#80289-EUP-1 Orthosulfamuron Technical
P. C. Code 108209

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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

12/OCT/2004

MEMORANDUM

Subject: EPA File Symbol: 80289-EUP-1 Orthosulfamuron Technical
DP Barcode: D304895
Decision No: 342749
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	98.0
Inert Ingredients	2.0
Total:	100.0

ACTION REQUIRED: Review of acute toxicity data for File Symbol #80289-EUP-1, Benzamide Technical.

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BACKGROUND: The product contains Benzamide (Orthosulfamuron). The animal studies for this product were conducted in Italy.

RECOMMENDATIONS: All six toxicity studies (MRID 46219019-24 and 60101) for the technical 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). Guinea pig assay for sensitization has been replaced by Local Lymph Node Assay (LLNA) in mice. There may be a data gap if this study is not presented in the new format.

The eye study meets Category III. Only group data is presented and not the individual animal data. However, we have accepted the product as a moderate irritant. We may revise this category if individual data support Category IV.

The toxicology profile for the File Symbol # 80289-EUP-1 is as follows:

acute oral toxicity	IV	acceptable	MRID 46219019
acute dermal toxicity	IV	acceptable	MRID 46219020
acute inhalation	IV	Acceptable	MRID 46219021
primary eye irritation	III	acceptable	MRID 46219022
primary dermal irritation	IV	acceptable	MRID 46260101
dermal sensitization	neg.	acceptable	MRID 46219024

LABELING:

PRODUCT ID #: **0080289-EUP-1**

PRODUCT NAME: **Benzamide Technical (Orthosulfamuran)**

SIGNAL WORD: **CAUTION**

PRECAUTIONARY STATEMENTS

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.

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Reviewer: M. Hashim

Risk Manager (EPA): 25 **Date:** 5/OCT/2004

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

TEST MATERIAL: Benzamide or IR 5878 Technical (93.7%), White powder, Batch FCF/T/159-99 (20274/71)

CITATION: Yu, P. (1999). Acute Oral Toxicity Study in Rats Treated with the Test article IR5878. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. 990496 dated 9-17-99. MRID 46219019.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46219019), five young adult rats/sex (Wist - SPF, wt. 280-350 g, fe 200-252 g, Source- Charles River, Italia S.p.A, Calco, [Lecco]) were dosed with Benzamide (Orthosulfamuron 93.7% Batch FCF/T/159-99 [20274/71]) at 5000 mg/kg. The dose was divided in two equal parts in deionized water and given at two hours interval (10 mg/kg/time). Evaluation parameters included signs of gross toxicity and mortality for a subsequent period of 14 days. Initial and weekly body weights and necropsy findings were recorded on all animals.

Oral LD_{50} for Benzamide **in m/f rats was >5000 mg/kg bw**

There were no deaths on the study. There were no clinical signs. Animals gained normal body weight during 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)*	Mortality No. dead/ No. of animals	
5000	males 0 / 5	females 0 / 5

A. **Mortality** - Table 1. None of the animals died at 5000 mg/kg dose.

B. **Clinical observations** - There was no death on the study. There were no clinical signs. Animals gained body weight during the study.

C. **Gross Necropsy** - Necropsy findings were unremarkable.

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

E. **Deficiencies** - none.

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Reviewer: M. Hashim

Risk Manager (EPA): 25 **Date:** 10/OCT/2004

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

TEST MATERIAL: Benzamide or Orthosulfamuron or IR5878 Technical (93.7%), White powder, Batch FCF/T/159-99 (20274/71)

CITATION: Yu, P (1999). Acute Dermal Toxicity Study in Rats Treated with the Test article IR5878. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. 990497 dated 9-17-99. MRID 46219020.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: An acute dermal toxicity study (MRID 46219020) was conducted to determine the LD_{50} of Benzamide/Orthosulfamuron (93.7% Batch FCF/T/159-99 [20274/71] in 0.9% saline mg/kg in male and female SD rats (Wt. males- 334-350g, females 200-221 g, Source- Charles River, Via Indipendenza, Calco [Lecco]). The test sites were covered with a gauze and a tape for 24 hours. The gauze pads were removed and the residual test substance was wiped/cleaned. Animals were then observed for 14 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. There were no adverse effects on the body weight gains. Necropsy findings were unremarkable.

The test substance has a **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.

C. **Gross Necropsy** - Necropsy findings were unremarkable.

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

E. **Deficiencies** - None.

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Reviewer: M. Hashim

Date: 10/OCT/2004

Risk Manager (EPA): RM 25

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

TEST MATERIAL: Benzamide or Orthosulfamuron Technical (93.7%) or IR5878, White solid-crystalline. Batch FCF/T/168-00 (ex 20525/03/9)

CITATION: Doti, A. (1999). IR 5878: 4-hour acute Inhalation Toxicity Study in the Rat. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. RO6390 dated 9-29-99. MRID 46219021.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: (MRID 46219021) In an acute inhalation toxicity study (LC_{50}), Wistar rats (5/sex , Wt. males- 180-195 g, females 183-189 g, Source- RCC Biotechnology and Breeding Division, Wolferstrasse 4, Fullinsdorf, Switzerland) were treated with the aerosol of Benzamide (Orthosulfamuron 93.7% Batch FCF/T/168-00 (ex 20525/03/9) at a (gravimetric) concentration of 2.19 mg/L for 4 hours. The MMAD was 3.03 microns. Animals were then observed for 14 days. Terminal necropsy findings were recorded.

LC_{50} Males > 2.19 mg/L
Females> 2.19 mg/L
Combined >2.19 mg/L

All animals survived the test. There were no clinical signs due to the test exposure, and no adverse effects on the body weight gains. There were no gross lesions at necropsy.

The test substance is of **Low Toxicity** as based on the dose. It has EPA Toxicity Category IV.

This acute inhalation study is classified as Acceptable. It does satisfy the guideline requirement of an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

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

RESULTS and DISCUSSION:

Table 1. Total deaths / Total number of animals

Conc.	MMAD	GSD	male	female
2.19	3.03	2.92	0 / 5	0 / 5

Test Atmosphere / Chamber Description:

Exposure air flow rate	32 L per min
Chamber Temperature:	22.4^0 C
Relative Humidity:	6.4%

Statistics - The LC_{50} was calculated on less than or more than the 50% mortality (Schaper et al (1994)

A. **Mortality** - None.

B. **Clinical observations** - All animals survived the test. There were no toxic signs and no adverse effect on the weight gains.

C. **Necropsy** - Unremarkable.

D. **Reviewer's Conclusions:** Reviewer agrees with the study author's report.

E. **Deficiencies** - The humidity seems to be low for an inhalation test.

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Reviewer: M. Hashim

Risk Manager (EPA): 25 **Date:** 10/OCT/2004

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

TEST MATERIAL: Benzamide or Orthosulfamuron Technical or IR5878 Technical (93.7%), White crystalline powder, Batch FCF/T/159-99 (20274/71)

CITATION: Renoldi, A. (1999). Acute Eye Irritation Study in New Zealand White Rabbits treated with the Test article IR5878. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. 990499 dated 9-28-99. MRID 46219022.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: (MRID 46219022) In a primary eye irritation study, six NZW rabbits (Source: Charles River Italia, S.p.A., Calco [Lecco], Italy) were treated with Benzamide (orthosulfamuron 93.7% Batch FCF/T/159-99 [20274/71]). The conjunctival sac of the left eye of each rabbit was instilled with 0.1 g of the test substance. The other eye served as the control. Animals were then observed for 72 hours for ocular irritation.

Table 1 shows Ocular irritation showing conjunctivitis (redness and chemosis).

In this study Benzamide (93.7%) 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
corneal opacity	0 / 6	0 / 6	0 / 6	0 / 6
iritis	0 / 6	0 / 6	0 / 6	0 / 6
conjunctivitis	4 / 6	0 / 6	0 / 6	0 / 6

A. **Observations** - Table 1. Table 1. Ocular irritation showed conjunctivitis.

B. **Reviewer's Conclusions:** We are in agreement with the study director.

C. **Deficiencies** : Individual eye score was not presented, therefore, we have to retain Category III as suggested by the study author. This category may be revised if individual animals data support Category IV for the product.

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Reviewer: M. Hashim

Risk Manager (EPA): 25 **Date:** 10/OCT/2004

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

TEST MATERIAL: Benzamide or Orthosulfamuron Technical (93.7%) or IR5878, White crystalline powder, Batch FCF/T/159-99 (20274/71)

CITATION: Renoldi, A (1999). Acute Dermal Irritation Study in New Zealand White Rabbits treated with the Test article IR5878. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. 990498 dated 9-28-99. MRID 46260101.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46260101), 6 young adult NZW rabbits (Source: Charles River Italia, S.p.A., Calco [Lecco], Italy) were topically treated with 0.5 g of Benzamide (Orthosulfamuron 93.7% Batch FCF/T/159-99 [20274/71]) 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 of 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.

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Reviewer: M. Hashim

Date: October 10, 2004

Risk Manager (EPA): 25

TYPE OF STUDY: Dermal Sensitization Guinea Pig; OPPTS 870.2600

TEST MATERIAL: Benzamide or Orthosulfamuron Technical (93.7%) or IR5878 White crystalline powder, Batch FCF/T/159-99 (20274/71)

CITATION: Vigna, E. (1999). Skin Sensitization Test in Guinea Pigs Treated with the Test article IR5878. Instituto Ricerche Biomediche, 10010 Colleeretto Giacosa (TO), Italy. Study No. 990500 dated 10-28-99. MRID 46219024.

SPONSOR: US address: Isagro (c/o James Messina), 1730 Rhode Island Ave (NW), Washington, D.C. 20036

EXECUTIVE SUMMARY: A Maximization study (MRID 46219024) was conducted to assess the potential of Benzamide technical (Orthosulfamuron 93.7% Batch FCF/T/159-99 [20274/71]) to elicit a sensitization reaction in guinea pigs (Source Charles River Italia, S.p.A., Calco [Lecco], Italy). Fifteen animals were used for the procedure. Each animal was given 3 pairs of intradermal injections. The Group I (test) consisted of 0.1 mL FCA emulsion (1:1 mixture v/v FCA/water), 0.1 mL test article, 0.1 mL test article in FCA (1:1 mixture v/v FCA/water). Vehicle, Group 2 consisted of 0.1 mL FCA emulsion (1:1 mixture v/v FCA/water), 0.1 mL vehicle, and 0.1 mL vehicle in FCA. Challenge was given by an occlusive patch for 24 hours. Forty eight hours from the start of the challenge, observations were recorded for dermal reaction. A second observation was also made the next day. (For details refer page 19 MRID 46219024).

Results showed no dermal reaction at (0 / 20) at the challenge. Similarly control showed the same results in 20 animals.

Based on the above results Benzamide Technical **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 study was conducted to assess the potential of Benzamide technical (93.7% Batch FCF/T/159-99 [20274/71]) to elicit a dermal sensitization reaction in guinea pigs (Source Charles River Italia, S.p.A., Calco [Lecco], Italy). Fifteen animals were used for the procedure. Each animal was given 3 pairs of intradermal injections. The Group I (test) consisted of 0.1 mL FCA emulsion (1:1 mixture v/v FCA/water), 0.1 mL test article, 0.1 mL test article in FCA (1:1 mixture v/v FCA/water). Vehicle, Group 2 consisted of 0.1 mL FCA emulsion (1:1 mixture v/v FCA/water), 0.1 mL vehicle, and 0.1 mL vehicle in FCA. Challenge was given by an occlusive patch for 24 hours. Forty eight hours from the start of the challenge, observations were recorded for dermal reaction. A second observation was also made the next day. (For details refer page 19 MRID 46219024).

A. **Induction** - Intradermal and epidermal route.

B. **Challenge** - A skin patch was used for 24 hours (topical).

C. **Naive Controls** - Twenty 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.

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Acute Tox One Liner:
#80289-EUP-1
D304895 date 10-10-04

Study/ Species/ #/ Lab/ date	MRID #	Results	Tox Cat.	Core grade
acute oral toxicity/rat/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/#990496/ 9-17-1999.	46219019	Oral LD_{50} >5000 m+f	IV	A
acute dermal toxicity/rat/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/#990497/ 9-17-04	46219020	Dermal LD_{50} >5000 m+f	IV	A
acute inhalation study/ rat/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/ #RO6390/ 9-29-99	46219021	LC50 > 2.19 mg/L m/f	IV	A
primary eye irritation/rabbit/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/#990499/ 9-28-99	46219022	mod. irritant	III	A
acute dermal irritation/rabbit/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/#990498/ 9-28-99	46260101	not an irritant	IV	A
dermal sensitization/ guinea pigs/ Instituto Ricerche Biomediche-Colleretto Giacosa-Italy/#990500/ 9-28-99	46219024	negative	-	A