal risk is not required for this route of exposure due to the lack of acute dermal, systemic, neurological, and developmental toxicity concerns. Therefore, a dermal risk assessment was not conducted.

Inhalation Endpoint: For short-, intermediate- and long-term inhalation exposure, a chronic oral toxicity study in the dog was used to set the endpoint of 155 mg/kg/day (NOAEL), based on the increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs and chronic superficial gastritis at 574 mg/kg/day (LOAEL). This study is considered appropriate for the route and duration of exposure concern as absorption via inhalation is assumed to be equivalent to oral absorption, and the use of an endpoint from a long-term study is protective of shorter durations of exposure.

MOE for Occupational Risk Assessment: For occupational short-, intermediate-, and long-term inhalation exposure risk assessments, the Target MOE is 100. This is based on the conventional uncertainty factor of 100X, which includes the 10X for intraspecies extrapolation and 10X for interspecies variation. No residential uses are proposed for mesosulfuron-methyl at the present time.

Table 4. Summary of Toxicological Doses and Endpoints for Mesosulfuron-methyl for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary: All populations	**An endpoint attributable to a single dose was not 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** = chronic RfD / 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	**Quantification of dermal risk is not required for this route of exposure due to the lack of dermal, systemic, neurological, and developmental toxicity concerns.**		
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 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

3.4 Endocrine Disruption

Evidence of endocrine disruption due to mesosulfuron-methyl was not observed in the studies reviewed. EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Mesosulfuron-methyl is a new systemic herbicide; therefore, there are currently no registered uses. Two water-dispersible granular formulations are proposed: OSPREY™ Herbicide (4.5% ai) for control of annual grasses and broadleaf weeds in winter wheat and SILVERADO™ Wild Oat Herbicide (2.0% ai) for control of wild oat and wild mustard in wheat, including durum. The proposed uses for this Section 3 petition are summarized in Table 5.

Table 5. Summary of Use Patterns and Formulation Information for 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 (WDG 4.5% a.i.)	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 or a basic blend. In the Pacific Northwestern states of WA, OR, and ID, a non-ionic 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), Bronate Advanced™ Herbicide (or equivalent bromoxynil products), Curtail™, Harmony® Extra, Harmony® GT, MCP esters, Peak®, Starane™, 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, 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.

Table 5. Summary of Use Patterns and Formulation Information for 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
			Wheat			
SILVERADO™ Wild Oat Herbicide (WDG 2.0% a.i.)	post-emergence up to the jointing stage of wheat; broadcast, foliar spray; ground or aerial equipment	0.002-0.003	not stated	0.006	forage: 30 grain: 55 straw: 55	Apply to young actively growing weeds in vigorously growing wheat, including durum. Apply from wheat emergence up to the jointing stage of wheat. Apply broadcast 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: Herbicides: Allyl® Extra, Buctril® Herbicide (or equivalent bromoxynil products), Bronate Advanced™ Herbicide (or equivalent bromoxynil products), Curtail™ M, Express™, Harmony® Extra, Harmony® GT, MCPA esters, Starane™, or Stinger™ ; 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 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.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

References:

Mesosulfuron-methyl. Petition for the Establishment of Permanent Tolerances on Wheat. Summary of Analytical Chemistry and Residue Data. PP#1F06298. N. Dodd. 2/18/2004. (Attachment 2)

Mesosulfuron-methyl Chronic Dietary Exposure Assessment for the Section 3 Registration Action on Wheat. N. Dodd. 2/17/2004. (Attachment 3)

Mesosulfuron-methyl. Meeting Report of the Metabolism Assessment Review Committee. N. Dodd. 1/28/2004. (Attachment 4)

See Appendix 1 (Figure 1) for chemical structures of mesosulfuron-methyl and its metabolites.

Permanent and temporary tolerances for residues of mesosulfuron-methyl and its metabolites are not currently established.

Nature of the Residue - Plants

The nature of the residue in wheat is adequately defined. HED's Metabolism Assessment Review Committee (MARC) determined in a meeting on 1/28/04 that the residue to be included in the tolerance expression and risk assessment for wheat is the parent compound only.

Wheat: The qualitative nature of the residue in wheat is adequately understood based on acceptable wheat metabolism studies, one with [pyrimidyl-2-^{14}C]mesosulfuron-methyl and one with [phenyl-U-^{14}C]mesosulfuron-methyl. 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. Parent and the three metabolites (AE F147447, AE F160459, and AE F140584) were identified in wheat straw and forage. The pyrimidyl-label study, using [pyrimidyl-2-^{14}C]mesosulfuron-methyl, was conducted at the total rate of 0.0178 lb ai/A (20 g ai/ha; 1.4x the maximum proposed seasonal rate). The phenyl-label study, using [phenyl-U-^{14}C]mesosulfuron-methyl, was conducted at the total rate of 0.0535 lb ai/A (60 g ai/ha; 4.1x the maximum proposed seasonal rate). In both the pyrimidyl-label study and the phenyl-label study, the parent and each identified metabolite in forage, hay, and straw (pyrimidyl-label) and forage and straw (phenyl-label) were individually <0.010 ppm. The characterization and identification of residues in wheat grain was not possible due to extremely low levels of total radioactive residues (0.001 ppm).

Nature of the Residue - Livestock

The nature of the residue in livestock is adequately defined. HED's Metabolism Assessment Review Committee (MARC) determined in a meeting on 1/28/04 that the residue to be included in the tolerance expression and risk assessment for livestock commodities is the parent compound only.

The qualitative nature of the residue in livestock is adequately understood based on acceptable ruminant and poultry metabolism studies. Mesosulfuron-methyl is rapidly excreted in both ruminants and poultry with minimal metabolism. The metabolic route of mesosulfuron-methyl in ruminants and 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. Metabolism studies were conducted using the phenyl-label in a dairy cow at 20.54 ppm in the diet (13x the maximum theoretical dietary burden) and the phenyl-label in poultry at 10.24 ppm in the diet (341x the maximum theoretical dietary burden). Total radioactive residue levels in milk, meat, poultry, and eggs were low (i.e., ranged from <0.002 ppm to 0.058 ppm). The major component identified in milk, liver, and kidney of ruminants and liver and abdominal fat of poultry was unchanged parent compound.

Residue Analytical Methods - Plants

A proposed enforcement method for mesosulfuron-methyl in wheat commodities (EM F08/99-0; MRID 45386517) has been submitted. Using this LC/MS/MS method, the determination of residues of mesosulfuron-methyl is possible in the presence of other sulfonylureas including amidosulfuron (AE F075032), metsulfuron-methyl (AE F075736), iodosulfuron-methyl-sodium (AE F115008), and foramsulfuron (AE F130360). Briefly, homogenized samples of cereal grain, straw, and shoot (forage) are extracted with acetonitrile:triethylamine (4:1, v:v). After liquid/liquid partitions, residues are analyzed by LC/MS/MS. The transition ions monitored are m/z 504.2 to m/z 182.0 for mesosulfuron-methyl. The validated limits of quantitation (LOQs) for mesosulfuron-methyl are 0.01 ppm for cereal grain and 0.05 ppm for cereal straw and forage. Successful independent laboratory validations (ILVs) have been completed using wheat shoot/forage, straw, and grain as the matrices. Satisfactory radiovalidation data have also been submitted for wheat commodities (shoot/forage and straw). **Pending satisfactory validation of the method by the Agency, Method EM F08/99-0 is adequate for tolerance enforcement.**

Residue Analytical Methods - Livestock Commodities

No analytical methods were submitted for mesosulfuron-methyl on livestock commodities. 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**. Residues in the kidney, liver, and/or meat byproducts of cattle, goats, and sheep have been included in the risk assessment at the expected LOQ of the method (0.05 ppm).

Multiresidue Methods

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.

Storage Stability

Adequate storage stability data are available for wheat grain, forage, and straw for a conditional registration. The available data indicate that residues of mesosulfuron-methyl are relatively stable in wheat forage, straw, and grain for up to 18 months under freezer storage conditions (-18°C).

As a condition of registration, additional storage stability data will be required to demonstrate the stability of mesosulfuron-methyl residues in/on wheat forage stored frozen for up to 26 months and in/on wheat grain and straw stored frozen for up to 25 months.

No storage stability data were submitted for residues of mesosulfuron-methyl in aspirated grain fractions (AGFs) or processed wheat fractions (bran, flour, middlings, shorts, and germ); however, the storage stability data on wheat grain can be translated to aspirated grain fractions and wheat processed commodities (i.e., flour, bran, shorts, middlings, and germ) since the matrices are similar and the AGFs/processed commodities were stored for less than 18 months.

Crop Field Trial Data

Based on the submitted data, residues of mesosulfuron-methyl may be found in wheat raw agricultural commodities following foliar treatment. Residues in wheat grain will be small (<0.03 ppm). Ten field trials were conducted for spring wheat; the residue levels found in each of the commodities (i.e., forage, hay, straw, and grain) ranged from <0.05 ppm to 0.47 ppm. For winter wheat, 14 field trials were conducted for which residues ranged from <0.01 ppm to 0.55 ppm.

Processed Food/Feed

Based on the submitted data, residues of mesosulfuron-methyl may be found in wheat processed commodities. 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. Tolerances are required on "grain, aspirated fractions" at 0.60 ppm, "wheat, grain" at 0.03 ppm, and "wheat, germ" at 0.10 ppm.

Confined Accumulation in Rotational Crops

The submitted confined rotational crop studies reflect the maximum proposed seasonal use rate of 0.013 lb ai/A. Overall, the results suggest that no significant residues of mesosulfuron-methyl and/or its metabolites are taken up in succeeding crops. Total radioactive residues in spinach, carrot roots, carrot tops, and wheat grain were less than 0.010 ppm at the three plantback intervals tested. Analysis of wheat straw samples from the 31/32-day rotation detected the parent as well as the metabolites AE F140584, AE F154851, and AE F092944 at a level below 0.01 ppm. Based on these findings, the Agency concludes that rotational field trials need not be conducted, and tolerances for inadvertent residues of mesosulfuron-methyl need not be established; however, **the petitioner must submit revised Section Bs/labels 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 interval (PBI) for wheat is not needed because wheat is a crop included on the label.

Meat, Milk, Poultry, and Eggs

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 (<0.006 ppm) in fat, meat, and milk 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, as 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 Harmonization

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

4.2.2 Dietary Exposure Analyses

Based on available data, a suitable endpoint for acute dietary risk assessment was not identified by the HIARC because no effects were observed in oral toxicity studies (including developmental studies) which could be attributed to a single-dose exposure. Therefore, an acute dietary risk assessment was not performed.

For assessing chronic dietary risk, the HIARC selected a **chronic reference dose (RfD) of 1.55 mg/kg/day** by applying an uncertainty factor (UF) of 100 to the NOAEL (no-observable-adverse-effect level) of 155 mg/kg/day from the chronic toxicity study in the dog. The systemic toxicity LOAEL (lowest-observable-adverse-effect level) is 574 mg/kg/day based on increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs and chronic superficial gastritis. Because the FQPA safety factor was removed (i.e., reduced to 1X), the chronic population-adjusted dose (cPAD) also equals 1.55 mg/kg/day.

The mesosulfuron-methyl chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 1.30) and the Lifeline™ Model Version 2.0.

DEEM-FCID™ Information. This model incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food-form is summed with the residue consumption estimates for all other food/food-forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

Lifeline™ Information. This model uses the same consumption data as the DEEM-FCID™ (CSFII, 1994-1996 and 1998 consumption data with FCID), but uses the recipe file to relate RACs to foods "as-eaten." Lifeline™ converts the RAC residues into food residues by randomly selecting an RAC residue value from the "user defined" residue distribution (created from the residue, percent crop treated, and processing factor data), and calculating a net residue for that food based on the ingredients' mass contribution to that food item. For example, 'apple pie' will have a residue distribution based on the residues provided for apples (adjusted by the appropriate processing factors and percent crop treated), as well as the residues for each of the other ingredients in the apple pie recipe for which there may be tolerances. Lifeline™ calculates dietary exposure from 'apple pie' based on the amount eaten, and the residue drawn from the 'apple pie' residue distribution for that eating occasion.

Lifeline™ models the individual's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ groups CSFII diaries based on the respondents' age and the season during which the food diary was recorded. Further information regarding the Lifeline™ model can be found at the following web site: www.theLifeline™group.org.

DEEM-FCID™ (Ver. 1.30) and Lifeline™ Model Version 2.0 estimate the dietary exposure for the U.S. population and 28 population subgroups. Based on an analysis of 1994-96, 98 CSFII consumption data which took into account dietary patterns and number of survey respondents, HED determined that the following population groupings were appropriate for regulatory purposes (only the exposure estimates for these populations are reported in this document): U.S. Population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and/or adults 50+ years old.

4.2.2.1 Acute Dietary

An acute dietary assessment was not conducted for mesosulfuron-methyl because an endpoint of concern attributable to a single dose was not identified; therefore, an acute reference dose (RfD) was not established.

4.2.2.2 Chronic Dietary

A Tier I chronic dietary exposure analysis was performed using both the DEEM-FCID™ and Lifeline™ models. This Tier I analysis used tolerance level residues, default (1x) processing factors, and 100% crop treated data, with no refinements. The results of the Lifeline™ analysis are fully consistent with the DEEM-FCID™ results. As shown in Table 6 exposures from both the DEEM-FCID™ and Lifeline™ analyses were **<1% of the cPAD for the general US population and <1% of the cPAD for all population subgroups** included in the analysis, which are below HED's level of concern (cPAD = cRfD because the FQPA safety factor is 1X). The results of this dietary exposure analysis should be viewed as very conservative (health protective). The use of anticipated residues, empirical processing factors, and projected market share data would refine HED's exposure and risk estimates.

Table 6. Chronic Dietary Exposure Estimates [1]

Population Subgroup	cPAD (mg/kg/day)	DEEM™-FCID		LifeLine™	
		Exposure (mg/kg/day)	%cPAD [2]	Exposure (mg/kg/day)	% cPAD [2]
General U.S. Population	1.55	0.000053	<1	0.000059	<1
All Infants (< 1 year old)	1.55	0.000023	<1	0.000025	<1
Children 1-2 years old	1.55	0.000125	<1	0.000128	<1
Children 3-5 years old	1.55	0.000128	<1	0.000135	<1
Children 6-12 years old	1.55	0.000089	<1	0.000093	<1
Youth 13-19 years old	1.55	0.000053	<1	0.000058	<1
Adults 20-49 years old	1.55	0.000042	<1	0.000052	<1
Adults 50+ years old	1.55	0.000035	<1	0.000050	<1
Females 13-49 years old	1.55	0.000040	<1	0.000058	<1

[1] Acute and cancer dietary assessments are not applicable.

[2] Percent Chronic PAD = (Exposure ÷ Chronic PAD) x 100%.

4.2.3 Cancer Dietary

A cancer dietary assessment was not conducted because mesosulfuron-methyl was classified as "not likely to be carcinogenic to humans".

4.3 Water Exposure/Risk Pathway

Reference:

Drinking Water Assessment for Mesosulfuron-Methyl and Its Major Metabolites New Chemical- Uses on Winter Wheat (OSPREY; 4.5% mesosulfuron-methyl) and Spring Wheat, Including Durum (SILVERADO, 2.0% mesosulfuron-methyl). S. Termes. 3/03/2004. (Attachment 5)

Mesosulfuron-methyl. Meeting Report of the Metabolism Assessment Review Committee. N. Dodd. 1/28/2004. (Attachment 4)

Because mesosulfuron-methyl is a new chemical pending registration, there are no drinking water monitoring data available. Therefore, the Agency is presently relying on computer-generated estimated drinking water concentrations (EDWCs). For mesosulfuron-methyl, the Tier 1 screening model FIRST (FQPA Index Reservoir Screening Tool) was used in predicting the *surface* water concentrations; and the Tier 1 regression model SCI-GROW (Screening Concentrations In Ground Water) was used in predicting *ground* water concentrations. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal or transformation of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for determining that pesticides residues (and metabolites) in water are not of concern.

Environmental Profile: The environmental fate database is adequate to characterize drinking water exposure for the parent compound. Limited fate data are available for the degradates of mesosulfuron-methyl. The data indicate that mesosulfuron-methyl is persistent in soils and is also mobile; therefore, it is likely to run off into surface water. Lab 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. These indicate that aerobic soil and both aerobic and anaerobic aquatic metabolism can be major routes of degradation. AE F154851, AE F160459, and AE F160460 were found in all three studies (aerobic soil, aerobic and anaerobic aquatic metabolism), ranging from 5% to 20% of the applied dose. These degradates are similar in structure to the parent and, therefore, are believed to have similar toxicity and mobility compared to the parent.

MARC Decision: The HED Metabolism Assessment Review Committee (MARC) concluded that mesosulfuron-methyl and the metabolites designated as AE F154851, AE F160459, and AE F160460 are considered to be the major metabolites in water and should be included in the drinking water assessment.

The drinking water assessment was designed to assess concentrations of the parent compound and relevant degradates. A cumulative residue approach was employed to provide conservative estimated concentrations in drinking water for mesosulfuron-methyl and its degradation products.

Estimated Drinking Water Concentrations (EDWCs):

There are several uncertainties and assumptions in the water assessment of mesosulfuron-methyl and its degradates. Primary among these is the lack of environmental fate data for the metabolites. A very conservative approach was used to generate the drinking water estimates of the total concentrations of parent plus the other three degradates (AE F154851, AE F160459, and AE F160460). The parent concentrations were estimated using FIRST and SCI-GROW. Then, the maximum fraction of each degradate observed in the aerobic soil metabolism studies was multiplied by the parent residue concentrations. The total estimated concentrations of mesosulfuron-methyl residues (parent plus metabolites) were obtained by adding these to the parent estimates. The observed maximum percentages are 16%, 5%, and 7%, respectively, for AE F154851, AE F160459, and AE F160460.

The appropriate FIRST and SCI-GROW input parameters were selected from the environmental fate data submitted by the registrant and in accordance with US EPA/OPP/ EFED water model parameter selection guidelines - Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides, Version II, February 28, 2002. The environmental fate data has been evaluated by the EFED as part of the review process and risk characterization of mesosulfuron-methyl and its end-use products. The needed information on application rates and methods was taken from the proposed labels for the end-use products OSPREY™ and SILVERADO™. Table 7 summarizes the estimated concentrations in drinking water.

Table 7. Estimated Concentrations of Mesosulfuron-methyl in Drinking Water

Product	Surface Water (µg/L)				Ground Water (µg/L)	
	Peak (Acute)		Annual Average (Chronic)		Acute and Chronic	
	Parent Only	Total Residues	Parent Only	Total Residues	Parent Only	Total Residues
Osprey™	0.710	0.937	0.110	**0.145**	0.011	**0.015**
Silverado™	0.300	0.396	0.046	0.061	0.005	0.007

4.4 Residential Exposure/Risk Pathway

4.4.1 Home Uses

Mesosulfuron-methyl is proposed for use as an herbicide for wheat. It is not intended for use in public or residential settings. Therefore, residential exposure is not expected (whether handler or postapplication), and no residential risk assessment was performed.

4.4.2 Other Exposure Sources (Spray Drift)

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

5.0 AGGREGATE RISK ASSESSMENTS and RISK CHARACTERIZATION

Short- and intermediate-term aggregate risk is made up of the combined exposures from food, water, dermal, inhalation and incidental oral sources (residential). These exposures are then compared to the appropriate short- or intermediate-term endpoint. Acute aggregate and chronic aggregate risk is made up of the combined dietary exposures from food and water sources.

HIARC did not identify an acute dietary endpoint. Therefore, an acute aggregate risk assessment was not performed. The chronic aggregate risk assessment was performed using the chronic PAD. Short- and intermediate-term aggregate risk assessment is based on oral, inhalation and dermal exposures which are then compared to relevant NOAELs identified by HIARC. HIARC did not identify dermal endpoints for mesosulfuron-methyl. HIARC recommended that for aggregate risk assessment, oral and inhalation exposures be combined because the inhalation and oral routes of exposure have the same endpoint. However, because there are no residential uses proposed for this herbicide, short- and intermediate-term aggregate risk assessments based on exposure from oral, inhalation and dermal routes of exposure were not performed.

5.1 Acute Risk

An acute aggregate risk assessment was not performed because HIARC did not identify an acute dietary endpoint for mesosulfuron-methyl.

5.2 Short- and Intermediate-Term Risk

There are no residential uses proposed for this herbicide. Short- and intermediate-term aggregate risk assessments based on exposure from oral, inhalation, and dermal routes of exposure were not performed.

5.3 Chronic Risk

HIARC identified a chronic RfD (1.55 mg/kg/day), based on increased mucus secretion in the cardiac and fundic sections of the stomach of the male dogs (HDT) and chronic superficial gastritis at the LOAEL of 574 mg/kg/day. The chronic PAD is the same as the chronic RfD because the FQPA safety factor was removed (i.e., reduced to 1X). The chronic PAD was used to assess chronic aggregate risk.

5.3.1 Chronic Aggregate Risk Assessment

No drinking water monitoring data are available for mesosulfuron-methyl. Models were used to calculate EDWCs for mesosulfuron-methyl and its metabolites. The Tier 1 screening model FIRST was used to predict the surface water concentrations; and the Tier 1 regression model SCI-GROW was used to predict ground water concentrations. Degradates of concern (as determined by the MARC) are included in the modeled drinking water estimates.

Tier I (FIRST) modeling estimates that mesosulfuron-methyl residues (mesosulfuron-methyl + degradation products) in surface water, from aerial and ground application, are not likely to exceed 0.145 µg/L for the annual average concentration (chronic). The SCI-GROW model predicted concentration of mesosulfuron-methyl residues (mesosulfuron-methyl + degradation products) in shallow ground water is not expected to exceed 0.015 µg/L.

5.3.2 Chronic DWLOC Calculations

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EDWCs provided by computer modeling (SCI-GROW and FIRST).

The surface and ground water EDWCs were used to compare against back-calculated DWLOCs for aggregate risk assessment. To calculate the DWLOC for chronic exposure relative to a chronic endpoint, the chronic dietary food exposure from DEEM-FCID™ and Lifeline™ (presented in Table 6, previously) was subtracted from the cPAD (i.e., 1.55 mg/kg/day) to obtain the acceptable chronic exposure to mesosulfuron-methyl in drinking water. The DWLOCs calculated for mesosulfuron-methyl are presented in Table 8.

Table 8. Chronic DWLOC Calculations

Population Subgroup	Chronic Scenario					
	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)[1]	Maximum Water Exposure (mg/kg/day)[2]	EDWC Ground Water (µg/L)[3]	EDWC Surface Water (µg/L)[3]	Chronic DWLOC (µg/L)[4]
General U.S. Population	1.55	0.000059	1.55	0.015	0.145	54,000
All Infants (< 1 year old)	1.55	0.000025	1.55			16,000
Children 1-2 years old	1.55	0.000128	1.55			16,000
Children 3-5 years old	1.55	0.000135	1.55			16,000
Children 6-12 years old	1.55	0.000093	1.55			16,000
Youth 13-19 years old	1.55	0.000058	1.55			47,000
Adults 20-49 years old	1.55	0.000052	1.55			54,000
Adults 50+ years old	1.55	0.000050	1.55			54,000
Females 13-49 years old	1.55	0.000058	1.55			47,000

[1] The exposure from the model (DEEM-FCID™ or Lifeline™) with the highest estimated values was reported.
[2] Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - Dietary (Food) Exposure
[3] The value from the label producing the highest level was used.
[4] DWLOC(µg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L) x 10^{-3} mg/µg]
Body weight is assumed to be 70 kg for adults in general, 60 kg for females and youth, and 10 kg for children; water consumption is assumed to be 2 L for adults and youth, and 1 L for children.

Chronic Aggregate Risk Conclusions:

As shown in Table 6 previously, the resulting dietary food exposures occupy **<1% of the Chronic PAD** for all population subgroups included in the analysis. The results of this dietary exposure analysis should be viewed as very conservative (health protective). Refinements such as use of percent crop-treated information and/or anticipated residue values would yield even lower estimates of chronic dietary exposure.

The EDWCs provided by EFED for assessing chronic aggregate dietary risk are **0.015 µg/L** (for ground water, based on SCI-GROW) and **0.145 µg/L** (in surface water, based on FIRST modeling, annual average). The back-calculated DWLOCs (Table 8) for assessing chronic aggregate dietary risk **range from 16,000 µg/L** for the population subgroup with the highest food exposure (all children subgroups) **to 54,000 µg/L** for the U.S. Population (total) and Adult subgroups.

The chronic EDWCs are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for mesosulfuron-methyl residues in drinking water as a contribution to chronic aggregate exposure. HED thus concludes with reasonable certainty that residues of mesosulfuron-methyl in drinking water will not contribute significantly to the aggregate chronic human health risk, and that the chronic aggregate exposure from mesosulfuron-methyl residues in food and drinking water **will not exceed the Agency's level of concern** (100% of the chronic PAD) for chronic dietary aggregate exposure by *any* population subgroup. EPA generally has no concern for exposures below 100% of the chronic PAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, very conservative, and very protective of human health.

5.4 Cancer Risk

The HIARC classified mesosulfuron-methyl as "not likely to be carcinogenic to humans". Therefore, an aggregate cancer risk assessment was not performed.

6.0 CUMULATIVE RISK

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

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

7.0 OCCUPATIONAL EXPOSURE

Reference:

Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Mesosulfuron-methyl on Wheat. S. Winfield, 3/03/2004. (Attachment 6)

Mesosulfuron-methyl is a new systemic herbicide proposed for use on wheat. The formulated end use products evaluated in this assessment are labeled under the trade names Silverado™ and Osprey™. The formulations of mesosulfuron-methyl evaluated in this assessment are water-dispersible granules (i.e., Silverado™ 2.0% ai and Osprey™ 4.5% ai).

7.1 Occupational Handler

There is a potential for exposure to mesosulfuron-methyl during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HIARC was performed. Handler's exposure and risk were estimated for the following scenarios: (1) mixer/loader: open mixing and loading water-dispersible granules for aerial; (2) aerial application of liquid: closed cockpit; (3) flagging for aerial applications; (4) mixer/loader: open mixing and loading water-dispersible granules for groundboom; and (5) groundboom application of liquid: open cab.

No chemical-specific handler exposure data were provided to support this Section 3 registration. It is the policy of HED to use data as presented in PHED Surrogate Exposure Guide when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99) because HED believes this provides a more consistent and reliable (i.e., pooled data yields a larger number of replicates) exposure estimate than individual subsets.

Handler MOEs range from 900,000 (mixer/loader: open mixing water-dispersible granules for aerial) to 10,000,000 (aerial application of liquid: closed cockpit). The unit exposure values used in this inhalation assessment reflect a baseline protection level (i.e., no respirator) for all scenarios; however, for the aerial applicator, an enclosed cockpit is assumed because no data are available for open cockpit. All occupational handler MOEs are greater than HED's target of 100, and therefore, are not of concern. Exposure assumptions and estimates for occupational handlers are summarized in Table 9.

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

Table 9. Occupational Inhalation Exposures and Risks from Mesosulfuron-methyl							
PHED Exposure Scenario	**Maximum Application Rate (lb ai/A)**	**PHED Unit Exposure [1] (mg/lb ai)**	**PHED Data Confidence**	**Area Treated per Day (acres)**	**Body Weigh t (kg)**	**Daily Inhalation Dose [2] (mg/kg/day)**	**Short- and intermediate-term MOE[3]**
1. mixer/loader: open mixing and loading dry flowable for aerial	0.013	0.00077	High	1200	70	0.00017	900,000
2. aerial application of liquid: closed cockpit	0.013	0.000068	Medium	1200	70	0.000015	10,000,000
3. flagging for aerial applications	0.013	0.00035	High	350	70	0.000023	6,800,000
4. mixer/loader: open mixing and loading dry flowable for groundboom	0.013	0.00077	High	200	70	0.000029	5,400,000
5. groundboom application of liquid: open cab	0.013	0.00074	High	200	70	0.000027	5,600,000

[1] PHED unit exposure values are for baseline protection (*i.e.*, no respirator).
[2] Daily Dose =[Application Rate (lb ai/A) x Area Treated (A/day) x Unit Exposure (mg/lb ai) x Absorption Factor (100%) /Body Weight:70 kg
[3] MOE = NOAEL/ Daily Dose. Short-and intermediate-term inhalation NOAEL=155 mg/kg/day.

7.2 Occupational Postapplication

This Section 3 action on mesosulfuron-methyl involves foliar applications. Therefore, there is a potential for postapplication exposure to scouts, harvesters and other field workers. However, as no appropriate dermal endpoints were identified for this exposure potential, a dermal risk assessment was not conducted. Postapplication inhalation exposure is expected to be negligible; therefore, a risk assessment for this route was also not performed.

The mesosulfuron-methyl technical material has been classified in Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for primary skin irritation. Per the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III or IV. The REIs indicated on the proposed Silverado™ and Osprey™ labels are both 12 hours, and thus are in compliance with the WPS.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

Data which remain outstanding for wheat are listed below by guideline series.

WHEAT

As conditions of registration (for continued registration), the data needs pertaining to residue analytical methods (860.1340) and additional storage stability data (860.1380) must be resolved.

860.1200 Directions for Use

- 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.

- The proposed end-use product labels for SILVERADO™ Wild Oat Herbicide and OSPREY™ Herbicide must be revised to specify a plantback interval (PBI) of at least 30 days for barley. HED has no objection to longer crop rotation restrictions as specified on the labels. No PBI for wheat is needed.

860.1340 Residue Analytical Methods

- A successful EPA method validation of the proposed enforcement method for mesosulfuron-methyl on wheat commodities (EM F08/99-0) is needed as a condition of registration.

- No analytical methods were submitted for mesosulfuron-methyl on livestock commodities. 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. (An enforcement method must be supported by an independent laboratory validation and an EPA method validation.)

- Upon submission of an acceptable livestock enforcement method as a condition of registration, the petitioner must propose tolerances in ruminant liver and kidney (or meat byproducts) at the demonstrated LOQ of that method.

860.1380 Storage Stability

- Storage stability data must be submitted to demonstrate the stability of mesosulfuron-methyl residues in/on wheat forage stored frozen for up to 26 months and in/on wheat grain and straw stored frozen for up to 25 months.

860.1550 Proposed Tolerances

- A revised Section F must be submitted to delete the proposal to establish a tolerance for wheat milled byproducts, revise the tolerance expression for aspirated grain fractions from "wheat, aspirated grain fractions" to "grain, aspirated fractions", and to raise the proposed tolerance for " grain, aspirated fractions" to 0.60 ppm.

8.2 Toxicology

The HIARC requested that a 21/28-day inhalation study, and a 21/28-day dermal toxicity study be conducted to better characterize route-specific hazard. However, at a subsequent meeting which took place on March 3, 2004, HED's Risk Assessment Review Committee (RARC) recommended that the requirement for these studies should be waived. For the dermal study, this recommendation was based on the fact that, qualitatively, the oral endpoint, assuming 100% dermal absorption, when compared to the highest occupational dermal exposure potential, would not indicate a dermal risk concern. The waiver recommendation was made for the inhalation study because the possible concern for portal of entry effects is greatly diminished given the low exposure potential, and that the lowest calculated inhalation MOE was 900,000 (compared to a target of 100).

9.0 ATTACHMENTS

Attachment 1: *Mesosulfuron-methyl: Report of the Hazard Identification Assessment Review Committee*, J. Facey, 3/4/2004

Attachment 2: *Mesosulfuron-methyl. Petition for the Establishment of Permanent Tolerances on Wheat. Summary of Analytical Chemistry and Residue Data. PP#1F06298.* N. Dodd. 2/18/2004.

Attachment 3: *Mesosulfuron-methyl Chronic Dietary Exposure Assessment for the Section 3 Registration Action on Wheat.* N. Dodd. 2/17/2004.

Attachment 4: *Mesosulfuron-methyl. Meeting Report of the Metabolism Assessment Review Committee.* N. Dodd. 1/28/2004.

Attachment 5: *Drinking Water Assessment for Mesosulfuron-Methyl and Its Major Metabolites New Chemical- Uses on Winter Wheat (OSPREY; 4.5% mesosulfuron-methyl) and Spring Wheat, Including Durum (SILVERADO, 2.0% mesosulfuron-methyl).* S. Termes. 3/03/2004.

Attachment 6: *Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Mesosulfuron-methyl on Wheat.* S. Winfield, 3/03/2004.

cc: RF, Mesosulfuron-methyl Risk Assessment Team Members
RDI: RAB3 RA Team (Reviewers: W. Wassell & J. Arthur) 3/1/2004 :S. Dapson 3/4/2004

Appendix 1

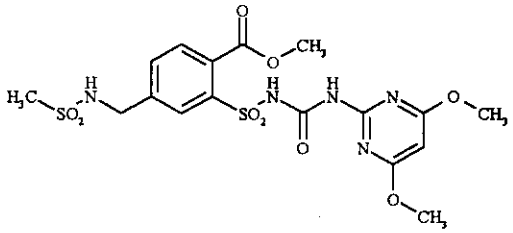
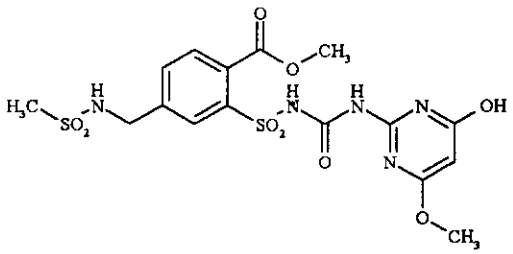
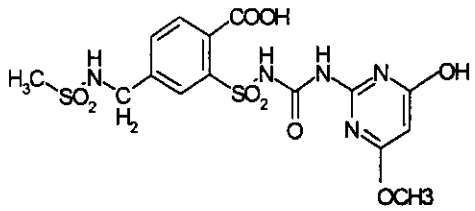
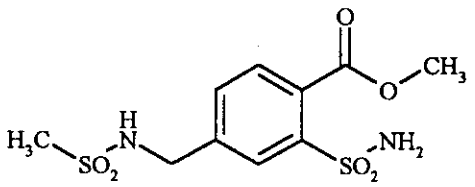
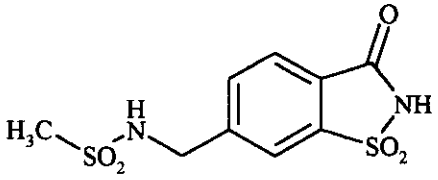
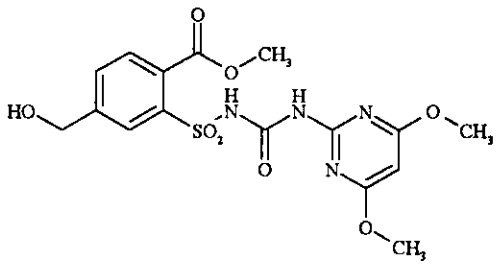
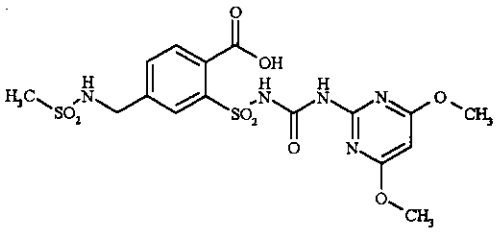
Figure 1. Chemical Names and Structures of Mesosulfuron-methyl and its Transformation Products		
Common name/code	Chemical name [Matrix where the compound was identified]	Chemical structure
Mesosulfuron-methyl/ AE F130060	Methyl 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]-sulfonyl]-4-[[(methylsulfonyl)-amino]methyl]benzoate (CAS) [Identified in wheat forage, hay, and straw; cow milk, liver, kidney, and renal fat; poultry liver and abdominal fat; and rotated wheat straw.]	
AE F160459	Methyl 2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate (IUPAC) [Identified in wheat forage, hay, and straw; cow milk; poultry liver. Also identified in aerobic soil and aquatic metabolism studies.]	
AE F160460	2-[3-(4-Hydroxy-6-methoxypyrimidine-2-yl)ureidosulfonyl]-4-methanesulfonamidomethyl benzoic acid (IUPAC) [Identified in aerobic soil and aquatic metabolism studies.]	
AE F140584	Methyl 4-methanesulfonamidomethyl-2-sulfamoylbenzoate (IUPAC) [Identified in wheat forage and straw; cow liver and kidney; poultry liver; and rotated wheat straw.]	
AE F147447	6-Methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (IUPAC) [Identified in wheat forage and straw; cow liver and kidney; and rotated wheat straw]	

Figure 1. Chemical Names and Structures of Mesosulfuron-methyl and its Transformation Products		
Common name/code	Chemical name [Matrix where the compound was identified]	Chemical structure
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. [Identified in cow kidney and renal fat; and poultry liver.]	
AE F154851	2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethyl benzoic acid (IUPAC) [Identified in rotated wheat straw. Also identified in aerobic soil and aquatic metabolism studies.]	
AE F092944	2-amino-4,6-dimethoxypyrimidine (IUPAC) [Identified in rotated wheat straw.]