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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

Granular

27/SEPT/2004

MEMORANDUM

Subject: EPA File Symbol: 80289-EUPE
DP Barcode: D304888
Decision No: 345729
PC Code: 108209

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505C)

To: James Tompkins, RM 25
Herbicide Branch
Registration Division

Applicant: Isagro (c/o James Messina)
1730 Rhode Island Ave., NW (Suite 1100)
Washington, D.C. 20036

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Orthosulfamuron	00.51
Inert Ingredients	99.49
Total:	100.0

ACTION REQUIRED: Review of acute toxicity data for File Symbol #80289-EUPU.

BACKGROUND: The US address for this Italian based Company is c/o J. Messina, 1730 Rhode Island Ave, N.W., Washington D.C. 20036. The animal studies for the product were conducted in Switzerland. There is a waiver request for the inhalation study for this end use product with the rationale being "the large size of the product granules", 100-300 fold greater than 10 microns.

ACTION REQUIRED: Review of acute toxicity data for File Symbol #80289-EUPU.

BACKGROUND: The US address for this Italian based Company is c/o J. Messina, 1730 Rhode Island Ave, N.W., Washington D.C. 20036. The animal studies for the product were conducted in Switzerland. There is a waiver request for the inhalation study for this end use product with the rationale being "the large size of the product granules", 100-300 fold greater than 10 microns.

The deposition of the product particles in the lungs is highly unlikely (Project Identification IR5878 04-04 dated 2-27-04).

RECOMMENDATIONS: All five toxicity studies (MRID 46219052-56) for the product are in compliance with the Sub-Division F guidelines.

The Company should use the format of OECD 425 for acute oral toxicity (up and Down Method). The current procedure (423) may not be acceptable for the future.

The Company asked for a waiver for the inhalation study, with rationale given in the previous paragraph (Background). A waiver has been granted for the inhalation study.

acute oral toxicity	IV	acceptable	MRID 46219052
acute dermal toxicity	IV	acceptable	MRID 46219053
acute inhalation	IV	waived	See text
primary eye irritation	III	acceptable	MRID 46219054
primary dermal irritation	IV	acceptable	MRID 46219055
dermal sensitization	neg.	acceptable	MRID 46219056

LABELING:

PRODUCT ID #: 0080289-EUPE

PRODUCT NAME: Benzamide (Orthosulfamuran)

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear protective eye wear.

First Aid:

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment.

#80289-EUPE Orthosulfamuron
P.C. Code 108209

Reviewer: M. Hashim **Date:** 26/SEPT/2004
Risk Manager (EPA): 25

TYPE OF STUDY: Acute Oral Study in Rats (OPPTS 870.1100, OECD 423)

TEST MATERIAL: Orthosulfamuron (0.5%), Batch No. G 003/03, Granules

SYNONYMS: IR5878 0.5 GR

CITATION: Arcelin, G. (2003). IR5878 0.5 GR: Acute Oral Toxicity Study in Rats. RCC Ltd Toxicology, Wolferstrasse 4 CH 4414 Fullinsdorf, Switzerland, Study No. 849643 dated 8-26-03. MRID 46219052.

SPONSOR: Isagro S.p.A, 20153 Milano, Italy.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46219052), three young adult female rats (Wist - SPF, wt. 183-189 g, Source-RCC Ltd. Laboratory Animal Services, Fullinsdort / Switzerland) were dosed with Orthosulfamuron (0.5%) at 5000 mg/kg. Purified water was used for dilution of the test substance at 0.5 g/mL. Evaluation parameters included signs of gross toxicity and mortality for a subsequent period of 15 days. Initial and weekly body weights and necropsy findings were recorded on all animals.

Oral LD_{50} for Orthosulfamuron in Female rats was >5000 mg/kg bw

There were no deaths on the study. There were no clinical signs. One animal lost weight, and the other one did not gain any on the study. Necropsy findings were unremarkable.

The test substance is of **low toxicity** based on the LD_{50} in female rats, EPA Toxicity Category IV.

This acute oral study is classified as Acceptable. This study does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Outcome No. of deaths/ No. of animals-females
5000	0 / 3

A. Mortality - Table 1. None of the animals died on 5000 mg/kg.

B. Clinical observations - There was no death on the study. There were no clinical signs. One animal did not gain weight on the study and the other lost some weight.

C. Gross Necropsy - Necropsy lesions were unremarkable.

D. Reviewer's Conclusions: TRB accepts the study authors conclusion.

E. Deficiencies - none.

#80289-EUPE Orthosulfamuron
P.C. Code 108209

Reviewer: M. Hashim **Date:** 26/SEPT/2004
Risk Manager (EPA): 25

STUDY TYPE: Acute Dermal Toxicity- Rats; OPPTS 870-1200; OECD 402.

TEST MATERIAL: Orthosulfamuron 0.5%, Batch No. G 003/03, Granules

SYNONYMS: IR5878 0.5 GR

CITATION: Arcelin, G. (2003). IR5878 0.5 GR: Acute Dermal Toxicity Study in Rats. RCC Ltd Toxicology, Wolferstrasse 4 CH 4414 Fullinsdorf, Switzerland, Study No. 849645 dated 9-16-03. MRID 46219053.

SPONSOR: Isagro S.p.A, 20153 Milano, Italy.

EXECUTIVE SUMMARY: An acute dermal toxicity study (MRID 46219053) was conducted to determine the LD_{50} of Orthosulfamuron in male and female rats (HanBrl: Wist[SPF] rats -Wt. males- 235-252 g, females 188-199 g, Source-RCC Ltd. Laboratory Animal Services, Fullinsdort / Switzerland). Five animals/sex were topically treated with the test substance at 5000 mg/kg bw. The test sites (10% body surface area) were covered with a gauze and semi occlusive dressing for 24 hours. The gauze pads and dressing were removed and the residual test substance was wiped/cleaned. Animals were then observed for 15 days. Terminal necropsy findings were recorded.

Dermal LD_{50} Males >5000 mg/kg bw
Females > 5000 mg/kg bw
Combined > 5000 mg/kg bw

There were no deaths on the study. There were no toxic signs. There were no local dermal lesions. One female animal lost body weight during the study (0.8%) around 8th day. Necropsy findings were unremarkable.

The test substance has **low toxicity** and is classified as EPA Toxicity Category IV.

This acute dermal study is classified Acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/ Number Tested		
	Male	Female	Combined
5000	0 / 5	0 / 5	0 / 10

A. Mortality - None.

B. Clinical observations - There were no deaths on the study. There were no toxic signs. There were local dermal lesions. One animal lost body weight during the second week.

C. Gross Necropsy - Necropsy findings were unremarkable.

D. Reviewer's Conclusions: TRB agrees with the Study author's conclusion.

E. Deficiencies - None.

#80289-EUPE Orthosulfamuron
P.C. Code 108209
Reviewer: M. Hashim **Date:** 26/SEPT/2004
Risk Manager (EPA): 25

TYPE OF STUDY: Primary Eye Irritation Study in Rabbits, OECD 405

TEST MATERIAL: Orthosulfamuron 0.5%, Batch No. G 003/03, Granules

SYNONYMS: IR5878 0.5 GR

CITATION: Arcelin, G. (2003). IR5878 0.5 GR: Primary Eye Irritation Study in Rabbits (4-Hour Semi Occlusive Application), RCC Ltd Toxicology, Wolferstrasse 4 CH 4414 Fullinsdorf, Switzerland, Study No. 849648 dated 10-20-03. MRID 46219054.

SPONSOR: Isagro S.p.A, 20153 Milano, Italy.

EXECUTIVE SUMMARY: (MRID 46219054) In a primary eye irritation study, three NZW rabbits (Source: Elevage Scientific des Dombes, Chatillon sur Chalaronne / France) were treated with (0.5%) Orthosulfamuron. The left eye of each rabbit was instilled (into the conjunctival sac) with 0.1 g of the test substance. The other eye served as the control. Animals were then observed for 10 days for ocular irritation.

Table 1. Ocular irritation showed conjunctivitis (redness, chemosis, discharge) which subsided within 48 hours. Any remaining score was <2, and not positive. Primay Eye Irritation Score was 1.44.

In this study Orthosulfamuron is a **moderate irritant** to the rabbit eye. The test substance meets EPA Toxicity Category III.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Table 1. No of Animals affected / Total No. of animals

lesion	One hr	24 hrs	48 hrs	72 hrs	7 days	10 days
corneal opacity	0 / 3	0 / 3	0 / 3	0 / 3	0 / 3	0 / 3
iritis	0 / 3	0 / 3	0 / 3	0 / 3	0 / 3	0 / 3
conjunctivitis	3 / 3	2 / 3	0 / 3	0 / 3	0 / 3	0 / 3

A. Observations - Table 1. Table 1. Ocular irritation showed conjunctivitis (redness, chemosis,discharge) which subsided by within 48 hours. Any remaining score was <2, and not positive. Primay Eye Irritation Score was 1.44.

B. Reviewer's Conclusions: The Reviewer agrees with the Study Author's conclusion.

C. Deficiencies : None.

#80289-EUPE Orthosulfamuron
P.C. Code 108209
Reviewer: M. Hashim **Date:** 26/SEPT/2004
Risk Manager (EPA): 25

TYPE OF STUDY: Primary Skin Irritation Study in Rabbits 870-2500, OECD 404.

TEST MATERIAL: Orthosulfamuron 0.5%, Batch No. G 003/03, Granules

SYNONYMS: IR5878 0.5 GR

CITATION: Arcelin, G. (2003). IR5878 0.5 GR: Primary Skin Irritation Study in Rabbits (4-Hour Semi Occlusive Application), RCC Ltd Toxicology, Wolferstrasse 4 CH 4414 Fullinsdorf, Switzerland, Study No. 849647 dated 9-18-03. MRID 46219055.

SPONSOR: Isagro S.p.A, 20153 Milano, Italy.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46219055), 3 young adult NZW rabbits (Source: Elevage Scientific des Dombes, Chatillon sur Chalaronne / France) were topically treated with 0.5 g of Orthosulfamuron (0.5%, Batch No. G 003/03) on the left flank. The test sites were covered with a dressing for 4 hours. Irritation was scored by Draize Method for 72 hours.

The test substance caused no skin irritation in any of the rabbits.

The test substance is not an irritant to the rabbit skin. It meets EPA Tox Category IV.
This study is classified as Acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations - The test substance caused no irritation in 72 hours.

B. Results -The score was 0.0 throughout the study.

C. Reviewer's Conclusions: The Reviewer is in agreement with the Study Author.

D. Deficiencies - none.

#80289-EUPE Orthosulfamuron
P.C. Code 108209

Reviewer: M. Hashim **Date:** Sept. 25, 2004
Risk Manager (EPA): 25

TYPE OF STUDY: Dermal Sensitization Guinea Pig; OPPTS 870.2600

TEST MATERIAL: Orthosulfamuron 0.5%, Batch No. G 003/03, Granules

SYNONYMS: IR5878 0.5 GR

CITATION: Arcelin, G. (2003). IR5878 0.5 GR: Contact Hypersensitivity in Albino Guinea Pigs, Maximization Test. RCC Ltd Toxicology, Wolferstrasse 4 CH 4414 Fullinsdorf, Switzerland, Study No. 849649 dated 9-23-03. MRID 46219056.

SPONSOR: Isagro S.p.A, 20153 Milano, Italy.

EXECUTIVE SUMMARY: A Maximization test (MRID 46219056) was conducted to assess the potential for (0.5%) Orthosulfamuron (Batch No. G 003/03) to elicit a dermal sensitization reaction. Fifteen guinea pigs were used for the procedure (10 test and 5 controls, Source: RCC Ltd, Laboratory Animal Services, Fullinsdorf / Switzerland). Induction: The intradermal injection consisted of 20% test substance* and emulsion of Freund's Complete Adjuvant (FCA) / physiological saline. One week following the intradermal injection, an Epidermal induction was performed, under occlusion with 25% test substance*.The control animals were also (intra-dermally) induced with purified water (under occlusion). Two weeks after the epidermal test the control and test groups were challenged by a 10% test substance* by epidermal route.
(*in purified water)

Results showed no dermal reaction at (0 / 10) 24 or 48 hours in the test group. Similarly control showed the same results in 5 animals.

Based on the above results the test substance **is not a contact sensitizer**.

COMPLIANCE: The test (870-2600) meets GLP requirements. It is Acceptable in accordance with the Sub Division F guidelines.

This study is classified as Acceptable. It does satisfy the guideline requirements for a sensitization study (OPPTS 870.2600) in the Guinea pig .

I. PROCEDURE: A Maximization test (MRID 46219056) was conducted to assess the potential for (0.5%) Orthosulfamuron (Batch No. G 003/03) to elicit a dermal sensitization reaction. Fifteen guinea pigs were used for the procedure (10 test and 5 controls, Source: RCC Ltd, Laboratory Animal Services, Fullinsdorf / Switzerland). Induction: The intradermal injection consisted of 20% test substance* and emulsion of Freund's Complete Adjuvant (FCA) / physiological saline. One week following the intradermal injection, an Epidermal induction was performed, under occlusion with 25% test substance*.The control animals were also (intra-dermally) induced with purified water (under occlusion). Two weeks after the epidermal test the control and test groups were challenged by a 10% test substance* by epidermal route.
(*in purified water)

A. Induction - Intradermal and epidermal route.

B. Challenge - 10% test in purified water, epidermal**.**

C. Naive Controls - 5 animals.

II. RESULTS and DISCUSSION: -

A. Reactions and duration - none.

B. Positive control - -

C. Reviewer's Conclusions: The Reviewer agrees with the Study Author.

D. Deficiencies - none.

#80289-EUPE Orthosulfamuron
P.C. Code 108209

Acute Tox One Liner:
#80289-EUPE
D304488 date 9-27-04

Study/ Species/ #/ Lab/ date	MRID #	Results	Tox Cat.	Core grade
acute oral toxicity/rat/ RCC-Switzerland/ 849643/ 8-26-03	46219052	LD_{50} >5000	IV	A
acute dermal toxicity/rat/ RCC-Switzerland/ 849645/ 9-16-03	46219053	LD_{50} >5000	IV	A
primary eye irritation/rabbit/ RCC-Switzerland/ 849648/10-20-03	46219054	mod. Irritant	III	A
primary dermal irritation /rabbit RCC-Switzerland/ 849647/ 9-18-03	46219055	not an irritant	IV	A
dermal sensitization/ guinea pigs/ RCC-Switzerland/ 849649/ 9-23-03	46219056	negative	-	A