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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

23/MAY/2003

MEMORANDUM

Subject: Penoxsulam Technical
EPA File Symbol 62719-UOO
DP Barcode: D288004
Case No: 065248
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
Technical Review Branch
Registration Division (7505C)

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

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

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s):	
Penoxsulam: 2-(2,2-difluoroethoxy) - 6-trifluoromethyl-N-(5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl) benzenesulfonamide	98.0
Inert Ingredient(s)	2.0
Total:	100.00

ACTION REQUESTED: PM requests review of acute toxicity data for new chemical Penoxsulam, EPA File Symbol 62719-UOO.

BACKGROUND: Dow AgroSciences LLC has submitted six acute toxicity studies in support of registration of the technical of the new chemical Penoxsulam, EPA File Symbol 62719-UOO. This is a "manufacturing use only" product for formulation into an herbicide for use only on rice. The studies (MRIDs 45830812, 45830815, 45830820, 45830823, 45830826, and 45830902) were conducted at Springborn Laboratories, Inc., Ohio Research Center, 640 North Elizabeth Street, Spencerville, Ohio 45887. The inhalation study (MRID 45830818) was conducted at Huntingdon Life Sciences, East Millstone, NJ.

RECOMMENDATIONS:

The acute toxicity profile for EPA File Symbol 62719-UOO is as follows:

Acute oral toxicity	IV	Acceptable	MRID 45830812
Acute dermal toxicity	IV	Acceptable	MRID 45830815
Acute inhalation toxicity	-	**Unacceptable**	MRID 45830818
Primary eye irritation	IV	Acceptable	MRID 45830820
Primary skin irritation	IV	Acceptable	MRID 45830823
Dermal sensitization	No	Acceptable	MRID 45830826

OF NOTE: The acute inhalation study is **unacceptable**. The average gravimetric concentration of test substance that the test animals were exposed to in hours 1-3 differs significantly from the measurement recorded during the 4th hour of exposure. The performing laboratory states the following:

"...the (gravimetric) exposure averaged 4.23 mg/L during the first 3 hours of the exposure but only 1.3 mg/L during the 4th hour of exposure. The cause of the low exposure during the 4th hour was not clearly determined. A total of 16.7 g of test substance was used during the exposure, resulting in a nominal concentration of 2.7 mg/L The difference between the measured and nominal concentrations was atypical for this type of exposure and was considered either a result of the low exposure conditions of the 4th hour of exposure or a weighing error affecting the nominal concentration measurement."

The difference between the measured and nominal concentrations is (as the performing laboratory admits) not usual. 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. Clearly, as the performing laboratory itself indicates, a significant and unexplainable error occurred in the study. The results of the study must be considered suspect and are therefore not acceptable to support this new chemical (particularly when an acute toxicity category of "4" is claimed).

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: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint

CITATION : Bonnette, Kimberly L. (2000) XDE-638: An Acute Oral Toxicity Study in Rats. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.19. January 20, 2000. MRID 45830812. Unpublished.

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

EXECUTIVE SUMMARY: This study assessed the acute oral toxicity of XDE-638, Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint 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 170-211g, females 122-149g. Source: Harlan Sprague Dawley, Inc.). On the day before study initiation animals were weighed and fasted overnight. On day "0" of the study a single dose of XDE-638 was administered by gavage to both sexes; for administration the test article was mixed with 0.5% w/v methylcellulose in distilled water. The dosage was at 10 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 (transient, and only in a few animals) observed during the study included dark material around the mouth during the first 2 days of the study, mucoid stools, abnormal colored feces, and fecal/urine stain.

At necropsy, "3 incidences of foci on the lungs were observed on day 14. The relationship of these foci to the test material could not be determined".

The Oral LD_{50} is greater than 5000 mg/kg for both male and female rats.

XDE-638 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.

Deviations from Protocol: "A retention sample of the test article was inadvertently collected and subsequently discarded on the same day".

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 (transient, and only in a few animals) observed during the study included dark material around the mouth during the first 2 days of the study, mucoid stools, abnormal colored feces, and fecal/urine stain.

GROSS NECROPSY: At necropsy, "3 incidences of foci on the lungs were observed on day 14. The relationship of these foci to the test material could not be determined".

DATA EVALUATION RECORD

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

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint

CITATION : Bonnette, Kimberly L. (2000) XDE-638: An Acute Dermal Toxicity Study in Rabbits. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.20. January 20, 2000. MRID 45830815. Unpublished.

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

EXECUTIVE SUMMARY: This study assessed the acute dermal toxicity of XDE-638, Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint in New Zealand White rabbits 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 12 weeks. Weight: males 2.4-2.6 kg, females 2.4-2.9 kg. Source: Mrytles Rabbitry, Thompson Station, TN). 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 XDE-638 (moistened with deionized water at 1 mL for every gram of test article applied) was applied to the skin at a dose level of 5000 mg/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 secured with a tape around the trunk at the caudal and cranial ends". 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 3 times on day 0 (post application) and daily thereafter". 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.

No animals died during the study. Clinical abnormalities "were transient and usually occurred with the first 4 days of the study post dose". They included dark material around the facial area, decreased defecation, scabs, hairloss, lacrimation, and soft stools. Dermal irritation (erythema and edema) was observed at the test site, usually through day 4, in all animals. One female exhibited a slight body weight loss at the 0-7 day interval and another female at the 7-14 day interval. All animals surpassed their initial bodyweight by study termination.

At necropsy, one animal exhibited reddened mammary glands and another liver tabs. Two instances of cysts on the oviducts were also observed. These findings may have been incidental.

The Dermal LD_{50} for both male and female rats is greater than 5000 mg/kg (observed).

XDE-638 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.

Deviations from Protocol: "A retention sample of the test article was inadvertently collected and subsequently discarded on the same day". The range in temperature was greater than that recommended by 870.1200 however it is unlikely that this would have effected study results.

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 "were

transient and usually occurred with the first 4 days of the study post dose". They included dark material around the facial area, decreased defecation, scabs, hairloss, lacrimation, and soft stools. Dermal irritation (erythema and edema) was observed at the test site, usually through day 4, in all animals. One female exhibited a slight body weight loss at the 0-7 day interval and another female at the 7-14 day interval. All animals surpassed their initial bodyweight by study termination.

GROSS NECROPSY: At necropsy, one animal exhibited reddened mammary glands and another liver tabs. Two instances of cysts on the oviducts were also observed. These findings may have been incidental.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE INHALATION TOXICITY TESTING (870.1300 formerly §81-3)

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 . Lot No. ND05167938, Purity 97.5%, off white powder

CITATION : Hoffman, Gary M. (1999) XDE-638: Acute (4 -hour) inhalation toxicity study in the fischer 344 rat via nose-only exposure. Huntingdon Life Sciences, P.O. Box 2360, Mettlers Road, East Millstone, New Jersey 08875-2360. Laboratory Project ID 99-5402. December 23, 1999. MRID 45830818. Unpublished.

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

EXECUTIVE SUMMARY: This study assessed the acute inhalation toxicity of XDE-638, Lot No. ND05167938, Purity 97.5%. off white powder, in Albino (Inbred) Fischer 344 (Fischer CDF®(F-344)/CrlBR) rats. Test subjects were exposed to a four hour "Nose only" chamber average exposure concentration of 3.50 mg/L (gravimetrically determined). Five male and 5 female Albino (Inbred) Fischer 344 rats were used (Age: 10 weeks. Weight: males 224-243g, females 134-156g. Source: Charles River Laboratories, Raleigh, North Carolina, 27610). On day "1" selected animals were placed in nose-only exposure tubes and the tubes inserted into a 40 litre nose-only inhalation chamber. The testing substance was aerosolized to an average exposure level of 3.50 mg/L. "Animals were observed individually immediately prior to exposure, as a group at approximately fifteen minute intervals during the first hour of exposure, and hourly for the reminder of the exposure period. Animals were observed individually upon removal from the chamber and hourly for 2 hours post exposure". Animals were observed once daily for study days 2-15. Weights were taken prior to exposure and again on 2, 4, 8, 11 and 15. A necropsy was performed on all test animals on study day 15.

No animals died during the study. Animals received an average of 4.23 mg/L during the first 3 hours of exposure, but only 1.3 mg/L during the fourth. Signs of toxicity during exposure included labored breathing in 2/10 animals. Upon removal from the chamber

animals exhibited labored breathing, moist rales, dried red material on the facial area, chromodacryorrhea, excessive salivation, clear nasal discharge and lacrimation. Animals were "generally" free of these symptoms after the first few days. Animals additionally exhibited wet fur, matted coat and white material on fur following exposure however this was considered "artifacts of the nose-only regimen". Although most test animals lost weight on the day after exposure, all test animals surpassed their initial body weight by study termination.

No abnormalities were observed at necropsy.

The acute Inhalation LC_{50} and resulting toxicity category of XDE-638 can not be determined due to the unacceptability of this acute inhalation study. The average gravimetric concentration of test substance that the test animals were exposed to in hours 1-3 differs significantly from the measurement recorded during the 4th hour of exposure. The performing laboratory states the following:

"...the (gravimetric) exposure averaged 4.23 mg/L during the first 3 hours of the exposure but only 1.3 mg/L during the 4th hour of exposure. The cause of the low exposure during the 4th hour was not clearly determined. A total of 16.7 g of test substance was used during the exposure, resulting in a nominal concentration of 2.7 mg/L The difference between the measured and nominal concentrations was atypical for this type of exposure and was considered either a result of the low exposure conditions of the 4th hour of exposure or a weighing error affecting the nominal concentration measurement."

The difference between the measured and nominal concentrations is (as the performing laboratory admits) not usual. 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. Clearly, as the performing laboratory itself indicates, a significant and unexplainable error occurred in the study. The results of the study must be considered suspect and are therefore not acceptable to support this new chemical (particularly when an acute toxicity category of "4" is claimed).

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

RESULTS

Average Exposure Concentration (mg/L)*	Number of Deaths/Number Tested		
	Males	Females	Combined
3.50	0/5	0/5	0/10

*Nominal concentration for exposure 2.78 mg/L

Chamber atmosphere

GravimetricConcentration (mg/L)*	Exposure Hour	MMAD (µm)	GSD
4.0	1	4.966	1.887
4.4	2	3.679	1.768
4.3	3	4.083	1.739
1.3	4	2.769	1.687

*Nominal concentration for exposure 2.78 mg/L

Chamber Environment

Chamber volume (L)	40
Mean Airflow Rate (L/min)	25
Temperature (C)	23-24
Relative Humidity(%)	33-54

OBSERVATIONS: No animals died during the study. Animals received an average of 4.23 mg/L during the first 3 hours of exposure, but only 1.3 mg/L the fourth. Signs of toxicity during exposure included labored breathing in 2/10 animals. Upon removal from the chamber animals exhibited labored breathing, moist rales, dried red material on the facial area, chromodacryorrhea, excessive salivation, clear nasal discharge and lacrimation. Animals were "generally" free of these symptoms after the first few days. Animals additionally exhibited wet fur, matted coat and white material on fur following exposure however this was considered "artifacts of the nose-only regimen". Although most test animals lost weight on the day after exposure, all test animals surpassed their initial body weight by study termination.

GROSS NECROPSY: No abnormalities were observed at necropsy.

DATA EVALUATION RECORD

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

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint

CITATION : Bonnette, Kimberly L. (2000) XDE-638: A Primary Eye Irritation Study in New Zealand White Rabbits. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.21. January 20, 2000. MRID 45830820. Unpublished.

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

EXECUTIVE SUMMARY: This study assessed the potential irritating or corrosive effects of XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint, in the eyes of 3 young adult New Zealand white rabbits. Three males were used in the study (Age: approximately 15 weeks. Weight: 3.1-3.4 kg. Source: Myrtle's Rabbitry, Thompson Station, TN). At study initiation a volume of 0.1 mL (0.0630 g) of XDE-638 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 at study termination.

XDE-638 is classified as Toxicity Category IV based on the absence of positive irritation effects at 24 hours and subsequently.

No animal exhibited corneal opacity or positive signs of conjunctivitis at any time. At 1

hour all animals (3/3) exhibited positive signs of iritis, resolving within 24 hours. Grade 1 (not considered positive effects) conjunctivitis was noted through the 48 hour observation.

Deviations from Protocol: "A retention sample of the test article was inadvertently collected and subsequently discarded on the same day".

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	3/3	0/3	0/3	0/3
Conjunctivae:				
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 or positive signs of conjunctivitis at any time. At 1 hour all animals (3/3) exhibited positive signs of iritis, resolving within 24 hours. Grade 1 (not considered positive effects) conjunctivitis was noted through the 48 hour observation.

DATA EVALUATION RECORD

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

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint

CITATION : Bonnette, Kimberly L. (2000) XDE-638: A Primary Skin Irritation Study in New Zealand White Rabbits. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.22. January 20, 2000. MRID 45830823. 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 XDE-638 , Lot No. ND05167938, Purity 97.5%, an off white powder with a pink tint in NZW rabbits. . Three males were used in the study (Age: approximately 12 weeks. Weight: males 2.7 kg -2.8 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 g of test article moistened with 0.5ml of deionized water 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 hour period of exposure, all binding materials were removed and the corners of the test site outlined with a marker. Any residual test article was removed via a gauze moistened with deionized water followed by 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 study termination.

The Primary Dermal Irritation Index (PDII) = 0.33. All animals (3/3) exhibited very slight erythema (grade 1) at 1 hour, resolving within 24 hours in 2/3 animals and within 48 hours in the remaining animal.

XDE-638 is classified as Tox Category IV based on the clearing of very slight erythema (grade 1) by 48 hours.

Deviations from Protocol: "A retention sample of the test article was inadvertently collected and subsequently discarded on the same day".

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: The Primary Dermal Irritation Index (PDII) = 0.33. A summary of the noted effects is listed (below)

Rabbit	**Observations**	**Hours**			
		1	24	48	72
R1126/M	Erythema	1	0	0	0
	Edema	0	0	0	0
R1136/M	Erythema	1	1	0	0
	Edema	0	0	0	0
R1137/M	Erythema	1	0	0	0
	Edema	0	0	0	0

OBSERVATIONS: The Primary Dermal Irritation Index (PDII) = 0.33. All animals (3/3) exhibited very slight erythema (grade 1) at 1 hour, resolving within 24 hours in 2/3 animals and within 48 hours in the remaining animal.

DATA EVALUATION RECORD

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

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint

CITATION : Bonnette, Kimberly L. (2000) XDE-638: A Dermal Sensitization Study in Hartley Albino Guinea Pigs-Maximization Design. Springborn Laboratories, Inc., Spencerville, Ohio. SLI Study No. 3504.23. January 20, 2000. MRID 45830826. Unpublished.

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

EXECUTIVE SUMMARY: This study assessed the dermal sensitization potential of XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint, in Hartley-derived albino guinea pigs. Ten male and 10 female Hartley-derived albino guinea pigs were used in the main sensitization study (Main Sensitization Study: males approximately 6 weeks, 363-434g, females approximately 8 weeks, 336-376g Source: Hilltop Lab animals, Inc. Scottsdale, PA). Based on the intradermal and topical range finding studies it was determined that concentrations of 5.0% w/v XDE-638 and 100% XDE-638 would be used for the intradermal and topical applications, respectively. On the day prior to the intradermal induction test and control animals were weighed and their hair removed from the scapular area with animal clippers. "On day "0" 3 pairs of intradermal injections were made in the clipped area of all sensitization study animals. The injections were kept within an approximate 2 x 4 cm area with one row of 3 injections on each side of the backbone". The induction injections for the test animals were as follows: Injection Pair A: 0.1 mL of FCA emulsion, Injection B: 0.1 mL of 5.0% w/v XDE-638 in propylene glycol, Injection pair C: 0.1 mL of 5.0 % w/v XDE-638/FCA emulsion. Injections for the 10 (5 male, 5 female) control animals were as follows: Injection Pair A: 0.1 mL of FCA emulsion, Injection Pair B: 0.1 mL of 5.0% w/v XDE-638 in propylene glycol, Injection pair C: 0.1 mL of 5.0 % w/v XDE-638/FCA emulsion. On the day prior to the topical induction (day 6) hair was removed from the guinea pigs

On the day prior to the topical induction (day 6) hair was removed from the guinea pigs with animal clippers. After the clipping, 0.5 mL of 10% w/w sodium lauryl sulfate in petrolatum was spread over the injection sites of all study animals. The following day (study day 7) residual sodium lauryl sulfate was removed with a dry gauze. The topical induction applications (applied over the injection sites) were as follows: test animals were given 0.30 g of XDE-638 (100% concentration) moistened with 12 drops of propylene glycol. Propylene glycol (100% concentration) was applied to the challenge control animals. A 2 x 4 cm Webril patch was placed over the injection sites and secured with adhesive tape. After 48 hours all binding materials were removed and the test sites were wiped with a gauze moistened with deionized water.

On the day prior to challenge application (study day 20) hair was removed from the right side of the test and challenge control animals with animal clippers. On study day 21 0.25g of 100% concentration XDE-638 moistened with 8 drops of propylene glycol was applied to the animals and covered with a 25 mm Hilltop chamber. The trunk of each animal was wrapped with elastic wrap secured with adhesive tape. After 24 hours all binding materials were removed and the test sites wiped with a gauze moistened with deionized water followed by a dry gauze to remove any remaining test material. Challenge sites were scored for dermal irritation at approximately 24 and 48 hours after chamber removal. Bodyweights were taken prior to intradermal induction, (for test and challenge control animals) prior to challenge dosing and prior to euthanasia. Two positive control studies using DNCB and HCA were performed within approximately 6 months of this study to validate the test system.

XDE-638 is classified as a non sensitizer based on the results in this study.

Following challenge, slight patchy erythema (grade ±) was observed in 6/20 test animals and 2/10 challenge control animals at the 24 hour observation, decreasing to 1/20 test animals and 0/10 challenge control animals at the 48 hour observation. All of the test and challenge control animals exhibited dermal irritation outside of the test site at the 24 and (for the challenge control animals) 48 hour observation. Ten of the 20 test animals additionally exhibited desquamation at the 48 hour observation following challenge. All animals gained weight and "appeared in good health" during the study. The results of the positive control studies were appropriate.

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

Deviations from protocol: "A retention sample of the test article was inadvertently

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

PROCEDURE: This study assessed the dermal sensitization potential of XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint, in Hartley-derived albino guinea pigs. Ten male and 10 female Hartley-derived albino guinea pigs were used in the main sensitization study (Main Sensitization Study: males approximately 6 weeks, 363-434g, females approximately 8 weeks, 336-376g Source: Hilltop Lab animals, Inc. Scottsdale, PA). Based on the intradermal and topical range finding studies it was determined that concentrations of 5.0% w/v XDE-638 and 100% XDE-638 would be used for the intradermal and topical applications, respectively. On the day prior to the intradermal induction test and control animals were weighed and their hair removed from the scapular area with animal clippers. "On day "0" 3 pairs of intradermal injections were made in the clipped area of all sensitization study animals. The injections were kept within an approximate 2 x 4 cm area with one row of 3 injections on each side of the backbone". The induction injections for the test animals were as follows: Injection Pair A: 0.1 mL of FCA emulsion, Injection B: 0.1 mL of 5.0% w/v XDE-638 in propylene glycol, Injection pair C: 0.1 mL of 5.0 % w/v XDE-638/FCA emulsion. Injections for the 10 (5 male, 5 female) control animals were as follows: Injection Pair A: 0.1 mL of FCA emulsion, Injection Pair B: 0.1 mL of 5.0% w/v XDE-638 in propylene glycol, Injection pair C: 0.1 mL of 5.0 % w/v XDE-638/FCA emulsion. On the day prior to the topical induction (day 6) hair was removed from the guinea pigs with animal clippers. After the clipping, 0.5 mL of 10% w/w sodium lauryl sulfate in petrolatum was spread over the injection sites of all study animals. The following day (study day 7) residual sodium lauryl sulfate was removed with a dry gauze. The topical induction applications (applied over the injection sites) were as follows: test animals were given 0.30 g of XDE-638 (100% concentration) moistened with 12 drops of propylene glycol. Propylene glycol (100% concentration) was applied to the challenge control animals. A 2 x 4 cm Webril patch was placed over the injection sites and secured with adhesive tape. After 48 hours all binding materials were removed and the test sites were wiped with a gauze moistened with deionized water.

On the day prior to challenge application (study day 20) hair was removed from the right side of the test and challenge control animals with animal clippers. On study day 21 0.25g of 100% concentration XDE-638 moistened with 8 drops of propylene glycol was applied to the animals and covered with a 25 mm Hilltop chamber. The trunk of each animal was wrapped with elastic wrap secured with adhesive tape. After 24 hours all binding materials were removed and the test sites wiped with a gauze moistened with deionized water followed by a dry gauze to remove any remaining test material.

binding materials were removed and the test sites wiped with a gauze moistened with deionized water followed by a dry gauze to remove any remaining test material. Challenge sites were scored for dermal irritation at approximately 24 and 48 hours after chamber removal. Bodyweights were taken prior to intradermal induction, (for test and challenge control animals) prior to challenge dosing and prior to euthanasia. Two positive control studies using DNCB and HCA were performed within approximately 6 months of this study to validate the test system.

RESULTS: Following challenge, slight patchy erythema (grade ±) was observed in 6/20 test animals and 2/10 challenge control animals at the 24 hour observation, decreasing to 1/20 test animals and 0/10 challenge control animals at the 48 hour observation. All of the test and challenge control animals exhibited dermal irritation outside of the test site at the 24 and (for the challenge control animals) 48 hour observation. Ten of the 20 test animals additionally exhibited desquamation at the 48 hour observation following challenge. All animals gained weight and "appeared in good health" during the study. The results of the positive control studies were appropriate.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D288004
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:** May 23, 2003
4. **TEST MATERIAL:** XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder with a pink tint (pink tint not present in acute inhalation study)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Springborn Laboratories, Inc. Study # 3504.19 January 20, 2000	45830812	LD_{50} is greater than 5000 mg/kg for both males and females	IV	A
Acute dermal toxicity/rabbit Springborn Laboratories, Inc. Study # 3504.20 January 20, 2000	45830815	LD_{50} is greater than 5000 mg/kg for both males and females	IV	A
Acute inhalation toxicity/rat* Huntingdon Life Sciences Laboratory Project ID 99-5402 December 23, 1999	45830818	-	-	U
Primary eye irritation/rabbit Springborn Laboratories, Inc. Study # 3504.21 January 20, 2000	45830820	Presence of Iritis, resolving within 24 hours	IV	A
Primary dermal irritation/rabbit Springborn Laboratories, Inc. Study # 3504.22 January 20, 2000	45830823	(PDII) = 0.33. Slight erythema (grade 1) at 1 hour, resolving within 48 hours.	IV	A
Dermal sensitization/guinea pig Springborn Laboratories, Inc. Study # 3044.898 October 8, 2002	45830826	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 study