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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

Date: October 31, 2005

MEMORANDUM

Subject: EPA File Symbol: 80289-U: IR5878 TECHNICAL
DP Barcode: D319036
Decision No.: 358188
PC Code: 108209 Orthosulfamuron (CAS #213464-77-8)

From: Byron T. Backus, Ph.D. Byron T. Backus 10/31/05
Technical Review Branch
Registration Division (7505C)

To: Jim Tompkins RM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

Registrant: ISAGRO S.P.A.

FORMULATION DECLARATION FROM LABEL:

Active Ingredient(s):	% by wt
ORTHOSULFAMURON (CAS #213464-77-8)	98.0%
Inert Ingredients:	2.0%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

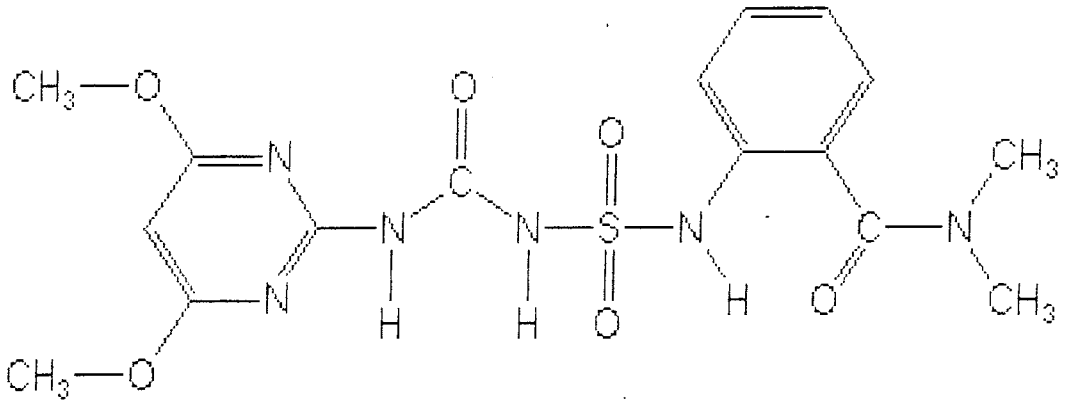
"...Please review the attached studies in support of registration."

BACKGROUND:

This package contains the following: an acute inhalation toxicity study with IR5878 (MRID 46578990); an acute oral toxicity study (acute toxic class method) with IR8181 (MRID 46578922); an acute oral toxicity study with IR7863 (; and an acute oral toxicity study with IR7825. No information is provided as to the chemical identities or structures of IR7863 or IR7825, or as to their relationship (metabolities? impurities?) to IR5878. However, IR8181 is identified as 1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-

hydroxy-6-methoxy-2-pyrimidinyl) urea.

The structure of IR5878 (orthosulfamuron, a pyrimidinylsulfonylurea herbicide) is the following:



The CAS Reg. No. is 213464-77-8; the IUPAC is 1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl] urea and the CAS is 2-[[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]amino]-*N,N*-dimethylbenzamide. The formula is $C_{16}H_{20}N_6O_6S$.

COMMENTS AND RECOMMENDATIONS:

1. The acute oral toxicity study (acute toxic class method) in MRID 46578915 with IR7825 indicates the test material is in toxicity category III (with an oral LD_{50} > 2000 mg/kg)in terms of potential oral exposure. However, no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical. If this information is provided the study can probably be graded to acceptable. Without this information, the study does not currently satisfy the guideline requirement for an acute oral toxicity study (OPPTS 870.1100; OECD 423) in the rat.

2. The acute oral toxicity study (acute toxic class method) with IR8181 (chemical name: 1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea) in MRID 46578922 indicates the test material is in toxicity category III (with an oral LD_{50} > 2000 mg/kg) in terms of potential oral exposure. As the test material is identified by its chemical name the study is classified as acceptable - guideline, and satisfies the guideline requirement for an acute oral toxicity study (OPPTS 870.1100; OECD 423) in the rat.

3. The acute oral toxicity study (acute toxic class method) in MRID 46578918 with IR7863 indicates the test material is in toxicity category III (with an oral LD_{50} > 2000 mg/kg) in terms of potential oral exposure. However, no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical. If this information is provided the study can probably

be graded to acceptable. Without this information, the study does not currently satisfy the guideline requirement for an acute oral toxicity study (OPPTS 870.1100; OECD 423) in the rat.

4. The acute inhalation study for IR5878 0.5% GR in MRID 46578990 has been classified as acceptable - guideline. It indicates an LC_{50} > 1.871 mg/L and defines a toxicity category III hazard by this exposure route. While the analytically determined concentration was 3.238 mg/L, the MMAD value (6.89 µm) was greater than that recommended in Agency guidelines (approximately 20% of the particles had diameters less than 3 µm, and approximately 30% were less than 4 µm), and it was concluded that this precludes a toxicity category IV inhalation categorization.

Reviewer: Byron T. Backus, Ph.D. October 31, 2005
Risk Manager: 25

STUDY TYPE: Acute Oral Toxicity (Acute Toxic Class Method) - WIST (SPF) Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: IR7825, Batch No. FCF/T/198-01 (ex 20687/38) purity 99.3%, described as a white solid; expiry date July 2005. For the purposes of dosage this test material was administered (as a suspension and/or solution) in Polyethylene Glycol 300 (PEG 300) with an application volume of 10 mL/kg (0.2 g test material/mL).

CITATION: Arcelin, G. (2003) IR7825: Acute Oral Toxicity Study in Rats. RCC Ltd., Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Study No. 848210. July 2, 2003. 20 pages. MRID 46578915. Unpublished.

SPONSOR: ISAGRO SpA, Milano, Italy

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46578915) 6 female HanBrl: WIST (SPF) 12-week-old rats (source: RCC Ltd. Laboratory Animal Services, CH-4414 Füllinsdorf, Switzerland; weights 180.4-195.8 g at dosage) were orally gavaged with a dose of 2000 mg/kg IR7825, Batch No. FCF/T/198-01 (ex 20687/38), 99.3% purity. The test material was diluted in PEG 300 to 0.2 g/mL and the suspension/solution was administered by gavage on Day 1 at a constant dose volume of 10 mL/kg. Rats were observed for 14 days after administration. There were no clinical signs of toxicity and no mortalities. All rats gained weight from Day 1 to 8. One female showed a weight loss of 2.1% (4.1 g) from Day 8 to 15; all other rats gained in this period. Post-sacrifice necropsies showed no macroscopic findings.

Oral LD_{50} (Female rat) > 2000 mg/kg (0/6 died).

Toxicity based on the absence of mortality at the limit dose of 2000 mg/kg. EPA Toxicity Category III.

Currently, the study is classified as Supplementary. Although this study defines an EPA Toxicity Category III oral hazard potential for the test material (IR 7825, purity 99.3%), no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical. If this information is provided, the study can probably be upgraded to acceptable. Without this information, the study does not currently satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP (p. 3) , Quality Assurance (p. 9), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	n/a	0/6	0/6

A. **Mortality** - as noted in table.

B. **Clinical observations** - All animals survived the 2000 mg/kg dose without clinical signs. All gained weight in the period from Day 1 (the day of dosage) to 8, and 5/6 gained weight in the period from Day 8 to 15. One rat had a weight loss of 4.1 g between Day 8 and 15.

C. **Gross Necropsy** - Post-sacrifice gross necropsy results were normal.

D. **Reviewer's Conclusions:** The test material (IR 7825, purity 99.3%) is in EPA Toxicity Category III in terms of its oral hazard potential, However, as no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical the study does not currently satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat. If this information is provided, the study can probably be upgraded to acceptable.

Reviewer: Byron T. Backus, Ph.D. October 28, 2005
Risk Manager: 25

STUDY TYPE: Acute Oral Toxicity (Acute Toxic Class Method) - WIST Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: IR8181, chemical name: 1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea; Batch No. 30072/85, purity 97.02%, described as a whitish fine odorless powder; expiry date October 2005. For the purposes of dosage this test material was administered by gavage (as a suspension and/or solution) in 1% CMC (Carboxymethylcellulose) in aqua ad inject. at a volume of 10 mL/kg (0.2 g test material/mL).

CITATION: Haist, I. (2204) Acute Oral Toxicity: Acute Toxic Class Method with IR8181. BSL Bioservice Scientific, 82152 Planegg, Germany. Study No. 040381. April 27, 2004. 23 pages. MRID 46578922. Unpublished.

SPONSOR: ISAGRO SpA, Milano, Italy

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46578922) 3 female and 3 male HanBrl: WIST (Full-Barrier) rats (source: Harlan Winkelmann GmbH, D-33178 Borchen; body weights: females: 136-141 g; males: 158-160 g) were orally gavaged with a dose of 2000 mg/kg IR8181 [chemical name: 1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea]; Batch No. 30072/85, purity 97.02%, described as a whitish fine odorless powder]. The test material was diluted in 1% CMC (Carboxymethylcellulose) in aqua ad inject. to 0.2 g/mL and the suspension/solution was administered on Day 0 at a constant dose volume of 10 mL/kg. Rats were observed for 14 days after administration. There were no clinical signs of toxicity and no mortalities. All rats gained weight from Day 0 to 7 and again from Day 7 to 14. Post-sacrifice necropsies showed no macroscopic findings.

Oral LD_{50} (Female rat) > 2000 mg/kg (0/3 died)
Oral LD_{50} (Male rat) > 2000 mg/kg (0/3 died)

Toxicity based on the absence of mortality at the limit dose of 2000 mg/kg. EPA Toxicity Category III.

This study defines an EPA Toxicity Category III oral hazard potential for the test material (IR8181, purity 97.02%). As the test material is identified by its chemical name (1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea) the study is classified as acceptable - guideline. This study satisfies the guideline requirement for an acute oral toxicity study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP (p. 10), Quality Assurance (p. 11), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/3	0/3	0/6

A. **Mortality** - as noted in table.

B. **Clinical observations** - All animals survived the 2000 mg/kg dose without clinical signs. All gained weight in the period from Day 0 (the day of dosage) to 7, and from Day 7 to 14.

C. **Gross Necropsy** - Post-sacrifice gross necropsy results were normal.

D. **Reviewer's Conclusions:** The test material (IR 8181, purity 97.02%) is in EPA Toxicity Category III in terms of its oral hazard potential. Since information is provided as to its chemical identity [chemical name: 1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea] the study satisfies the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

Reviewer: Byron T. Backus, Ph.D. October 28, 2005
Risk Manager: 25

STUDY TYPE: Acute Oral Toxicity (Acute Toxic Class Method) - WIST (SPF) Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: IR7863, Batch No. 20687/50, purity 97.8%, described as a white solid; expiry date July 2005. For the purposes of dosage this test material was administered (as a suspension and/or solution) in purified water with a dosage volume of 10 mL/kg (0.2 g test material/mL).

CITATION: Ott, M. (2003) IR7863: Acute Oral Toxicity Study in Rats. RCC Ltd., Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Study No. 850107. September 17, 2003. 20 pages. MRID 46578918. Unpublished.

SPONSOR: ISAGRO SpA, Milano, Italy

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46578918) 3 female and 3 male HanBrl: WIST (SPF) 12-week-old rats (source: RCC Ltd. Laboratory Animal Services, CH-4414 Füllinsdorf, Switzerland; females: 12 weeks; males: 9 weeks; weights: females: 183.0-203.1 g; males: 225.4-238.5 g at dosage) were orally gavaged with a dose of 2000 mg/kg IR7863 (97.8%). The test material was diluted in purified water to 0.2 g/mL and the suspension/solution was administered on Day 1 at a constant dose volume of 10 mL/kg. Rats were observed for 14 days after administration. There were no clinical signs of toxicity and no mortalities. All rats gained weight from Day 1 to 8 and again from Day 8 to 15. Post-sacrifice necropsies showed no macroscopic findings.

Oral LD_{50} (Female rat) > 2000 mg/kg (0/3 died).
Oral LD_{50} (Male rat) > 2000 mg/kg (0/3 died).

Toxicity based on the absence of mortality at the limit dose of 2000 mg/kg. EPA Toxicity Category III.

Currently, the study is classified as Supplementary. Although this study defines an EPA Toxicity Category III oral hazard potential for the test material (IR 7863, purity 97.8%), no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical. If this information is provided, the study can probably be upgraded to acceptable. Without this information, the study does not currently satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP (p. 3) , Quality Assurance (p. 9), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/3	0/3	0/6

A. **Mortality** - as noted in table.

B. **Clinical observations** - All animals survived the 2000 mg/kg dose without clinical signs. All gained weight in the period from Day 1 (the day of dosage) to 8, and again from Day 8 to 15.

C. **Gross Necropsy** - Post-sacrifice gross necropsy results were normal.

D. **Reviewer's Conclusions:** The test material (IR 7863, purity 97.8%) is in EPA Toxicity Category III in terms of its oral hazard potential, However, as no information is given as to the chemical identity (structure) of this test material or its relationship (metabolite? impurity?) to IR5878 technical the study does not currently satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat. If this information is provided, the study can probably be upgraded to acceptable.

Reviewer: Byron T. Backus, Ph.D. October 31, 2005
Risk Manager: 25

STUDY TYPE: Acute Inhalation Toxicity - WIST rats; OPPTS 870.1300; OECD 403

TEST MATERIAL: IR5878 0.5% GR, Batch No. G 003/03, containing 0.49% active, described as solid granules with an expiry date of September 2005.

CITATION: Decker, U., Knuppe, C. & Ullrich, A. (2004) IR5878 0.5 GR: 4-Hour Acute Inhalation Toxicity Study in Rats. RCC Ltd., Wölferstrasse 4, CH-4452 Füllinsdorf, Switzerland. Study No. 849646. May 14, 2004. 86 pages. MRID 46578990. Unpublished.

SPONSOR: ISAGRO SpA, Milano, Italy

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46578990), five/sex of HanBrl:WIST(SPF) young (males: 9 weeks; females: 10 weeks) adult albino rats (Source: RCC Ltd. Laboratory Animal Services, CH-4414 Füllinsdorf, Switzerland; Weights: Males: 242.7-252.3 g; females: 201.7-211.2 g) were exposed nose only via the inhalation route to IR5878 0.5 GR (Batch No. G 003/03 0.49% IR5878, described as solid granules) for 4 hours at a mean gravimetric concentration of 1.871 mg/L, and a chemically-determined (based on amount of IR5878) concentration of 3.238 mg/L. Prior to its use in this study the test material was ground twice in a granulation machine, twice in a pin mill, and four times in an air jet mill. The nominal concentration was 9.41 mg/L. The MMAD was 6.89 µm and the mean GSD was 2.78. Approximately 20% of the particles had diameters less than 3 µm, and approximately 30% of the particles had diameters less than 4 µm.

LC_{50} Males = > 1.871 mg/L (gravimetric concentration) - 0/5 died
LC_{50} Females = > 1.871 mg/L (gravimetric concentration) - 0/5 died
LC_{50} Combined = > 1.871 mg/L (gravimetric concentration) - 0/10 died.

All animals survived following exposure at 1.871 mg/L (gravimetric concentration). No clinical signs were noted during or after the exposure. All males and 3/5 females gained weight in the period from Day 1 (day of exposure) through Day 4; two females had slight weight losses (0.2 and 1.7 g). All rats gained weight in the period from Day 4 to 8 and again from Day 8 to 15.

Necropsy results were normal for all 10 animals.

Toxicity based on lack of deaths following 4-hour exposure to 1.871 mg/L. EPA Toxicity Category III.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat for this specific formulation (IR5878 0.5% GR, Batch No. G 003/03, containing 0.49% active, described as solid granules).

COMPLIANCE: Signed and dated GLP (p. 3), Quality Assurance (p. 5), and Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Nominal Concentra -tion(mg/L)	Analytical Concentra-tion (mg/L)	Gravimetric Concentra-tion (mg/L)	MMAD µm	GSD µm	Mortality/Number Tested		
					Males	Females	Combined
9.41	3.238	1.871	6.89	2.78	0/5	0/5	0/10

Test Atmosphere / Chamber Description:

Chamber Volume:	not reported
Airflow:	33.0 LPM
Temperature:	21.7 - 23.1°C
Relative Humidity:	2.8-4.7%
Time to Equilibrium:	not reported

A. Mortality - None, as noted in table.

B. Clinical observations - There were no deaths during or following the 4 hour exposure at 1.871 mg/L (gravimetric concentration). No clinical signs were noted during or after the exposure. All males and 3/5 females gained weight in the period from Day 1 (day of exposure) through Day 4; two females had slight weight losses (0.2 and 1.7 g). All rats gained weight in the period from Day 4 to 8 and again from Day 8 to 15.

C. Gross Necropsy - Necropsy results were normal for all 10 animals.

D. Reviewer's Conclusions: The test material, IR5878 (containing 0.49% of the active ingredient Orthosulfamuron) is in EPA Toxicity Category III based on lack of deaths following 4-hour exposure to 1.871 mg/L. We would not recommend using the analytically-determined concentration of 3.238 mg/L, as particle sizes were somewhat high (only about 30% of the particles were smaller than 4 µm).

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D319036
2. **PC CODE:** 108209 Orthosulfamuron
3. **CURRENT DATE:** 31 October 2005
4. **TEST MATERIALS:** IR7825 99.3% (an otherwise unidentified metabolite and/or impurity of Technical IR5878, also known as Orthosulfamuron) in MRID 46578915; IR8181 97.02% (chemical name:(1-[2-(dimethylcarbamoyl)phenylsulfamoyl]-3-(4-hydroxy-6-methoxy-2-pyrimidinyl) urea) in MRID 46578922; IR7863 97.8% (an otherwise unidentified metabolite and/or impurity of Technical IR5878, also known as Orthosulfamuron) in MRID 46578918; IR5878 (Orthosulfamuron) 0.49% in MRID 46578990.

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/RCC Ltd., Füllinsdorf, Switzerland/Study No. 848210/JUL-2-2003	46578915	rat female LD_{50} > 2000 mg/kg; no signs of toxicity, all normal at post-sacrifice necropsy. However, test material (IR7825 99.3%) not adequately identified.	(III)	S
Acute oral toxicity/rat/BSL Bioservice Scientific, Germany/Study No. 040381/APR-27-2004	46578922	rat male and female LD_{50} >2000 mg/kg (0/3 males & 0/3 females died). No signs of toxicity, all normal at post-sacrifice necropsy.	III	A
Acute oral toxicity/rat/ RCC Ltd., Füllinsdorf, Switzerland/Study No. 850107/SEP-17-2003	46578918	rat male and female LD_{50} >2000 mg/kg (0/3 males & 0/3 females died). No signs of toxicity, all normal at post-sacrifice necropsy. However, test material (IR7863 97.8%) not adequately defined.0	III	S
Acute inhalation toxicity/rat/ RCC Ltd., Füllinsdorf, Switzerland/Study No. 849646/MAY-14-2004	46578990	rat male and female LC_{50} > 1.871 mg/L (4-hr exposure) with 0/5 males and 0/5 females dying. No signs of toxicity, all normal at post-sacrifice necropsy. 1.871 mg/L is gravimetrically determined concentration; the MMAD was 6.89 µm and the GSD was 2.78. Approx. 20% of the particles had diameters less than 3 µm and approx. 30% were less than 4 µm.	III	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**