received 8-23-05
R. Comm for DAS

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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

31/JAN/2005

MEMORANDUM

AcuteTox
Rev.
01-31-05

Subject: Name of Pesticide Product: GF-982
EPA Reg. No. /File Symbol: 62719-LEL
DP Barcode: D312229
Decision No: 352343
PC Codes: 005100, 128968

From: Eugenia McAndrew, Biologist EM
Technical Review Branch
Registration Division (7505C)

To: Eugene Wilson, RM Team 23
Herbicide Branch
Registration Division (7505C)

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

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
005100	Aminopyralid TIPA salt	1.92
128968	Fluroxpyr 1-methylheptyl ester	20.22
	Inert Ingredient(s):	77.86
	Total:	100.00

ACTION REQUESTED: RM requests review of acute toxicity data for GF-982, EPA File Symbol 62719-LEL.

BACKGROUND: Dow AgroSciences LLC has submitted a six pack of acute toxicity studies to support the registration of GF-982, EPA File Symbol 62719-LEL. The acute oral toxicity, acute dermal toxicity and primary skin irritation studies were conducted at Charles River Laboratories, Inc., Discovery and Development Services, Springborn Division, Spencerville, Ohio. The acute inhalation toxicity study was conducted at Toxicology & Environmental Research and Consulting, Midland, Michigan. The primary eye irritation and dermal sensitization stud were conducted at Product Safety Labs, Dayton, New Jersey. The assigned MRID numbers are 464342-03, -04, -06, -07, -08 and 46438902.

RECOMMENDATIONS: The six studies have been reviewed and are classified as acceptable.

The acute toxicity profile for GF-982, EPA File Symbol 62719-LEL, is as follows:

acute oral toxicity	III	Acceptable	MRID 46434203
acute dermal toxicity	IV	Acceptable	MRID 46434204
acute inhalation toxicity	IV	Acceptable	MRID 46438902
primary eye irritation	I	Acceptable	MRID 46434206
primary skin irritation	III	Acceptable	MRID 46434207
dermal sensitization	Negative	Acceptable	MRID 46434208

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

PRODUCT ID #: 062719-00525

PRODUCT NAME: GF-982

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: DANGER

SPANISH SIGNAL WORD: PELIGRO
Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification.

Corrosive. Causes irreversible eye damage. Harmful if swallowed. Avoid contact with skin or clothing. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Barrier Laminate, Butyl Rubber, Nitrile Rubber, Viton, Barrier Laminate, Viton, Selection Category F, G). If the Selection Category F, G gloves do not provide adequate protection for this product, the registrant should indicate a specific glove category from the EPA chemical resistance glove selection chart that will provide adequate protection.

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.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give any liquid to the person.
-Do not give anything by mouth to an unconscious person.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

Note to physician: Probable mucosal damage may contraindicate the use of gastric lavage. The proposed label should contain a Note to Physician which addresses the category I Primary Eye Irritant toxicity. The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

User Safety Recommendations:

Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Eugenia McAndrew January 31, 2005
Risk Manager: 23

STUDY TYPE: Acute Oral Toxicity - S-D Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

CITATION: Smedley, J. GF-982: An Acute Oral Toxicity Study in Fischer 344 Rats (Up/ Down Design). Charles River Laboratories, Inc., Springborn Division, Spencerville, Ohio. Laboratory Report Number 3504.337. November 18, 2003. MRID 46434203. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, Indiana

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46434203), fifteen female young adult Fischer 344 rats (Age: 8-12 weeks; Source: Charles River Laboratories, Inc., Raleigh, NC; 123-162 g) were given a single oral dose of GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid) using the Up and Down Procedure. The study was initiated at a dose level of 2000 mg/kg. (The 2000 mg/kg dose level was utilized as an alternate level to 1750 mg/kg in consideration of European Regulatory categorization criteria.) "Based on the OECD 425 Acute Oral Toxicity Statistical Program, as each level was dosed, the dose level was increased or decreased (2000 mg/kg, 5000 mg/kg) pending the mortality outcome." Animals were then observed for 14 days.

Oral LD_{50} Females = 5000 mg/kg bw (95% C.L. 3417-9770 mg/kg)

The six animals dosed at 2000 mg/kg survived and gained weight. Clinical signs noted were incidences of few feces, unkempt appearance, urine staining-urogenital region, rough coat, increased lacrimation and increased salivation. No gross observations were noted at necropsy. At 5000 mg/kg, 5/9 animals died by day 2. Toxic signs noted prior to death included decreased resistance to removal, labored breathing, shallow breathing, slow breathing, no feces, decreased food consumption, hunched posture, cool to the touch, urine staining, activity decrease, palpebral closure, decreased pupil size, increased lacrimation, increased salivation, decreased muscle tone, decreased extensor thrust response, decreased reactivity to handling, decreased responsiveness to touch, gait evaluations of poor coordination and inability to walk. Clinical signs noted for the four surviving animals were transient incidences of decreased resistance to removal, labored breathing, shallow breathing, few feces, no feces, dark material around the facial area, decreased food consumption, hunched posture, cool to the touch, urine staining, unkempt appearance, rough coat, activity decrease increased lacrimation, increased salivation, decreased muscle tone, decreased extensor thrust response and decreased reactivity to handling. The surviving animals gained weight during the study. Gross necropsy of the decedents revealed abnormal content of the digestive system, dark red areas on the lungs, dark red thymus, pale liver, foci on the stomach and no fecal content in the colon. No gross observations were noted at necropsy for the animals surviving to study termination.

Toxicity based on the LD_{50} in females. EPA Toxicity Category III.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

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

RESULTS and DISCUSSION:

Individual animals were dosed as follows:

Main Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	Short Term Outcome	14 Day Outcome
1	A7782	2000	O	O
2	A7790	5000	X	X
3	A7798	2000	O	O
4	A7801	5000	O	O
5	A7808	5000	X	X
6	A7818	2000	O	O
7	A7947	5000	X	X
8	A7954	2000	O	O
9	A7946	5000	O	O
10	A7955	5000	X	X
11	A7961	2000	O	O
12	A7944	5000	O	O
13	A7949	5000	X	X
14	A7958	2000	O	O
15	A7952	5000	O	O

O= survival X = death

Statistics - The Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or oral LD_{50} and confidence limit calculations.

A. **Mortality** - as noted in table.

B. **Clinical observations** - The six animals dosed at 2000 mg/kg survived and gained weight. Clinical signs noted were incidences of few feces, unkempt appearance, urine staining-urogenital region, rough coat, increased lacrimation and increased salivation. No gross observations were noted at necropsy. At 5000 mg/kg, 5/9 animals died by day 2. Toxic signs noted prior to death included decreased resistance to removal, labored breathing, shallow breathing, slow breathing, no feces, decreased food consumption, hunched posture, cool to the touch, urine staining, activity decrease, palpebral closure, decreased pupil size, increased lacrimation, increased salivation, decreased muscle tone, decreased extensor thrust response, decreased reactivity to handling, decreased responsiveness to touch, gait evaluations of poor coordination and inability to walk. Clinical signs noted for the four surviving animals were transient incidences of decreased resistance to removal, labored breathing, shallow breathing, few feces, no feces, dark material around the facial area, decreased food consumption, hunched posture, cool to the touch, urine staining, unkempt appearance, rough coat, activity decrease increased lacrimation, increased salivation, decreased muscle tone, decreased extensor thrust response and decreased reactivity to handling. The surviving animals gained weight during the study.

C. **Gross Necropsy** - Gross necropsy of the decedents revealed abnormal content of the digestive system, dark red areas on the lungs, dark red thymus, pale liver, foci on the stomach and no fecal content in the colon. No gross observations were noted at necropsy for the animals surviving to study termination.

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

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Friday, January 28, 2005, 9:19:41 AM
Data file name: GF-982.dat
Last modified: 1/28/2005 9:19:39 AM

Test/Substance: GF-982
Test type: **Main Test**
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 5000, 1750, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	A7782	2000	O	O
2	A7790	5000	X	X
3	A7798	2000	O	O
4	A7801	5000	O	O
5	A7808	5000	X	X
6	A7818	2000	O	O
7	A7947	5000	X	X
8	A7954	2000	O	O
9	A7946	5000	O	O
10	A7955	5000	X	X
11	A7961	2000	O	O
12	A7944	5000	O	O
13	A7949	5000	X	X
14	A7958	2000	O	O
15	A7952	5000	O	O

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

WARNING:
Please review the data for accuracy.
Starting the Main Test above the likely LD50 will induce bias toward the starting dose. See OECD Guideline 425.

Stopping criteria met: Maximum number of animals tested.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
2000	6	0	6
5000	4	5	9
All Doses	10	5	15

Statistical Estimate based on long term outcomes:

Estimated LD50 = 5000 (The one dose with partial response).

95% PL Confidence interval is 3417 to 9770.

Reviewer: Eugenia McAndrew January 31, 2005
Risk Manager: 23

STUDY TYPE: Acute Dermal Toxicity - S-D Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

CITATION: Smedley, J. GF-982: An Acute Dermal Toxicity Study in Fischer 344 Rats. Charles River Laboratories, Inc., Springborn Division, Spencerville, Ohio. Laboratory Report Number 3504.338. September 30, 2003. MRID 46434204. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, Indiana

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46434204), 5/sex of young adult Fischer 344 rats (Age: 8 weeks; Source: Charles River Laboratories, Inc., Raleigh, NC; 183-190 g males and 130-137 g females) were dermally exposed to GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid). Five thousand mg/kg of the test substance was applied to approximately 10% of body surface area of each animal. The test sites were covered with a porous gauze dressing backed with a plastic wrap placed over the gauze dressing (occlusive binding) for a period of 24 hours. Animals were then observed for 14 days.

Dermal LD_{50} Males => 5000 mg/kg bw
Dermal LD_{50} Females => 5000 mg/kg bw
Dermal LD_{50} Combined => 5000 mg/kg bw

All animals survived and gained weight. Clinical signs noted were dark material around the facial area, soft stools, urine staining and increased lacrimation. Dermal irritation was noted at all test sites. No gross abnormalities were observed for any of the animals necropsied at the end of the study.

Toxicity based on the lack of deaths at the limit dose. EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

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

RESULTS and DISCUSSION:

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

A. Mortality - none

B. Clinical observations - All animals survived and gained weight. Clinical signs noted were dark material around the facial area, soft stools, urine staining and increased lacrimation. Dermal irritation was noted at all test sites.

C. Gross Necropsy - No gross abnormalities were observed for any of the animals necropsied at the end of the study.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew January 31, 2005
Risk Manager: 23

STUDY TYPE: Acute Inhalation Toxicity -S-D rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

CITATION: Landry, T.D. and Krieger, S.M.. GF-982: Acute Liquid Aerosol Inhalation Toxicity Study in Fischer 344 Rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory Report Number 031065. July 23, 2003. MRID 46438902. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, Indiana

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46438902), 5/sex of Fischer 344 rats (Age: 8 weeks; Source: Charles River Laboratories, Inc., Raleigh, NC; 171-189 g males and 121-134 g females) were exposed nose only via the inhalation route to GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid) to a test concentration of 5.26 mg/L for a period of four hours. Animals were then observed for 15 days.

LC_{50} Males = > 5.26 mg/L
LC_{50} Females = > 5.26 mg/L
LC_{50} Combined = > 5.26 mg/L

All animals survived the exposure. The only clinical sign noted during the exposure was soiling of the haircoat. Clinical signs noted post-exposure included partially closed eyes, and perinasal, perineal, abdominal and/or extensive body soiling. The animals recovered from these symptoms by day 3. Animals lost weight on day 2 but all animals exceeded initial body weights by day 8. No treatment related visible lesions were noted at necropsy. The gravimetric chamber concentration was 5.26 mg/L. The mass median aerodynamic diameter was estimated to be 2.13 µm and with a geometric standard deviation of 5.58.

Toxicity based on the lack of deaths at the limit dose. EPA Toxicity Category IV.

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

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

RESULTS and DISCUSSION:

Nominal Concentration (mg/L)	Gravimetric Concentration (mg/L)	MMAD µm	GSD µm	Mortality/Number Tested		
				Males	Females	Combined
6.25	5.26	2.13	5.58	0/5	0/5	0/10

Test Atmosphere / Chamber Description:

Chamber Volume:	**42 L**
Airflow:	**30 LPM**
Temperature:	**21-22°C**
Relative Humidity:	**29-30%**
Time to Equilibrium:	**not reported**

A. Mortality - None

B. Clinical observations - All animals survived the exposure. The only clinical sign noted during the exposure was soiling of the haircoat. Clinical signs noted post-exposure included partially closed eyes, and perinasal, perineal, abdominal and/or extensive body soiling. The animals recovered from these symptoms by day 3. Animals lost weight on day 2 but all animals exceeded initial body weights by day 8.

C. Gross Necropsy - No treatment related visible lesions were noted at necropsy.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew January 31, 2005
Risk Manager: 23

STUDY TYPE: Primary Eye Irritation - NW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

CITATION: Moore, G. Primary Eye Irritation Study in Rabbits. Product Safety Labs, Dayton, New Jersey. Laboratory Report Number 14300. December 1, 2003. MRID 46434206. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, IN

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46434206), 0.1 mL of GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid) was instilled into the conjunctival sac of the right eye of three female young adult New Zealand albino rabbits (Source: Robinson Services, Inc., Clemmons, NC). The left eye served as the control. Immediately following the one-hour observation, 1-2 drops of ocular anesthetic were placed into both the treated and control eye of each animal. At the end of day 0 and at the beginning of day 1, the animals also received 0.1 mL of Buprenex SQ (Buprenorphine) via intramuscular injection. This systemic treatment was terminated following the day 1 evaluation. Animals were observed at 1, 24, 48, 72 hours and at 4, 7,10, 14, 17 and 21 days post-instillation. Irritation was scored by the method of Draize.

Corneal opacity, iritis and conjunctivitis were noted in all three eyes at the one hour observation. Pannus was noted for one eye on days 17-21. The iritis and conjunctivitis resolved by day 17. The corneal opacity persisted in 2/3 eyes through day 21.

In this study, formulation is severely irritating. EPA Toxicity Category I.

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:

	Number "positive"/number tested									
	Hours				Days					
Observations	1	24	48	72	4	7	10	14	17	21
Corneal Opacity	3/3	3/3	3/3	3/3	3/3	3/3	3/3	2/3	2/3	2/3
Iritis	3/3	3/3	3/3	3/3	3/3	1/3	1/3	1/3	0/3	0/3
Conjunctivae:										
Redness	3/3	3/3	3/3	3/3	3/3	1/3	1/3	1/3	0/3	0/3
Chemosis	1/3	3/3	3/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3
Discharge	3/3	1/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3

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

A. **Observations** - Corneal opacity, iritis and conjunctivitis were noted in all three eyes at the one hour observation. Pannus was noted for one eye on days 17-21. The iritis and conjunctivitis resolved by day 17. The corneal opacity persisted in 2/3 eyes through day 21.

B. **Reviewer's Conclusions:** Agree with study author

Reviewer: Eugenia McAndrew
Risk Manager: 23

January 31, 2005

STUDY TYPE: Primary Dermal Irritation - NW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: GF-1004 (Lot TSN104111; Lot # E0993-44; 6.54% XDE-750 TIPA and 50.7% 2,4-dichlorophenoxyacetic acid; amber liquid)

CITATION: Smedley, J. GF-982: A Primary Skin Irritation Study in New Zealand White Rabbits. Charles River Laboratories, Inc., Springborn Division, Spencerville, Ohio. Laboratory Report Number 3504.339. August 28, 2003. MRID 46434207. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, Indiana

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46434207), three adult male New Zealand White rabbits (Source: Myrtle's Rabbitry, Thompson Station, TN) were dermally exposed to 0.5 mL of GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid) The test substance was applied to a 1 inch by 1 inch area of intact skin on the dorsal area of each animal. Test sites were covered with a gauze patch and held in place with semi-occlusive elastic wrap for a 4 hour period. Animals were then observed at 1, 24, 48 and 72 hours and up to 21 days after patch removal. Irritation was scored by the method of Draize.

In this study, formulation is a moderate irritant. EPA Toxicity Category III.

Primary Dermal Irritation Index (PDII) = 5.0 Well defined erythema was noted at all three test sites and very slight to slight edema at 2/3 sites at the one hour observation. This level of irritation persisted through 72 hours. The edema resolved by day 10. The erythema resolved by day 21. In addition, superficial lightening was noted at 2/3 sites and desquamation at 3/3 sites.

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** - Well defined erythema was noted at all three test sites and very slight to slight edema at 2/3 sites at the one hour observation. This level of irritation persisted through 72 hours. The edema resolved by day 10. The erythema resolved by day 21. In addition, superficial lightening was noted at 2/3 sites and desquamation at 3/3 sites.

B. **Results** - PDII - 5.0

C. **Reviewer's Conclusions** - Agree with study author

Reviewer: Eugenia McAndrew
Risk Manager: 23

January 31, 2005

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

CITATION: Merkel, D. Dermal Sensitization Study in Guinea Pigs (Buehler Method). Product Safety Labs, Dayton, New Jersey. Laboratory Report Number 13733. August 11, 2003. MRID 46434208. Unpublished.

CITATION: Smedley, J. GF-1004: A Dermal Sensitization Study in Hartley Albino Guinea Pigs. Modified Buehler Design. Charles River Laboratories, Inc., Springborn Division, Spencerville, Ohio. Laboratory Report Number 3504.322. Ocotber 22, 2003. MRID 46434308. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, Indiana

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46434208) with GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid), 30 young adult female Hartley albino guinea pigs (Source: Elm Hill Breeding Labs, Chelmsford, MA; 336-413 g) were tested using the Buehler design. The procedures were validated using alpha-Hexylcinnamaldehyde, technical grade (85% HCA) as the positive control substance.

Once each week for three weeks, 0.4 mL of undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. Twenty-seven days after the first induction, 0.4 mL of a 50% w/w mixture of the test substance in acetone (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Ten naive control guinea pigs were also treated with 0.4 mL of a 50% w/w mixture of the test substance in acetone at challenge only. Readings were made 24 and 48 hours after each induction application and after the challenge application.

In this study, the formulation is not a dermal sensitizer.

One animal was found dead after the second induction application. Very faint to moderate erythema (0.5-2) was noted at all test sites during the induction phase. Following the challenge, very faint erythema was noted at 4/19 test sites at 24 hours persisting at one site at 48 hours. In the naive control group, very faint erythema was noted at 4/19 test sites at 24 hours persisting at two sites at 48 hours. No positive responses were noted in either the test or control animals.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig.

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

I. PROCEDURE

A. Induction - Once each week for three weeks, 0.4 mL of undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. The dose site was relocated for the second induction due to irritation and desquamation found on the dose site prior to application. Readings were made 24 and 48 hours after each induction application.

B. Challenge - Twenty-seven days after the first induction, 0.4 mL of a 50% w/w mixture of the test substance in acetone (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Readings were made 24 and 48 hours after the challenge application.

C. Naive Controls - Ten naive control guinea pigs were also treated with 0.4 mL of a 50% w/w mixture of the test substance in acetone at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - One animal was found dead after the second induction application. Very faint to moderate erythema (0.5-2) was noted at all test sites during the induction phase. Following the challenge, very faint erythema was noted at 4/19 test sites at 24 hours persisting at one site at 48 hours. In the naive control group, very faint erythema was noted at 4/19 test sites at 24 hours persisting at two sites at 48 hours. No positive responses were noted in either the test or control animals.

B. Positive control - The results of the HCA positive control study was appropriate to validate test procedures.

C. Reviewer's Conclusions: Agree with study author

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D312229
2. **PC CODES:** 005100, 128968
3. **CURRENT DATE:** 31/JAN/2005
4. **TEST MATERIAL:** GF-982 (TSN104095; Lot # E0993-41; 1.9% XDE - 750 triisopropanalomine salt and 20.1% fluroxypyrmeptyl; yellow liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Charles River Laboratories, Inc. Springborn Division 3504.337/11-18-03	46434203	LD_{50} females = 5000 mg/kg	III	A
Acute dermal toxicity/rat Charles River Laboratories, Inc. Springborn Division 3504.338/9-30-03	46434204	LD_{50} > 5000 mg/kg (males, females combined)	IV	A
Acute inhalation toxicity/rat Toxicology & Environmental Research and Consulting 031065/7-23-03	46438902	LC_{50} > 5.26 mg/L (males, females combined)	IV	A
Primary eye irritation/rabbit Product Safety Labs 14300/12-1-03	46434206	Corneal opacity, iritis and conjunctivitis with corneal opacity persisting in 2/3 eyes through day 21.	I	A
Primary dermal irritation/rabbit Charles River Laboratories, Inc. Springborn Division 3504.339/8-28-03	46434207	PDII = 5.0 Well defined erythema and very slight to slight edema at 3/3 sites at 72 hours. Irritation resolved by day 21	III	A
Dermal sensitization/guinea pig Product Safety Labs 13733/8-11-03	46434208	Not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**