



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

09/JUN/2003

MEMORANDUM

Subject: GF-881 Manufacturing Use Concentrate
EPA File Symbol 62719-LNE
DP Barcode: D288069
Case No: 065245
PC Code: 119031 Benzenesulfonamide, 2-(2,2-difluoroethoxy) -
N-(5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl)
-6(trifluoromethyl) (DE-638, Penoxsulam)

From: Tracy Keigwin *TK*
Technical Review Branch
Registration Division (7505C) *SK*

To: Philip Errico, PM 23
Herbicide Branch
Registration Division (7505C)

Applicant: Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
Penoxsulam: 2-(2,2-difluoroethoxy) - 6-trifluoromethyl-N- (5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl) benzenesulfonamide	50.0
<u>Inert Ingredient(s)</u>	50.0
Total:	100.0

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ACTION REQUESTED: PM requests review of acute toxicity data for GF-881 Manufacturing Concentrate, EPA File Symbol 62719-LNE.

BACKGROUND: Dow AgroSciences LLC has submitted 5 acute toxicity studies and 1 acute inhalation toxicity waiver in support of registration of GF-881 Manufacturing Use Concentrate, EPA File Symbol 62719-LNE. This product contains the new chemical Penoxsulam, and will be used for formulation into herbicides for use on rice. The 5 studies (MRIDs 45830813, 45830816, 45830821, 45830824, and 45830827) were conducted at Springborn Laboratories, Inc., Ohio Research Center, 640 North Elizabeth Street, Spencerville, Ohio 45887.

RECOMMENDATIONS: The 5 acute studies and 1 acute inhalation toxicity waiver have been reviewed and have been classified as follows:

Acute oral toxicity	IV	Acceptable	MRID 45830813
Acute dermal toxicity	IV	Acceptable	MRID 45830816
Acute inhalation waiver	-	Unacceptable	
Primary eye irritation	IV	Acceptable	MRID 45830821
Primary skin irritation	IV	Acceptable	MRID 45830824
Dermal sensitization	No	Acceptable	MRID 45830827

OF NOTE: The waiver for the acute inhalation toxicity study is unacceptable. The registrant bases much of the rationale for the waiver on the "low acute toxicity" of the technical product, however that study was found unacceptable, recording a gravimetric concentration that was greater than the nominal concentration. It is not acceptable or even possible for the gravimetric concentration (concentration of test material in the breathing zone of the animal) to be greater than the nominal concentration (total amount of test substance fed into the inhalation equipment divided by volume of air) when a study is performed correctly. The performing laboratory itself indicated that a significant and atypical result occurred, negating the study to support product registration. Additionally, there are ingredients in the MUP that are not present in the technical product as well as a different formulation types (the technical is a powder, the MUP a liquid concentrate) and pHs - these must be reviewed in order to determine their effect on the toxicity profile. Finally, the registrant states that the MUP has a high viscosity making it difficult to perform an inhalation analysis but does not explain why the test material couldn't be diluted to overcome this. The inhalation waiver petition is denied.

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PRECAUTIONARY STATEMENTS: The precautionary labeling for this product can not be determined until an acceptable acute inhalation study has been submitted and reviewed.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE ORAL TOXICITY TESTING (870.1100 formerly §81-1)

Product Manager: 23

Reviewer: Tracy Keigwin

TEST MATERIAL PURITY: GF-881 , Lot No. C1413-26, Active 50.8%, tan liquid

CITATION : Bonnette, Kimberly L. (2000) GF-881: An Acute Oral Toxicity Study in Fischer 344 Rats. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.287. September 17, 2002. MRID 45830813. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the acute oral toxicity of GF-881 , Lot No. C1413-26, Active 50.8%, tan liquid in Fischer 344 rats when administered at a dose level of 5000 mg/kg. Five male and 5 female Fischer 344 rats were used in the study (Age: 10 weeks. Weight: males 198-223g, females 136-145g. Source: Charles River, Inc., Raleigh, NC). On the day before study initiation animals were weighed and fasted overnight. On day "0" of the study a single dose of GF-881 (100% concentration) was administered by gavage to both sexes. The dose volume was 3.85 mL/kg. Animals were observed for signs of clinical abnormalities twice on day "0" and daily thereafter. Health and mortality checks were made twice daily. Body weights were taken on day -1, prior to test substance ingestion and again on days 7 and 14. A gross necropsy examination was performed on all animals.

No animals died during the study. Clinical abnormalities seen in the first few days included dark material around the nose and mouth, rough coat, urogenital fecal staining, urogenital urine staining, feces small in size, soft stools, white colored feces, and congested breathing. All animals gained weight during the study.

At necropsy, one incidence of foci on the thymus was observed. The performing laboratory conjectures that this was not related to the test article, however it should be noted that there were 3 incidences of foci on the lungs at necropsy in the technical product.

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The Oral LD₅₀ is greater than 5000 mg/kg for both male and female rats.

GF-881 is classified as Tox category IV for acute oral toxicity based on the lack of mortality in male and female rats following dosage at 5000 mg/kg.

This study is classified as **Acceptable** (870.1100) and satisfies the guideline requirement for an acute oral study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No]Confidentiality statements were provided.

RESULTS

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Total
5000	0/5	0/5	0/10

OBSERVATIONS: No animals died during the study. Clinical abnormalities seen in the first few days included dark material around the nose and mouth, rough coat, urogenital fecal staining, urogenital urine staining, feces small in size, soft stools, white colored feces, and congested breathing. All animals gained weight during the study.

GROSS NECROPSY: At necropsy, one incidence of foci on the thymus was observed. The performing laboratory conjectures that this was not related to the test article, however it should be noted that there were 3 incidences of foci on the lungs at necropsy in the technical product.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE DERMAL TOXICITY TESTING (870.1200 formerly §81-2)

Product Manager: 23

Reviewer: Tracy Keigwin

TEST MATERIAL PURITY: GF-881 , Lot No. C1413-26, Purity 50%, tan liquid

CITATION : Bonnette, Kimberly L. (2000) GF-881: An Acute Dermal Toxicity Study in Fischer 344 Rats. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.288. September 13, 2002. MRID 45830816. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the acute dermal toxicity of GF-881 , Lot No. C1413-26, Purity 50%, tan liquid in Fischer 344 Rats when administered as a single dermal dose at a dose level of 5000 mg/kg. Five male and 5 female New Zealand White rabbits were used in the study (Age: approximately 9 weeks. Weight: males 198-212g, females 135-144g. Source: Charles River, Inc., Raleigh NC). On the day prior to study initiation, fur was removed from the dorsal trunk area of the test animals. This represented about 10% of the animals body surface area (BSA). On day "0" an area representing approximately 10% of the BSA was marked in the clipped area with an indelible marker and a single dose of GF-881 (100% concentration) was applied to the skin at a dose level of 5000 mg/kg (3.85 mL/kg). A 4-ply porous gauze dressing backed with a plastic wrap was placed over the treated area . Elastic wrap was placed over the trunk and test area to minimize removal and/or ingestion of the test substance. "The elastic wrap was further secured with a tape harness on the cranial end of the trunk and then secured with adhesive tape around the trunk at the caudal end". After 24 hours all binding materials were removed and the test area wiped with a gauze moistened with deionized water followed by a dry gauze to remove any remaining test substance. "Observations for clinical abnormalities occurred 2 times on day 0 (post application) and daily thereafter. Health and mortality checks were taken twice daily". Bodyweights were taken prior to dosing (day 0) and again on days 7 and 14. A necropsy was performed on all test animals on study day 14.

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No animals died during the study. Clinical abnormalities included dermal irritation (erythema and edema) at the test site, lacrimation, dark material around the facial area, unkempt appearance, mucoid stools and soft stools. One female exhibited a small weight loss during the day 0 - day 7 interval, however all animals surpassed their initial bodyweight at study termination.

At necropsy, no significant findings were observed.

The Dermal LD₅₀ for both male and female rats is greater than 5000 mg/kg (observed).

GF-881 is classified as Tox category IV for acute dermal toxicity based on the lack of mortality in male and female rats following a dermal application of 5000 mg/kg.

This study is classified as **Acceptable** (870.1200) and satisfies the guideline requirement for an acute dermal study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Confidentiality statements were provided.

RESULTS

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

OBSERVATIONS: No animals died during the study. Clinical abnormalities included dermal irritation (erythema and edema) at the test site, lacrimation, dark material around the facial area, unkempt appearance, mucoid stools and soft stools. One female exhibited a small weight loss during the day 0 - day 7 interval, however all animals surpassed their initial bodyweight at study termination.

GROSS NECROPSY: At necropsy, no significant findings were observed.

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DATA EVALUATION RECORD

STUDY TYPE: PRIMARY EYE IRRITATION STUDY (870.2400 formerly §81-4)

Product Manager: 23

Reviewer: Tracy Keigwin

TEST MATERIAL PURITY: GF-881 , Lot No. C1413-26, Purity 50.8%, tan liquid pink tint

CITATION : Bonnette, Kimberly L. (2002) GF-881: A Primary Eye Irritation Study in New Zealand White Rabbits. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.289. September 11, 2002 MRID 45830821. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the potential irritating or corrosive effects of GF-881 , Lot No. C1413-26, Active 50.8%, tan liquid, in the eyes of 3 adult New Zealand white rabbits. Two males and 1 female were used in the study (Age: males approximately 12-14 weeks, female approximately 13 weeks. Weight: males 2.6-3.1 kg, female 3.0 kg. Source: Myrtle's Rabbitry, Thompson Station, TN). At study initiation a volume of 0.1 mL of GF-881 was dropped into the conjunctival sac of the right eye of each animal. The eyelids were held together for (approximately) one second to avoid loss of the testing material. The left eye was untreated to serve as the control. Animals were examined for signs of irritation at 1, 24, 48 and 72 hours after dosing. After the 24 hour observation a fluorescein examination was repeated on all test and control eyes. Any residual test article was rinsed from the eye with physiological saline at this time. "If any findings were noted another fluorescein examination was conducted at each interval until a negative response was obtained and/or the corneal opacity had cleared, or as directed by the study director". Health and mortality checks were performed twice daily (am and pm). Bodyweights were taken prior to dosing and prior to euthanasia.

No animal exhibited corneal opacity, iritis or positive signs of conjunctivitis at any time. Grade 1 (not considered positive effects) conjunctivitis was noted only at the 1 hour observation. "All animals gained bodyweight during the study".

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GF-881 is classified as Toxicity Category IV based on the absence of positive irritation effects at 24 hours and subsequently.

COMPLIANCE: Signed and dated GLP, Quality Assurance and (No)Confidentiality statements were provided.

RESULTS

A summary of the noted effects is listed (below)

Table 1.

Observations	Hours (number positive/number tested)			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
<u>Conjunctivae:</u>				
Redness ^a	0/3	0/3	0/3	0/3
Chemosis ^a	0/3	0/3	0/3	0/3
Discharge ^a	0/3	0/3	0/3	0/3

^a Score of 2 or more required to be considered "positive."

OBSERVATIONS: No animal exhibited corneal opacity, iritis or positive signs of conjunctivitis at any time. Grade 1 (not considered positive effects) conjunctivitis was noted only at the 1 hour observation. "All animals gained bodyweight during the study".

DATA EVALUATION RECORD

STUDY TYPE: PRIMARY DERMAL IRRITATION TESTING (870.2500 formerly §81-2)

Product Manager: 23

Reviewer: Tracy Keigwin

TEST MATERIAL PURITY: GF-881, Lot No. C1413-26, Purity 50.8%, tan liquid

CITATION : Bonnette, Kimberly L. (2000) GF-881: A Primary Skin Irritation Study in New Zealand White Rabbits. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.290. September 11, 2002. MRID 45830824. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the potential for dermally irritating or corrosive effects of GF-881, Lot No. C1413-26, Active 50.8%, tan liquid in NZW rabbits. One male and 2 females were used in the study (Age: approximately 11 weeks. Weight: male 2.6 kg, females 2.5-2.6 kg. Source: Myrtle's Rabbitry, Thompson Station, TN.) On the day prior to study initiation, fur was removed from the dorsal trunk area of the selected animals with animal clippers. On day "0" 0.5 ml of test article was applied to an area of skin of approximately 1"x 1". The test substance was administered underneath a 1" x 1" gauze patch secured with adhesive tape. Elastic wrap was placed over the trunk and test area to minimize removal and/or ingestion of the test substance. The elastic wrap was secured with tape around the trunk at cranial and caudal ends. "After dosing, collars were placed on each animal and remained in place until removal on day 3." After a 4 hours all binding materials were removed and the corners of the test site outlined with a marker. Residual test article was removed with a gauze (moistened with deionized water) and then a dry gauze. Following patch removal animals were observed and scored for erythema and edema at 1 hour, 24 hours, 48 hours, and 72 hours. Animals were observed for health/mortality twice daily (morning and afternoon). Bodyweights were recorded prior to application on day 0 and at euthanasia.

The Primary Dermal Irritation Index (PDII) = 0.0. No treatment related erythema or edema was observed in the study at any time and all animals gained weight. "Clinical observations related to collars caught in the animal's mouth (not test article related) were observed in 2/3 animals on day 1 only."

GF-881 is classified as Tox Category IV based on the lack of erythema or edema observed at any time during the study.

This study is classified as **Acceptable** (870.2500) and satisfies the guideline requirement for a Primary Dermal Irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and (No)Confidentiality statements were provided.

RESULTS: A summary of the noted effects is listed (below)

Rabbit	Observations	Hours			
		1	24	48	72
R2485/M	Erythema	0	0	0	0
	Edema	0	0	0	0
R2490/F	Erythema	0	0	0	0
	Edema	0	0	0	0
R2498/F	Erythema	0	0	0	0
	Edema	0	0	0	0

OBSERVATIONS: The Primary Dermal Irritation Index (PDII) = 0.0. No treatment related erythema or edema was observed in the study at any time and all animals gained weight. Clinical observations related to collars caught in the animal's mouth (not test article related) were observed in 2/3 animals on day 1 only."

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DATA EVALUATION RECORD

STUDY TYPE : PRIMARY DERMAL SENSITIZATION TESTING (870.2600 formerly §81-2)

Product Manager: 23

Reviewer: Tracy Keigwin

TEST MATERIAL PURITY: GF-881, Lot No. C1413-26, Purity 50.8%, tan liquid

CITATION : Bonnette, Kimberly L. (2000) GF-881: A Dermal Sensitization Study in Hartley Albino Guinea Pigs-Modified Buehler Design. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.291. September 12, 2002. MRID 45830827. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the dermal sensitization potential of GF-881, Lot No. C1413-26, Purity 50.8%, tan liquid, in Hartley-derived albino guinea pigs. Two males and 2 females were used in the range finding study and 15 males and 15 females were used in the main study (Age: males approximately 7-8 weeks, females approximately 8-10 weeks. Weight: males 356-497g; females 321-456 g. Source: Hilltop Lab Animals, Inc. Scottsdale, PA). This study was divided into 3 "Induction" doses at day 0, 6, and 13 days, followed by a challenge dose at day 27. "A range finding study determined that a 100% concentration was appropriate for the induction since this was the highest non-irritating concentration". Test and challenge control animals were weighed on the day prior to the first induction and the hair was clipped from the left side of the test animals with animal clippers. "At each induction a dose of 0.3 mL (100% concentration) of the test substance was placed on a 25 mm Hilltop chamber backed by adhesive tape (occlusive patch). The trunk of each animal was then wrapped with elastic wrap secured with adhesive tape to prevent chamber removal". Duration of exposure was 6 hours. This process was repeated on study day 6 and 13. Test article was removed after each induction via a gauze moistened with deionized water followed by a dry gauze. The animals were rested for 2 weeks. The day prior to the challenge dose test and challenge control animals were again weighed and the right side of both test and control animals clipped with animal clippers. On day 27 a dose of 0.3 mL (100% concentration) of the test substance was placed on chambers and the chambers then attached to test and

control animals. "The trunk of each animal was then wrapped with elastic wrap secured with adhesive tape to prevent chamber removal". Duration of the challenge exposure was 6 hours. As with the induction phases, the test article was removed with a moistened gauze followed by a dry gauze. Reactions were scored 24 and 48 hours after chamber application (induction) or chamber removal (challenge). Animals were observed for health/mortality twice daily (morning and afternoon). Two positive control studies using HCA and DNCB were conducted within six months of the main study to validate the test system.

No erythema or edema was observed in test or challenge control animals following challenge (scores for both sets of animals were limited to "0"). Animals gained weight and appeared healthy. No clinical abnormalities were observed in the study. The results of the 2 positive control studies were appropriate.

GF-881 is classified as a non sensitizer based on the results in this study.

This study is classified as **Acceptable** (870.2600) and satisfies the guideline requirement for a Dermal Sensitization in the guinea pig.

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

PROCEDURE: This study assessed the dermal sensitization potential of GF-881, Lot No. C1413-26, Purity 50.8%, tan liquid, in Hartley-derived albino guinea pigs. Two males and 2 females were used in the range finding study and 15 males and 15 females were used in the main study (Age: males approximately 7-8 weeks, females approximately 8-10 weeks. Weight: males 356-497g; females 321-456 g. Source: Hilltop Lab Animals, Inc. Scottsdale, PA). This study was divided into 3 "Induction" doses at day 0, 6, and 13 days, followed by a challenge dose at day 27. "A range finding study determined that a 100% concentration was appropriate for the induction since this was the highest non-irritating concentration". Test and challenge control animals were weighed on the day prior to the first induction and the hair was clipped from the left side of the test animals with animal clippers. "At each induction a dose of 0.3 mL (100% concentration) of the test substance was placed on a 25 mm Hilltop chamber backed by adhesive tape (occlusive patch). The trunk of each animal was then wrapped with elastic

wrap secured with adhesive tape to prevent chamber removal". Duration of exposure was 6 hours. This process was repeated on study day 6 and 13. Test article was removed after each induction via a gauze moistened with deionized water followed by a dry gauze. The animals were rested for 2 weeks. The day prior to the challenge dose test and challenge control animals were again weighed and the right side of both test and control animals clipped with animal clippers. On day 27 a dose of 0.3 mL (100% concentration) of the test substance was placed on chambers and the chambers then attached to test and control animals. "The trunk of each animal was then wrapped with elastic wrap secured with adhesive tape to prevent chamber removal". Duration of the challenge exposure was 6 hours. As with the induction phases, the test article was removed with a moistened gauze followed by a dry gauze. Reactions were scored 24 and 48 hours after chamber application (induction) or chamber removal (challenge). Animals were observed for health/mortality twice daily (morning and afternoon). Two positive control studies using HCA and DNCB were conducted within six months of the main study to validate the test system.

RESULTS: No erythema or edema was observed in test or challenge control animals following challenge (scores for both sets of animals were limited to "0"). Animals gained weight and appeared healthy. No clinical abnormalities were observed in the study. The results of the 2 positive control studies were appropriate.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D288069
2. **PC CODE:** PC Code: 119031 Benzenesulfonamide, 2-(2,2-difluoroethoxy) - N-(5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl)-6(trifluoromethyl) (DE-638, Penoxsulam)
3. **CURRENT DATE:** June 9, 2003
4. **TEST MATERIAL:** GF-881, Lot No. C1413-26, Purity 50.8%, tan liquid

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Springborn Laboratories, Inc. Study # 3504.287 September 17, 2002	45830813	LD ₅₀ is greater than 5000 mg/kg for both males and females	IV	A
Acute dermal toxicity/rabbit Springborn Laboratories, Inc. Study # 3504.288 September 13, 2002	45830816	LD ₅₀ is greater than 5000 mg/kg for both males and females	IV	A
Acute inhalation toxicity/rat*		Waiver request	-	U
Primary eye irritation/rabbit Springborn Laboratories, Inc. Study # 3504.289 September 11, 2002	45830821	No positive sign of corneal opacity, iritis or conjunctivitis at any time	IV	A
Primary dermal irritation/rabbit Springborn Laboratories, Inc. Study # 3504.290 September 11, 2002	45830824	(PDII) = 0.0. No erythema or edema observed	IV	A
Dermal sensitization/guinea pig Springborn Laboratories, Inc. Study # 3504.291 September 12, 2002	45830827	Not a Sensitizer	No	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

*Toxicity category can not be assigned due to unacceptability of the acute inhalation waiver

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