United States Environmental Protection Agency

Office of Prevention, Pesticides and Toxic Substances (7501C)

Pesticide Fact Sheet

Name of Chemical: Mesosulfuron-methyl
Reason for Issuance: Conditional Registration
Date Issued: March 31, 2004

1. Description of Chemical

Generic Name:	Methyl 2-[[[[(4,6-dimethoxy-2-pyrimidinyl) amino]carbonyl]amino]sulfonyl]-4-[[(methylsulfonyl)amino]methyl]benzoate
Common Name:	Mesosulfuron-methyl
Trade Name:	Mesosulfuron-methyl Technical
EPA Shaughnessy Code:	122009
Chemical Abstracts Service (CAS) Number:	208465-21-8
Year of Initial Registration:	2004
Pesticide Type:	Herbicide
Chemical Family:	Sulfonyl Urea
U.S. Producer:	Bayer CropScience

2. Use Patterns and Formulations

Application Sites:	Mesosulfuron-methyl is registered as a Technical product for formulation for herbicides used on wheat.
Types of Formulations:	technical product (96.8% a.i.), two end use products (2.0% and 4.5% a.i.)

3. Science Findings

Summary Science Statements

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. Dermal sensitization was not determined because the study was unacceptable. 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, and chronic superficial gastristis (1/6) 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, it 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. Biotransformation is the major route of degradation of mesosulfuron in the environment, as evidenced by mineralization (i.e., formation of CO_2) in aerobic soils and persistence varying with microbial population and temperature. In water-sediment systems, persistence is also variable, mineralization is negligible and, like in soils, non-extractable residues increase with time. Mesosulfuron produces degradates that have been identified for other sulfonylurea herbicides as well as degradates that are unique to this chemical. As implied by the long replanting intervals recommended on the labels (up to 12 months), mesosulfuron remains phytotoxic in soils long after application.

Chemical Characteristics

Chemical Properties of Mesosulfuron-methyl Technical	
Property of Technical	Result
C o l o r	Cream color
Physical state	solid powder
Odor	weekly pungent
Stability to normal and elevated temperatures, metals, and metal ions	No significant change in the AI content (2.2% decrease) when stored for 14 days at 54^{0}C. The AI was found to be stable in presence of Fe & Al, Al acetate and Fe sulfate over a range of 30-205^{0}C.
Flammability	Nonflammable
pH	5.1 @ 25 ^{0}C
Melting point/ Melting range	189-192^{0}C.

Chemical Properties of Mesosulfuron-methyl Technical	
Property of Technical	Result
Relative Density	1.53 gm/cc at 23 ^{0}C
Dissociation constants in water	pKa = 4.35 ± 0.04 at 20 ^{0}C by photometric titration method
Partition coefficient (n-octanol/water), shake flask method	log Po/w = 1.90 (pH, 4); 1.39 (pH,5); -0.48 (pH,7); -2.06 (pH, 9); -2.10 (pH,10)
Water solubility: column elution method; shake flask method	water organic solvents
Vapor pressure	1.1 x 10^{-11} Pascal at 25 ^{0}C.

Toxicology Characteristics

Toxicology Profile for Mesosulfuron-Methyl

Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity rodents	NOAEL = 908/977 [M/F] mg/kg/day LOAEL = not observed.
870.3100 90-Day oral toxicity rodents	NOAEL = 1238.3/ 1603.4 [M/F] mg/kg/day LOAEL = not observed.
870.3150 90-Day oral toxicity in nonrodents	NOAEL = 648/ 734 [M/F] mg/kg/day LOAEL = not observed.
870.3200 21/28-Day dermal toxicity	Study not required.
870.3250 90-Day dermal toxicity	Study not required.
870.3465 90-Day inhalation toxicity	Study not required.
870.3700a Prenatal developmental in rodents	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not observed

Guideline No./ Study Type	Results
870.3700b Prenatal developmental in nonrodents	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = not observed **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not observed
870.3800 Reproduction and fertility effects	**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 rodents	NOAEL = 764/ 952 [M/F] mg/kg/day LOAEL = not observed.
870.4100b Chronic toxicity dogs	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	NOAEL = 764/ 952 [M/F] mg/kg/day LOAEL = not observed. **(no) evidence of carcinogenicity**
870.4300 Carcinogenicity mice	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	Negative ± S9 up to cytotoxic 5000 µg/ml plate
Gene Mutation 870.5300 Mammalian cell culture	Negative ± S9 up to cytotoxic 2500 µg/ml and precipitation 250 µg/ml
Cytogenetics 870.5395 Micronucleus test on mouse	Negative at the highest dose tested (limit dose) 2000 mg/kg.

Guideline No./ Study Type	Results
Cytogenetics 870.5375 Chromosomal aberrations	Negative ± S9 precipitation ≥100 µg/ml
Other Effects 870.5550 Unscheduled DNA	Negative ± S9 precipitation ≥100 µg/ml
870.6200a Acute neurotoxicity screening battery	Study not required
870.6200b Subchronic neurotoxicity screening battery	Study not required
870.6300 Developmental neurotoxicity	Study not required
870.7485 Metabolism and pharmacokinetics	Overall recovery of the radioactive dose was 98-103%, predominantly recovered in the feces within 24 hours (80-97% dose). The onset of absorption was quick (detected in the blood 15 minutes post-dose), but the quantity absorbed was low. At 72 hours post-dose (or 168 hours following the final dose of the repeated study), urinary excretion accounted for 1-4% (except 13-14% in the 10 mg/kg animals), and radioactivity in the bile of the 10 mg/kg animals was only 7-9% dose by 12 hours post-dose. The 10 mg/kg rats had slightly more radioactivity in urine and slightly less radioactivity in feces compared to the 1000 mg/kg rats. Bioaccumulation was not observed, and radioactivity in tissues was <0.1% dose in all animals at each study termination.
870.7600 Dermal penetration	100% dermal absorption factor (default value)
Special studies	Study not required.

Summary of Toxicological Doses and Endpoints for Mesosulfuron methyl for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary: All populations	No study in the toxicology database indicated there is an acute dietary endpoint of concern.		
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

DIETARY EXPOSURE:

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, mesosulfuron-methyl is not expected to pose an acute dietary risk. For chronic dietary consumption, exposure to mesosulfuron-methyl from food will utilize <1% of the cPAD for the U.S. population, <1% of the cPAD for infants < 1 year old, and <1% of the cPAD for children 1-12. In addition, there is potential for chronic dietary exposure to mesosulfuron-methyl in drinking water. After calculating DWLOCs and comparing them to the EECs for surface (0.15 ppb) and ground water (0.015 ppb), the aggregate exposure is not expected to exceed 100% of the cPAD. Mesosulfuron-methyl was classified as "not likely to be carcinogenic to humans".

EPA determined that the 10X FQPA Safety Factor to protect infants and children should be removed. The FQPA factor is removed because i) There is no evidence of increased quantitative/qualitative susceptibility in the available acceptable guideline studies; ii) There are no residual uncertainties for pre- and/or post-natal toxicity; iii) Clear NOAELs have been identified for the effects of concern; iv) 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; and v) There are no proposed residential uses.

NON-DIETARY EXPOSURE:

There are no residential uses for mesosulfuron-methyl that result in residential exposure to mesosulfuron-methyl.

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.

RESIDUE CHEMISTRY:

EPA has established tolerances for tolerances for residues of mesosulfuron-methyl on the raw agricultural commodities aspirated grain fractions at 0.60 ppm, meat byproducts of cattle, goat, horse, and sheep at 0.01 ppm, wheat forage at 0.60 ppm, wheat germ at 0.10 ppm, wheat grain at 0.03 ppm, wheat hay at 0.06 ppm, and wheat straw at 0.30 ppm. There are currently no Codex, Canadian, or Mexican MRL's or tolerances for mesosulfuron-methyl on wheat.

ENDANGERED SPECIES:

Endangered species Levels of Concern were exceeded for dicots in terrestrial habitats. At least one of eight listed endangered dicot plant species is located in counties where spring application to winter wheat is grown: Idaho (3 counties), Minnesota (5 counties), Montana (2 counties), Oregon (9 counties), Washington (8 counties), and Wyoming (1 county). This list was generated using a database which intersects AgCensus data (2001-2003) with endangered dicot plant species locations by county. It was not possible, given the constraints of a Tier 1 assessment, to analyze the spatial relationship of wheat acreage to endangered plant habitats on a county-by-county basis. The Tier 1 assessment has been

forwarded to FEAD for use in their endangered species assessment but FEAD has not started their assessment. Thus, the actual likelihood of exposure of specific endangered plants in specific counties is not known. In general, however, the high toxicity of mesosulfuron to plants indicate that it is likely that endangered plant species may be at risk from the proposed used of this chemical.

EPA is time limiting the registration of mesosulfuron-methyl for 2 years while the FEAD endangered species assessment is put in place. In the interim, to avoid adverse effects on endangered dicot species, the following mitigation measures will be imposed on the end use product labels in Counties where endangered species occur. For ground applications, the applicator must: 1) Apply only when there is sustained wind away from native plant communities, 2) Leave a 25 foot (Silverado) or 50 foot (Osprey) untreated buffer between treatment area and native plant communities, or 3) Use low pressure nozzles according to manufacturer's specifications that produce only coarse or very coarse droplets. For aerial applications, the applicator must: 1) Apply only when there is sustained wind away from native plant communities, or 2) Leave a 150 foot (Silverado) or 350 foot (Osprey) untreated buffer between treatment area and native plant communities.

ENVIRONMENTAL FATE:

Biotransformation is the major route of degradation of mesosulfuron in the environment, as evidenced by mineralization (i.e., formation of CO_2) in aerobic soils and persistence varying with microbial population and temperature. In water-sediment systems, persistence is also variable, mineralization is negligible, and non-extractable residues increase with time. Mesosulfuron produces degradates that have been identified for other sulfonylurea herbicides as well as degradates that are unique to this chemical.

Mesosulfuron exhibits weak binding to soils. Mesosulfuron, like other sulfonylurea herbicides, will predominate in the water phase and not in sediments. It has the potential to leach to ground water or reach surface water by runoff. Mesosulfuron has low potential to volatilize from soil or water or to bioaccumulate in fish.

Considering the widespread, potential use areas of variable soils, microbial population and activity, water bodies, climates/meteorology, and agricultural practices high variability in persistence in soil and water-sediment systems is expected.

ECOLOGICAL EFFECTS:

- Mesosulfuron is phytotoxic to endangered and non-endangered non-target terrestrial plants and and plants growing in semi-aquatic habitats. It is also phytotoxic to aquatic vascular plants. However, because the plant testing studies submitted were not performed using the appropriate proportions of active ingredient and safener to be representative of the products being proposed for registration, there is a large amount of uncertainty surrounding the degree of phytotoxicity that would be exhibited under actual use conditions. The data do suggest

that the principal risks to plants will be associated with foliar uptake (spray drift) compared with runoff exposure (seed emergence). In the absence of representative data, the endangered non-target terrestrial plant species spray drift assessment was performed using the most sensitive endpoint (lettuce EC05).

- A chronic reproductive effect (reduced number of live embryos to viable embryos) was observed in mallard duck; however, the NOAEC could not be determined (effects seen at lowest concentration tested - 38 ppm). No chronic reproductive effect was observed in the other bird species tested (bobwhite quail).

- Slightly toxic to freshwater fish (LC_{50} > 91.5 ppm) and freshwater aquatic invertebrates (LC_{50} > 90.2 ppm). In the chronic effects study for freshwater fish, the NOAEC /LOAEC is > 29.6 ppm, with no effects seen. In the chronic effects study for freshwater invertebrates, the NOAEC was 1.7 ppm and the LOAEC is 3.0 ppm, with the reproductive effects being a reduction in number of offspring/parent and body weight, and an increase in the time to first brood release.

- Practically non-toxic on an acute basis to the bobwhite quail and mallard duck (LD_{50} > 2,000 mg/kg), mammals (LD_{50} >7000 ppm), honey bee (LD_{50} > 13 ug/bee), and estuarine/marine fish (LC_{50} > 105 ppm). Practically non-toxic to the bobwhite quail and mallard on a sub-acute basis (LC_{50} > 4,750 ppm). Presumed nontoxic on a chronic basis to estuarine/marine fish based on the high LC_{50}s. No chronic or reproductive effects were observed in mammals (NOAEL of 1,000 ppm).

Mechanism of Pesticidal Action

Mesosulfuron-methyl belongs to the class of chemicals called sulfonyl ureas. The chemical works by inhibiting the enzyme acetolactate synthase (ALS), which leads to depletion of key amino acids that are necessary for protein synthesis and plant growth.

4. Summary of Regulatory Position and Rationale

Available data provide adequate information to support registration of the Mesosulfuron-methyl technical, Osprey Herbicide, and Silverado Wild Oat herbicide for use on wheat.

5. Required Labeling

- For OSPREY™ Herbicide, a preharvest interval (PHI) of 60 days for hay has been imposed.

- For SILVERADO™ Wild Oat Herbicide, only one application per growing season at up to 0.003 lb ai/A (2.25 oz/A) is allowed. Also, a preharvest interval (PHI) of 50

days for hay has been imposed.

- A plantback interval of 30 days has been imposed for barley.

6. Summary of Data Gaps

7. Contact Person at EPA

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