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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Pesticide Fact Sheet

Name of Chemical: Orthosulfamuron

Reason for Issuance: Conditional Registration

Date Issued: February 2007

Description of Chemical

Generic Name:	1-(4,6-dimethoxypryimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea
Common Name:	Orthosulfamuron
Trade Name:	IR5878
EPA PC Code:	108209
Chemical Abstracts Service (CAS) Number:	213464-77-8
Year of Initial Registration:	2007
Pesticide Type:	Herbicide
Chemical Class:	Sulfamoylurea
U.S. Producer:	Isagro S.p.A.

Use Patterns and Formulations

Application Sites:	Orthosulfamuron is registered for use on rice
Types of Formulations:	IR5878 Technical (EPA File Symbol 80289-4) IR5878 50 WG Herbicide (EPA File Symbol 80289-5) IR5878 0.5 GR Herbicide (EPA File Symbol 80289-6)

Application Methods And Rates:	IR5878 50 WG contains 50.0% orthosulfamuron in a water-dispersible granular formulation for use as an agricultural herbicide on wet-seeded or dry-seeded rice. The proposed application rate is 0.055-0.067 lbs ai/A, applied by groundboom and aerial equipment. IR5878 0.5 GR contains 0.50% orthosulfamuron in a granular formulation for use as an agricultural herbicide on permanently flooded rice. The proposed application rate is 0.067 lbs ai/A, applied by ground (tractor drawn spreader) and aerial equipment. Both proposed end-use products will be applied 1 time per year early in the growing season.

Regulatory Recommendations and Residue Chemistry Deficiencies

1. The registrant needs to submit an analytical reference standard to the National Pesticide Standards Repository.

2. For the submitted goat metabolism study (MRIDs 46578962 and 46578963), the registrant needs to provide the dates of sample extraction, initial TLC analysis, and metabolite identification analyses in order to determine sample storage intervals. If the initial quantitative TLC analyses were conducted within 6 months of sample collection, then supporting storage stability data will not be required to support the additional analyses for metabolite identification in goat matrices.

3. The registrant needs to submit radiovalidation data (using samples from the rice metabolism study) for the method chosen for tolerance enforcement purposes. A confirmatory method or method specificity data may also be needed. If the LC/MS/MS method (Report ISA-0102V) is proposed for tolerance enforcement, a separate confirmatory method would not be required if analyte identification is confirmed by analyzing sample extracts using LC/MS/MS and demonstrating that the ion ratios for the two MS/MS ion transitions acquired during analysis agree with the average ion ratios obtained from the calibration standards.

4. The registrant needs to follow specific directions for each multiresidue method used by FDA published in that Agency's Pesticide Analytical Manual, Vol. I (PAM Vol. I) and provide recovery data for orthosulfamuron through these methods.

Toxicology

Acute Oral Toxicity: IV
Acute Dermal Toxicity: IV
Acute Inhalation: IV
Primary Eye Irritation: III
Primary Dermal Irritation: IV

Endpoints

The chronic reference dose (0.05 mg/kg/day) is based on liver and kidney effects observed in a combined chronic/carcinogenicity study in rats, with a NOAEL of 5 mg/kg/day and a LOAEL of 500 mg/kg/day.

The short-term inhalation endpoint is based on kidney effects observed in a 2-generation study in rats, with a NOAEL of 88.6 mg/kg/day and LOAEL of 354.5 mg/kg/day.

Carcinogenicity

Orthosulfamuron is classified as demonstrating "suggestive evidence of carcinogenicity" based on thyroid follicular cell adenomas observed in male rats. The Agency has concluded that quantification of human cancer risk is not required and the NOEL selected for the cRfD is protective of cancer effects.

Neurotoxicity

There were decreases in motor activity seen in F1 male rats in a 2-generation reproduction study incorporated with Functional Observational Battery (FOB) observations at 5600 ppm (approximately equivalent to 354.5 mg/kg/day). The decrease in motor activity is considered an isolated finding since similar decreases were not seen in females or F2 animals.

Developmental Toxicity

There were no treatment-related effects observed in dams or offspring in the developmental toxicity studies in rats (LDT=1000 mg/kg/day) and rabbits (LDT=250 mg/kg/day).

Reproductive Toxicity

In the 2-generation reproduction study, increased incidences of kidney lesions were observed in the parental females of both generations. These lesions included tubular mineralization and urothelial hyperplasia observed at 5600 ppm (354.5 mg/kg/day). Additionally at 354.5 mg/kg/day, there were decreases in motor activity observed in F1 males (6 weeks of age). This finding is considered incidental since similar decreases were not seen in females or F2 animals.

FQPA Safety Factor

The FQPA safety factor has been reduced to 1X because there was no evidence of increased susceptibility, there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity, and the toxicological database is complete.

Dietary Exposure

Acute Risk. As there is no acute endpoint, an acute dietary risk assessment is not needed.

Chronic Risk. The chronic analysis is based on tolerance level residues and 100% crop treated assumptions. For drinking water, a conservative EDWC was used. This value was generated by EPA's Interim Rice Model for surface water. The general U.S. population and all population subgroups have risk estimates that are below the Agency's level of concern (i.e., 100% of the chronic population adjusted dose (cPAD)). The most highly exposed population subgroup is All Infants (<1 year old) which utilizes 57% of the cPAD. The general U.S. population utilizes 17% of the cPAD.

Aggregate risk. No residential uses are proposed. Therefore, aggregate risk consists of exposure from food and drinking water sources. See Acute Risk and Chronic Risk sections above.

Metabolism

Orthosulfamuron is a systemic herbicide belonging to the sulfamoylurea class of chemicals. The pesticidal mode of action (MOA) for orthosulfamuron is through inhibition of the plant enzyme acetolactate synthase, which is also known as acetohydroxy acid synthase. Inhibition of this enzyme blocks branch-chain amino acid biosynthesis of valine, leucine, and isoleucine involved in plant growth processes leading to death of the plant.

In rats, orthosulfamuron exposure results in increased incidences of thyroid follicular cell adenomas. The registrant has proposed a mitogenic mode of action for the tumorigenic effects of orthosulfamuron, which involves induction of uridinediphosphate-glucuronosyltransferase (UDP-GT), leading to increased elimination of thyroid hormone (T4) and subsequent pituitary release of thyroid stimulating hormone (TSH). The prolonged release of TSH results in thyroid hypertrophy, hyperplasia, and eventually, tumor formation. The CARC determined that it is possible that exposure to orthosulfamuron could cause thyroid tumors via perturbation of thyroid-pituitary functioning, due to enhanced hepatic clearance of thyroxin. However, the thyroid hormone data, which are critical to delineating a sequence of key events leading to tumor formation, are inadequate. Thus, the available data do not fully support the proposed MOA.

The nature of the residue in plants is adequately understood based on an acceptable rice metabolism study using two radiolabels. The parent was identified as a minor component (≤0.001-0.003 ppm), along with four metabolites. The nonextractable residues were shown to be incorporated into natural constituents. Based on the results of the study, parent orthosulfamuron is the residue of concern in rice for both tolerance expression and risk assessment. Orthosulfamuron appeared in rice grain at a very low level. DOP urea (N-(4,6-dimethoxypyrimidin-2-yl)urea) and DBS acid (2-sulfoamino-N,N-dimethylbenzamide) appeared in straw at 0.02 ppm and 0.04 ppm, respectively. Rice straw is not a human food commodity, however.

The nature of the residue in rotational crops is adequately understood. TRR ranged from 0.0007 to 0.8730 ppm in/on representative rotational crop commodities planted at various plantback intervals following treatment of soil with [^{14}C]orthosulfamuron at a 1x application rate (0.067 lb ai/A). Similar to the rice metabolism study, the parent was identified as a minor component along with other metabolites. Residues of DBS acid and DOP urea were found in carrot tops, wheat forage, and wheat straw. Wheat forage and straw are animal feed items only, however. In

carrot tops, the highest residue level for either DBS acid or DOP urea was only 0.0301 ppm (DOP urea at the 127-day plantback interval (PBI)). Rice may be rotated to any other crop after 30 days. Field rotational crop studies are not required at this time.

The nature of the residue in lactating ruminants is adequately understood pending submission of confirmatory storage stability data/information. The reviewed study showed low levels of total radioactive residues (TRR) in goat milk and tissues following oral dosing of goats with [^{14}C]orthosulfamuron, at feeding levels equivalent in the diet to 10.26-13.11 ppm (approximately 500-650x the theoretical dietary burden of 0.020 ppm for dairy cattle). The study found that the parent was degraded to metabolites either with the molecule bridge intact or broken between the pyrimidinyl and phenyl rings, and a significant amount of the residue in liver was eventually bound to protein. Based on the results of the study, determinations do not need to be made regarding residues of concern in ruminants. The theoretical dietary burdens for beef and dairy cattle are both 0.020 ppm.

The residue of concern in plants for both risk assessment and tolerance expression is parent orthosulfamuron. As there is no reasonable expectation of finite residues in animal commodities, the metabolites of concern in animal commodities are not being determined at the present time. Tolerances are not needed for rotational crops, therefore the residue of concern in rotational crops is not being determined at the present time.

The proposed use of orthosulfamuron on rice is considered to fall under Section 3 of 40 CFR §180.6(a) (no expectation of finite residues in animal commodities). Therefore, tolerances for meat, milk, poultry, and eggs are not required for the purposes of this petition only. At the present time, the Agency grants the waiver request for a poultry metabolism study. Residue analytical methods and storage stability data for animal commodities are not required. This determination is based on the results of the rice field trials and processing studies in which residues of orthosulfamuron were below the method LOQ of 0.05 ppm in/on all samples of rice grain and straw that were treated at a 1x application rate. The decision is also based on the low orthosulfamuron dietary burdens for dairy and beef cattle (0.020 ppm), poultry (0.022 ppm), and swine (0.013 ppm).

Based on the Interim Rice model and SCI-GROW models, the estimated environmental concentration (EECs) of orthosulfamuron in drinking water for chronic exposures is estimated to be 40.5 parts per billion (ppb) for surface water and 0.611 ppb for ground water.

No Codex maximum residue limits (MRLs) have been established for residues of orthosulfamuron on any crops at this time.

Worker Exposure

IR5878 50 WG contains 50.0% orthosulfamuron in a water-dispersible granular formulation for use as an agricultural herbicide on wet-seeded or dry-seeded rice. The proposed application rate is 0.055-0.067 lbs ai/A, applied by groundboom and aerial equipment. IR5878 0.5 GR contains 0.50% orthosulfamuron in a granular formulation for use as an agricultural herbicide on permanently flooded rice. The proposed application rate is 0.067 lbs ai/A, applied by ground

(tractor drawn spreader) and aerial equipment. Both proposed end-use products will be applied 1 time per year early in the growing season. Based on the number of seasonal applications indicated on the product labels, and information provided by the registrant, handler exposures are expected to be short-term in duration.

Handlers

No chemical-specific data for assessing handler exposures were submitted to the Agency in support of the proposed uses. As a result, surrogate data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1 was used, and standard values established by the Health Effects Division (HED) Science Advisory Council for Exposure, for acres treated per day, body weight, and the level of personal protective equipment worn by handlers. The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure (from PHED) and an upper-percentile assumption for the application rate, and are considered to be representative of high-end exposures. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgment.

A quantitative risk assessment for the dermal exposure route is not required. There were no adverse systemic or dermal effects seen up to the limit dose tested (LDT) of 1,000 mg/kg/day in the dermal toxicity study. The inhalation MOEs for short-term handler exposure range from 47,000 to 1,800,000 and the estimated risks do not exceed HED's level of concern (MOEs <100).

Postapplication

No postapplication chemical-specific data were submitted in support of this registration action. A dermal non-cancer agricultural short-term postapplication exposure assessment is not required due to the absence of systemic toxicity in the dermal toxicity study.

Orthosulfamuron has a medium vapor pressure of 1.1×10^{-4} mmHg at 20°C. Short-term postapplication inhalation exposures are expected to be minimal and less than the application exposures. Consequently, a quantitative postapplication inhalation exposure assessment was not performed.

Residential Exposure

Currently there are no proposed residential uses for orthosulfamuron.

Residue Chemistry

Tolerance levels are proposed as follows

Rice, grain……0.05 ppm
Rice, straw……0.05 ppm

Potential Risks to Non-Target Organisms

There is a potential for direct adverse acute effects to non-target non-vascular plants, freshwater vascular plants, and terrestrial and semi-aquatic plants. There is a limited potential for direct adverse effects to animal species associated with the use of orthosulfamuron on rice and indirect effects may result as a consequence of potential direct effects on plants. Potential risks appear to be greatest for aquatic vascular plant species and terrestrial and semi-aquatic dicotyledonous plants since these organisms appear to be very sensitive. Functionally, estimated risks may translate to reduced survival, reproduction, or growth in affected species with the potential for subsequent effects at higher levels of biological organization.

For federally listed endangered or threatened (hereafter "listed") species, acute risk levels of concern were exceeded for aquatic vascular plants, semi-aquatic monocot and dicot plants, and terrestrial monocot and dicot plants. No listed species acute or chronic LOCs were exceeded for any animal species evaluated in this assessment. Because aquatic plant risk quotients are above the non-endangered species level of concern, the Agency considers this to be indicative of a potential for adverse effects to those listed species that rely either on a specific plant species (plant species obligate) or multiple plant species (plant dependant) for some component of their life cycle.

There is a potential to affect some listed plant species and the species which depend upon listed or non-listed plant species. Indirect effects in this case should be considered for both terrestrial and aquatic animal species. The extent to which the proposed uses of orthosulfamuron will directly effect plant species and indirectly effect animal species will require further assessment; specifically, clear delineation of action area, identification of listed species that co-occur in areas of orthosulfamuron use, species-specific life history information, and an evaluation of critical habit.

Environmental Fate Characterization

Orthosulfamuron has low volatility and exhibits acid-base behavior, being increasingly soluble in water as pH increases. It readily hydrolyzes in hours to days at low pH (<7), but slowly hydrolyzes (half-life of months) at high pH (>7). Moderate biodegradation and slow photolysis (half-lives of months) also occur in aquatic environments. Orthosulfamuron is moderately mobile in soil and shows affinity to organic carbon. The compound presents a ground water concern in alkaline, sandy soils with a Freundlich soil-to-water partition coefficient (K_f) as low as 2.0 (1/n = 1.02).

Orthosulfamuron's major route of degradation in acidic to neutral rice paddy water is hydrolysis, with a half-life of hours to days. Aerobic biodegradation is the major route of degradation in alkaline rice paddy water, with a half-life of weeks to months. Both routes of degradation are expected at similar rates (*i.e.* half-lives of weeks) in paddy water of neutral pH.

Major degradates include hydrolysis products N-(4,6-dimethoxypyrimidin-2-yl)urea (DOP urea; S12), 2-dimethylcarbamoylphenyl sulfamic acid (DBS acid; S1), and 2 amino-N,N-dimethylbenzamide (DB amine; S4) and demethylation product 1-(4-hydroxy-6-

methoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea (o-desmethyl orthosulfamuron; S9). Both orthosulfamuron and its o-desmethyl degradate hydrolyze to DBS acid, which, in turn, hydrolyses to DB amine. However, all four degradates are moderately persistent, as peak detections of these degradates occurred at up to 100-186 days after application.

Environmental Effects Characterization

Orthosulfamuron is practically non-toxic to birds, mammals, and honeybees under acute exposure conditions and only slightly toxic to fish and freshwater aquatic invertebrates. Orthosulfamuron is highly toxic to aquatic vascular plants, non-vascular plants, and terrestrial plants following acute exposure. In terrestrial plants, dicotyledonous plants appear more sensitive to orthosulfamuron compared to monocotyledonous plants.

Data Gaps and Uncertainties

No data are available to assess the potential risks associated with the major degradates of orthosulfamuron, including the degradate of risk concern, o-desmethyl orthosulfamuron. While these data are not required, the potential toxicity of orthosulfamuron degradates is a source of uncertainty.

RQs That Exceed the Acute Risk LOC

The non-listed species acute risk LOC is exceeded for aquatic vascular plants (RQ = 55). For listed species, the acute risk LOC of 1.0 is exceeded for aquatic vascular plants and saltwater non-vascular plants with RQs of 148 and 1.8, respectively. For non-listed dicotyledonous terrestrial and semi-aquatic plants adjacent to orthosulfamuron treated paddies, the RQ exceeds the acute risk LOC (RQ = 5.75 ground spray & RQ = 28.8 aerial spray) as a result of drift. For listed terrestrial and semi-aquatic plants species, RQs exceeded the acute risk LOC for monocots (RQ = 2.45 tail water release & RQ = 2.04 aerial spray) and dicots (RQ = 2.45 tail water release, RQ = 25.56 ground spray, & RQ = 127.78 aerial spray). Restrictive label language including spray drift management and buffers of 25 feet for ground application and 200 feet for aerial application reduces the risk to non target organisms (similar to label language that has been imposed on other sulfamoylurea herbicides).

Required Labeling

Hazards to Humans and Domestic Animals: Harmful if swallowed, absorbed through skin, or inhaled. Causes moderate eye irritation. Avoid contact with skin, eyes, or clothing. Avoid breathing dust or spray. Wear protective eyewear.

Personal Protective Equipment (PPE): Long-sleeved shirt and long pants, Shoes plus socks, Chemical-resistant gloves made of any waterproof material, and protective eye wear.

Restricted Entry Interval (REI): 12 hrs.

User Safety Recommendations: Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet. Users should remove clothing/PPE immediately if pesticide gets inside. Then wash skin thoroughly and put on clean clothing.

IR5878 50 WG Herbicide (EPA File Symbol 80289-5) Labeling Language Proposed by Registrant to Protect Non-Target Organisms

Spray Drift Management

Avoiding spray drift is the responsibility of the applicator. The interaction of weather related factors and equipment determine the potential for spray drift. Application should only be made when there is little or no hazard of spray drift. The applicator, crop consultant, and/or grower are responsible for considering all factors when determining whether or not to apply this product. Avoid all direct or indirect contact with non-target plants. Do not apply directly to or near desirable vegetation. Allow an adequate distance between target application area and desirable plants to minimize any potential exposure.

Sensitive Areas: Pesticides should only be applied when the potential for spray drift to adjacent sensitive non-target areas (e.g., residential areas, known habitat for threatened or endangered plant species, bodies of water, non-target crops) is minimal (e.g., when wind is blowing away from the sensitive areas). Avoid disturbing (e.g. cultivation) treated areas for at least 7 days following application.

Sensitive Crops: For cotton, aerial applications shall not be made closer than 4 miles to the crop. Ground applications shall not be closer than 1 mile from sensitive crops, unless wind direction during the ground application is away from sensitive crops. When wind direction during the ground application is away from sensitive crops, ground applications shall not be made closer to 0.5 miles from sensitive crops.

The following drift management requirements must be followed to avoid off-target spray drift movement from aerial applications:

1. The distance between the outer most nozzles on the boom must not exceed 70% of the wingspan of fixed-wing aircraft or 80% of the helicopter rotor width

2. Nozzle set up must use a coarse spray quality category per ASAE S-572 Standard

States that have more stringent spray drift regulations must be followed.

The applicator should be familiar with and take into account the information covered in the Aerial Spray Drift Reduction Section. In general, the best spray drift management strategy is to apply the largest droplets that provide sufficient coverage and control.

Endangered Species

If endangered plant species occur in the proximity of the application site, the following mitigation measure is required to avoid adverse nontarget effects:

- Leave untreated downwind buffer zones of 25 feet for ground applications or 200 feet for aerial applications

To determine whether your county has an endangered terrestrial plant species, consult http:/www.epa.gov/espp/usa-map.htm. Endangered Species Bulletins may also be obtained from state or county extension offices or state pesticide agencies. If the bulletin is not available for your specific area, check with the appropriate local state agency to determine if known populations or terrestrial endangered plants occur in the area to be treated.

Contact Person at EPA

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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.

Physical and Chemical Properties

Physical and Chemical Properties of Orthosulfamuron.	
Color	White
Physical State	Fine Powder at 20°C
Odor	Odorless
pH	4.35 at 25°C (1% aqueous dispersion)
Density	1.45 g/mL at 20°C
Water solubility at 20°C	pH 4 buffer: 0.062 g/L pH 7 buffer: 0.63 g/L pH 8.5 buffer: 39 g/L
Solvent solubility at 20°C	n-heptane: 0.23 mg/L

	xylene: 130 mg/L acetone: 20 g/L ethyl acetate: 3.3 g/L dichloromethane: 56 g/L methanol: 8.3 g/L
Vapor pressure	1.1×10^{-4} mmHg at 20°C
Dissociation constant, pK_a	The test material becomes increasingly less soluble in water as the pH is lowered and undergoes degradation (hydrolysis) at neutral to acidic pHs. The test material is predicted to have 5 overlapping dissociation constants.
Octanol/water partition coefficient, $Log(K_{OW})$	pH 4: 2.0 pH 7: 1.3
UV/visible absorption spectrum	at pH 6.9, A=0.49 and $\varepsilon = 2.1 \times 10^4$ at 238 nm

Toxicology Characteristics

Acute Toxicity of Orthosulfamuron			
Guideline No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral - rat	$LD_{50} > 5000$ mg/kg	IV
870.1200	Acute Dermal - rat	$LD_{50} > 5000$ mg/kg	IV
870.1300	Acute Inhalation - rat	$LC_{50} > 2.19$ mg/L	IV
870.2400	Primary Eye Irritation - rabbit	Formulation is moderately irritating to the eye	III
870.2500	Primary Skin Irritation - rabbit	Not an irritat to the skin	IV
870.2600	Dermal sensitization - guinea pig	Not a dermal sensitizer	N/A

Subchronic, Chronic and Other Toxicity Profile for Orthosulfamuron				
Guideline No.	Study Type	MRID No. (year)/ Classification	Dose levels	Results
870.3100	90-Day oral toxicity (rat)	46260103 (2001) Acceptable/ Guideline	ppm= 0, 250, 1500, 9000 mg/kg/day= M: 0, 19, 113, 706 F: 0, 22, 131, 773	NOAEL = 706 mg/kg/day LOAEL = not determined
870.3100	90-Day oral toxicity (mouse)	46260102 (2001) Acceptable/ Guideline	ppm= 0, 250, 1250, 6000 mg/kg/day= M: 0, 36, 187, 865 F: 0, 47, 228, 1096	NOAEL = 865 mg/kg/day LOAEL = not determined
870.3150	90-Day oral toxicity (dog)	46219027 (2001) Acceptable/ Guideline	mg/kg/day= 0, 150, 450, 1000	NOAEL = 450 mg/kg/day LOAEL = 1000 mg/kg/day, based on increased alkaline phosphatase levels, increased absolute and relative liver weights
870.3200	21/28-Day dermal toxicity (rat)	46578911 (2004) Acceptable/ Guideline	mg/kg/day= 0, 1000	Systemic/Dermal NOAEL = 1000 mg/kg/day LOAEL = not determined
870.3700a	Prenatal developmental in (rat)	46219031 (2001) Acceptable/ Guideline	mg/kg/day= 0, 100, 300, 1000	Maternal NOAEL = 1000 mg/kg/day LOAEL = not determined Developmental NOAEL = 1000 mg/kg/day LOAEL = not determined
870.3700b	Prenatal developmental in (rabbit)	46219029 (2001) Acceptable/ Guideline	mg/kg/day= 0, 25, 75, 250	Maternal NOAEL = 250 mg/kg/day LOAEL = not determined Developmental NOAEL = 250 mg/kg/day LOAEL = not determined
870.3800	Reproduction and fertility	46219033 (2003)	ppm=(males/females) 0, 350/225,	Parental/Systemic NOAEL = M=-88.6-97.0/ F=102.2-111.2 mg/kg/day

	effects (rat)	Acceptable/ Guideline	1400/900, 5600/3600 mg/kg/day= F_0M: 0, 22.2, 88.6, 354.5 F_0F: 0, 25.6, 102.2, 408.9 F_1M: 0, 24.3, 97.0, 388.1 F_1F: 0, 27.8, 111.2, 444.6	LOAEL = M=-354.5-388.1/F=408.89-444.6 mg/kg/day, based on kidney lesions (tubular mineralization and urothelial hyperplasia) in F_0 and F_1 females. Reproductive NOAEL = M=-354.5-388.1/F=408.89-444.6 mg/kg/day LOAEL = not determined Offspring NOAEL = M=-88.6-97.0/ F=102.2-111.2 mg/kg/day LOAEL = M=-354.5-388.1/F=408.89-444.6 mg/kg/day, based on decreased motor activity in F_1 males at 6 weeks.
870.4100	Chronic toxicity (dog)	46578987 (2001) Acceptable/ Guideline	mg/kg/day= 0, 75, 300, 1000	NOAEL = 75 mg/kg/day LOAEL = 300 mg/kg/day, based on changes observed in body weights, body weight gains, food consumption (females), hematology and clinical chemistry, increased liver weights, and histopathological changes in the liver, and bone marrow of the sternum
870.4200	Carcinogenicity (rat)	46578913 (2001) Acceptable/ Guideline	mg/kg/day= 0, 1, 5, 500, 1000	NOAEL = 5 mg/kg/day LOAEL = 500 mg/kg/day, based on decreased body weight gains, slight hepatotoxicity, slight nephrotoxicity in both sexes, and thyroid effects in males. Evidence of carcinogenicity seen at 500 and 1000 mg/kg/day in the form of thyroid follicular cell adenoma in males.
870.4300	Carcinogenicity	46578912 (2003)	mg/kg/day= 0, 100, 500,	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day, based on increases in absolute

	(mouse)	Acceptable/ Guideline	1000	and relative liver weights, centrilobular hepatocyte hypertrophy and centrilobular hepatocyte vacuolation in males. There was no evidence of carcinogenicity in mice.
870.5100	BACTERIAL REVERSE MUTATION ASSAY (IR5878)	46219034	---	Negative
	BACTERIAL REVERSE MUTATION ASSAY (Metabolite-IR7863)	46578919	---	Negative
	BACTERIAL REVERSE MUTATION ASSAY (Metabolite-IR8181)	46578923	---	Negative
	BACTERIAL REVERSE MUTATION ASSAY (Metabolite-IR8181)	46578916	---	Negative
870. 5300	IN VITRO MAMMALIAN CELL GENE MUTATION TEST (IR5878)	46219036	---	Negative

	IN VITRO MAMMALIAN CELL GENE MUTATION TEST (Metabolite-IR7863)	46578920	---	Negative
	IN VITRO MAMMALIAN CELL GENE MUTATION TEST (Metabolite-IR8181)	46578925	---	Negative
	IN VITRO MAMMALIAN CELL GENE MUTATION TEST (Metabolite-IR7825	46578914	---	Negative

870. 5375	IN VITRO CHROMOSOME ABERRATION TEST (IR5878)	46219035	---	Negative
	IN VITRO CHROMOSOME ABERRATION TEST (Metabolite-IR7863)	46578921	---	Negative
	IN VITRO CHROMOSOME ABERRATION TEST (Metabolite-IR8181)	46578924	---	There was evidence of chromosome aberrations induced over background in the absence and presence of S9 activation.
	IN VITRO CHROMOSOME ABERRATION TEST (Metabolite-IR7825)	46578917	---	Negative
870.5395	MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST (IR5878)	46219037	---	Negative
	MAMMALIAN ERYTHROCYTE	46578926	---	Negative

	MICRONUCLEUS TEST (Metabolite-IR8181)			
870.7485	Metabolism and pharmacokinetics (species)	46578905-46578910	mg/kg/day = Low dose: 5 High dose: 1000 Repeated low dose = 5	Absorption was rapid in all groups, regardless of sex, dose, or number of doses. T_{max} values were 12 min for the 5 mg/kg repeated dose group, 24 min-1 h for the single 5 mg/kg dose group, and 1-4 h for the single 1000 mg/kg dose group. Following a single 5 mg/kg dose of [^{14}C-U-phenyl] IR5878, 76-82% of the dose was absorbed and found in the urine/cage wash, bile, and carcass, indicating extensive absorption. The half-life was similar regardless of sex, dose, or number of doses (8.9-13.3 h), with the exception of the females treated with a single 5 mg/kg dose of [^{14}C-5-pyrimidinyl] IR5878 (16.7 h).
Non-Guideline	Thyroid MOA Investigation Study	46578927	0, 5, and 1000 mg/kg/day	Transient decreases in T3 at 5 and 1000 mg/kg/day (D30), and no reductions in T4. In creased TSH levels at D 90 at 1000 mg/kg/day. TSH levels comparable to controls at all other doses and time points. Liver and thyroid histopathology, and enzyme changes,

Toxicological Endpoints

Toxicological Doses and Endpoints for Orthosulfamuron for Use in Dietary and Non-Occupational Human Health Risk Assessments			
Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
N/A	N/A	N/A	No appropriate endpoint attributable to a single dose identified for this population.
N/A	N/A	N/A	No appropriate endpoint attributable to a single dose identified for this population
NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Chronic RfD =0.05 mg/kg/day cPAD = 0.05mg/kg/day	Combined Chronic/Carcinogenicity-Rat LOAEL (mg/kg/day): 500, based on decreased body weight gains, hepatotoxicity and nephrotoxicity in both sexes.
Classification: "Suggestive Evidence of Carcinogenicity" Quantification is not required and the cRfD is considered protective of the cancer effects.			

(NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.)

Summary of Toxicological Doses and Endpoints for Orthosulfamuron for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal (all exposures)	N/A	N/A	N/A	The risk assessment is not required.
Inhalation Short-(1-30 days)	NOAEL= 88.6 mg/kg/day	UF_A=10x UF_H=10x IAF=100%	Occupational LOC for MOE = 100	2-Generation Reproduction -Rat LOAEL (mg/kg/day): 354.5, based on kidney lesions in F_0 and F_1 females.
Cancer (oral, dermal, inhalation)	Classification: "Suggestive Evidence of Carcinogenicity" Quantification is not required and the cRfD is considered protective of the cancer effects.			