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:

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>% by wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthosulfamuron</td>
<td>0.51</td>
</tr>
<tr>
<td>Inert Ingredients</td>
<td>99.49</td>
</tr>
<tr>
<td>Total:</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Route</th>
<th>Method</th>
<th>Status</th>
<th>MRID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral toxicity</td>
<td>IV</td>
<td>acceptable</td>
<td>MRID 46219052</td>
<td></td>
</tr>
<tr>
<td>Acute dermal toxicity</td>
<td>IV</td>
<td>acceptable</td>
<td>MRID 46219053</td>
<td></td>
</tr>
<tr>
<td>Acute inhalation</td>
<td>IV</td>
<td>waived</td>
<td>See text</td>
<td></td>
</tr>
<tr>
<td>Primary eye irritation</td>
<td>III</td>
<td>acceptable</td>
<td>MRID 46219054</td>
<td></td>
</tr>
<tr>
<td>Primary dermal irritation</td>
<td>IV</td>
<td>acceptable</td>
<td>MRID 46219055</td>
<td></td>
</tr>
<tr>
<td>Dermal sensitization</td>
<td>neg.</td>
<td>acceptable</td>
<td>MRID 46219056</td>
<td></td>
</tr>
</tbody>
</table>

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.
**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, Fullinsdorf / 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 LD₅₀ 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 LD₅₀ 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:

<table>
<thead>
<tr>
<th>Dose (mg/kg bw)</th>
<th>Outcome No. of deaths/ No. of animals-females</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>0 / 3</td>
</tr>
</tbody>
</table>

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.
**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 LD₅₀ 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, Fullinsdorf / 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 LD₅₀**

- 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:

<table>
<thead>
<tr>
<th>Dose (mg/kg bw)</th>
<th>Mortality/ Number Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>5000</td>
<td>0 / 5</td>
</tr>
</tbody>
</table>

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.
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. Primary 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

<table>
<thead>
<tr>
<th>lesion</th>
<th>One hr</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
<th>7 days</th>
<th>10 days</th>
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<tbody>
<tr>
<td>corneal opacity</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
</tr>
<tr>
<td>iritis</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
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<tr>
<td>conjunctivitis</td>
<td>3 / 3</td>
<td>2 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
<td>0 / 3</td>
</tr>
</tbody>
</table>

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. Primary Eye Irritation Score was 1.44.

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

C. **Deficiencies** : None.
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.
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

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