#80289-EUP-1 Orthosulfamuron (51.5%)
P. C. Code 108209

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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

15/OCT/2004

MEMORANDUM

Subject: EPA File Symbol: 80289-EUP-1 Orthosulfamuron 51.5% (Technical has the same number)
Barcode: D304811
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 | 51.5 |
| Inert Ingredients | 48.5 |
| Total: | 100.0 |

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ACTION REQUIRED: Review of acute toxicity data for File Symbol #80289-EUP-1, Benzamide or Orthosulfamuron 51.5%.

BACKGROUND: The product contains Bezamide (Orthosulfamuron 51.5%). The animal studies for this product were conducted in Switzerland. The technical product shares the same product number. #80289-EUP-1, except each one has a different Barcode.

RECOMMENDATIONS: All six toxicity studies (MRID 46219062-72) for the product are in compliance with the Sub-Division F guidelines.

The sensitization study in guinea pigs has been replaced by Lymph Node Assay in mice (LLNA). There may be a data gap if the LLNA is not used for sensitization in future studies.

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

| | | | |
|---|---|---|---|
| acute oral toxicity | IV | acceptable | MRID 46219062 |
| acute dermal toxicity | IV | acceptable | MRID 46219064 |
| acute inhalation | IV | Acceptable | MRID 46219066 |
| primary eye irritation | III | acceptable | MRID 46219068 |
| primary dermal irritation | IV | acceptable | MRID 46219070 |
| dermal sensitization | neg. | acceptable | MRID 46219072 |

LABELING:

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

**PRODUCT NAME:** **Benzamide (Orthosulfamuran 51.5%)**

**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

**Date:** 15/OCT/2004

**Risk Manager** (EPA): 25

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

**TEST MATERIAL:** Benzamide or IR5878 50 WG alone (Orthosulfamuron 49.9%), Batch No. G 038/02, Brown solid

**CITATION:** Arcelin, G. IR5878 50WG alone: Acute Oral Toxicity Study in Rats. RCC Ltd Toxicology, Wolferstrasse 4, CH 4414 Fullinsdorf, Switzerland. Study No. 849366 dated 9-23-03. MRID 46219062.

**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 46219052), three young adult HanBrl: Wistar (SPF) rats (Wt. 182-198 g, Source- RCC Lab Animal Services, Fullinsdorf / Switzerland) were dosed with IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02 ) in purified water at 5000 mg/kg . 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 IR 5878 50 WG alone in rats was >5000 mg/kg bw**

There were no deaths on the study. There were no clinical signs. Animals gained 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.

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**RESULTS and DISCUSSION:**

**Table 1.**

| Dose (mg/kg bw) | Gender | Mortality No. |
|---|---|---|
| 5000 | females | 0 / 3 |

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 author's conclusion.

E. **Deficiencies** - none.

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Reviewer: M. Hashim

Risk Manager (EPA): 25

Date: 15/OCT/2004

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

TEST MATERIAL: Benzamide or IR5878 50 WG alone (Orthosulfamuron 49.9%), Batch No. G 038/02 Brown solid

CITATION: Arcelin, G. (2003). IR5878 50WG alone: Acute Dermal Toxicity Study in Rats. RCC Ltd Toxicology, Wolferstrasse 4, CH 4414 Fullinsdorf, Switzerland. Study No. 849368 dated 9-16-03. MRID 46219064.

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 46219064 ) was conducted to determine the $LD_{50}$ of IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02 ) in male and female HanBrl: Wistar (SPF) rats (Wt. males- 241-257 g, females 181-203 g, Source- RCC Lab Animal Services, Fullinsdorf / Switzerland). The rats were topically treated with the test substance (in dist. water) at 5000 mg/kg. The test sites were covered with a semi occlusive dressing for 24 hours. 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. There were no adverse effects on the body weight gains, except one animal which had slight weight loss. 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.

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**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. There were no weight losses except one animal.

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:** 15/OCT/2004

**Risk Manager (EPA):** RM 25

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

**TEST MATERIAL**: Benzamide or IR5878 50 WG alone (Orthosulfamuron 49.9%), Batch No. G 038/02 Brown solid

**CITATION:** Decker et al (2003). IR5878 50WG alone: 4-Hour Acute Inhalation Toxicity Study in Rats. RCC Ltd Toxicology, Wolferstrasse 4, CH-44552 Itingen, Switzerland. Study No. 847655 dated 9-11-03. MRID 46219066.

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

**EXECUTIVE SUMMARY:** (MRID 46219066) An acute inhalation study ($LC_{50}$) was conducted with Benzamide in rats. Five animals/sex (HanBrl: Wistar (SPF) rats (Wt. males- 245-262 g, females 204-221 g, Source- RCC Lab Animal Services, Fullinsdorf / Switzerland) were exposed to the aerosol of IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02) at a (gravimetric) concentration of 4.38 mg/L for 4 hours. The MMAD was 2.87 microns. Animals were then observed for 14 days. Terminal necropsy findings were recorded.

**$LC_{50}$ Males > 4.38 and mg/L**
**Females> 4.38 mg/L**
**Combined >4.38 mg/L**

All animals survived the test. Clinical signs include salivation (mainly) during the exposure. Six rats showed poor body weight gain in the early part of the study, then gained back to normal 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.

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**RESULTS and DISCUSSION:**

**Table 1 Mortality No. affected / Total No.**

| Conc. | MMAD | GSD | male | female |
|---|---|---|---|---|
| 4.38 | 2.8 | 2.85 - 2.89 | 0 / 5 | 0 / 5 |

**Test Atmosphere / Chamber Description:**

| | |
|---|---|
| **Exposure air flow rate** | 32 L per min |
| **Chamber Temperature:** | 22.4$^0$ C |
| **Relative Humidity:** | 4.5% |

Particle size was determined once per hour by Anderson Cascade Impaction.

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. Toxic signs were limited to salivation mostly during exposure. There was adverse effect on the body weights of six animals, it was transient and in the first part of the study.

C. Necropsy - Unremarkable.

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

E. Deficiencies - The humidity seems to be low for the 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 IR5878 50 WG alone (Orthosulfamuron 49.9%), Batch No. G 038/02 Brown solid

**CITATION:** Arcelin, G. IR5878 50WG alone: Primary Eye Irritation Study in Rabbits. RCC Ltd Toxicology, Wolferstrasse 4, CH 4414 Fullinsdorf, Switzerland. Study No. 849370 dated 11-07-03. MRID 46219068.

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

**EXECUTIVE SUMMARY:** (MRID 46219068) In a primary eye irritation study, three NZW rabbits (Source: Elevage Scintifique des Dombes, F-01400 Chatillon sur Chalaronne / France) were treated with IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02. 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 10 days for ocular irritation.

Ocular irritation showed conjunctivitis (redness and chemosis) which subsided within 48 hours, Table 1. The ocular score was "1" up to 7 days, however, it is not considered positive.

In this study the test substance 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.

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## RESULTS AND DISCUSSION:

A. **Observations** - Ocular irritation showed conjunctivitis (redness and chemosis) which subsided within 48 hours, Table 1. The ocular score was "1" for 7 days, however, it is not considered positive for EPA guidelines.

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

C. **Deficiencies : None.**

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

| lesion | one hr | 24 | 48 | 72 | 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 |
| conjuncti-vitis | 0 / 3 | 2 / 3 | 0 / 3 | 0 / 3 | 0 / 3 | 0 / 3 |

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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, IR5878 50 WGl (Orthosulfamuron 49.9%), Batch No. G 038/02 Brown solid

**CITATION**: Arcelin, G. (2003). IR5878 50WG alone: Primary Skin Irritation in Rabbits RCC Ltd Toxicology, Wolferstrasse 4, CH 4414 Fullinsdorf, Switzerland. Study No. 849369 dated 9-19-03. MRID 46219070.

**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 46219070), 3 young adult NZW rabbits (Source: Elevage Scintifique des Dombes, F-01400 Chatillon sur Chalaronne / France) were topically applied with 0.5 g IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02) on the left flank. The test sites were covered with a dressing for 4 hours. Irritation was scored by Draize Method for 7 days.

The test substance caused minimal skin irritation in the rabbit: Erythema/eschar score in 3 rabbits was 1.33, 0.00, 0.33, respectively. There was no edema in any of the rabbits.

The test substance is a mild 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 minimal skin irritation in the rabbits. Erythema/eschar score in 3 rabbits.

B. **Results** - The irritation score was 0.55, mean for 3 rabbits.

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

D. **Deficiencies** - none.

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**Risk Manager (EPA):** 25

**TYPE OF STUDY:** Dermal Sensitization Guinea Pig; OPPTS 870.2600

**TEST MATERIAL:** Benzamide or IR5878 50 WGI (Orthosulfamuron 49.9%), Batch No. G 038/02 Brown solid

**CITATION:** Arcelin, G. IR5878 50WG alone: Contact Hypersensitivity in Albino Guinea Pigs, Maximization Test. RCC Ltd Toxicology, Wolferstrasse 4, CH 4414 Fullinsdorf, Switzerland. Study No. 849371 dated 9-22-03. MRID 46219072.

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

**EXECUTIVE SUMMARY:** A Maximization study (MRID 46219072) was conducted to assess the sensitization potential of IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02) in guinea pigs (Source- RCC Lab Animal Services, Fullinsdorf / Switzerland). Fifteen animals (10 test and 5 controls) were used for the procedure. Each animal in the test group was subject to an intradermal injection with a 25% dilution of the test substance in (purified)* water and an emulsion of Freund's Complete Adjuvant (FCA)/ physiological saline. Epidermal induction was conducted for 48 hours with 50% test substance in water* one week after the intradermal induction (following pretreatment of the test areas with 10% sodium laurel sulfate SLS). Controls were intradermally induced with water* and FCA/physiological saline and epideramaly induced with water* under occlusion following pretreatment with SLS. Two weeks later the test and the controls were challenged by an epidermal application of the test substance at 50% in water* and water* alone under occlusion.

Results showed no dermal reaction in the test group at the challenge. Similarly control showed the same results in all animals.

Based on the above results Benzamide 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 .

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**I. PROCEDURE:** A Maximization study was conducted to assess the potential of IR5878 50 WG alone (Orthosulfamuron 49.9%, Batch No. G 038/02) to elicit a sensitization reaction in guinea pigs (Source- RCC Lab Animal Services, Fullinsdorf / Switzerland). Fifteen animals (10 test and 5 controls) were used for the procedure. Each animal in the test group was subject to an intradermal injection with a 25% dilution of the test substance in (purified)* water and an emulsion of Freund's Complete Adjuvant (FCA)/ physiological saline. Epidermal induction was conducted for 48 hours with the test with 50% test substance in water* one week after the intradermal induction (following pretreatment of the test areas with 10% sodium laurel sulfate SLS). Controls were intraderamlly induced with water* and FCA/physiological saline and received epidemal induction with water* under occlusion following pretreatment with SLS. Two weeks later the test and controls were challenged by epidermal application of the test substance at 50% in water* and water* alone under occlusion.

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

B. **Challenge** - A skin patch used for challenge.

C. **Naive Controls** - Five animals.

II. **RESULTS and DISCUSSION**: -

A. **Reactions and duration** - None.

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

C. **Deficiencies** - none.

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**Acute Tox One Liner**:
D304811 date 10-15-04
#80289-EUP-1

| **Study/ Species/ #/ Lab/ date** | **MRID #** | **Results** | **Tox Cat.** | **Core grade** |
|---|---|---|---|---|
| acute oral toxicity/rat/ RCC Toxicology-Switzerland/ #849366 / 9-23-03 | 46219062 | oral $LD_{50}$ >5000 mg/kg m/f | IV | A |
| acute dermal toxicity/rat/ RCC Toxicology-Switzerland/ #849368 / 9-16-03 | 46219064 | dermal $LD_{50}$ >5000 mg/kg m/f | IV | A |
| acute inhalation /rat / RCC Toxicology-Itingen, Switzerland/ #847655 / 9-11-03 | 46219066 | 4.38 mg/L | IV | A |
| primary eye irritation/rabbit/ RCC Toxicology-Switzerland/ #849370 / 11-7-03 | 46219068 | mod. irritant | III | A |
| acute dermal irritation/rabbit/ RCC Toxicology-Switzerland/ #849369 / 9-19-03 | 46219070 | mild irritant | IV | A |
| dermal sensitization/ guinea pigs/ RCC Toxicology-Switzerland/849371/ 9-22-03 | 46219072 | negative | - | A |