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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

26 February 2007

MEMORANDUM

Subject:	Name of Pesticide Product:	GF-1883
	EPA Reg. No. /File Symbol:	62719-LTE
	DP Barcode:	D333097
	Decision No.:	370943
	PC Code:	116002 [Triclopyr TEA: 16.22%]
		005100 [Aminopyralid TIPA: 2.22%]
From:	Byron T. Backus, Ph.D., Toxicologist Technical Review Branch Registration Division (7505P)	Byron T. Backus 2-26-2007
To:	Eugene Wilson/Joanne Miller, RM 23 Herbicide Branch Registration Division (7505P)	
Registrant:	DOW AGROSCIENCES LLC	

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
005100 Triisopropanolammonium salt of 2-pyridine carboxylic acid, 4-amino-3,6-dichloro-	2.22%
116002 Acetic acid, ((3,5,6-trichloro-2-pyridinyl)oxy)-, compound with N,N-diethylethananamine (1:1)	16.22
Other Ingredient(s):	81.56%
Total:	100.00%

Acid Equivalents:
aminopyralid (2-pyridine carboxylic acid, 4-amino-3,6-dichloro-) – 1.15% (0.1 lb/gal)
triclopyr (3,5,6-trichloro-2-pyridinyloxyacetic acid) – 11.63% (1 lb/gal)

ACTION REQUESTED: The Risk Manager requests:

"Please review the acute tox data submitted in support of this new pesticide product registration application. The data were identified in the attached letter describing the requested action..."

BACKGROUND:

The material received for review includes a 6-pack of acute toxicity studies, a CSF and a proposed label.

RECOMMENDATIONS:

1. The six submitted acute toxicity studies have been reviewed and have been classified as acceptable. These studies satisfy the acute toxicity data requirements for the registration of this proposed product.

2. Based on the results of these acute toxicity studies, the following is the acute toxicity profile for EPA File Symbol 62719-LTE, GF-1883:

Acute oral toxicity	III	Acceptable	MRID 46942403
Acute dermal toxicity	IV	Acceptable	MRID 46942404
Acute inhalation toxicity	IV	Acceptable	MRID 46942405
Primary eye irritation	III	Acceptable	MRID 46942406
Primary dermal irritation	IV	Acceptable	MRID 46942407
Dermal sensitization (LLNA)	Negative	Acceptable	MRID 46942408

3. Based on the acute toxicity profile given above, as well as from information in the CSF and the proposed uses, the following is the precautionary and first labeling for EPA File Symbol 62719-LTE, GF-1883, as obtained from the Label Review System:

PRODUCT ID #: **062719-00572**

PRODUCT NAME: **GF-1883**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if swallowed. Causes moderate eye irritation. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Avoid contact with eyes or clothing. [Wear protective eyewear.]* Wear: Long-sleeved shirt and long pants, Socks, Shoes, and chemical-resistant gloves (such as Barrier Laminate, Butyl Rubber, Nitrile Rubber, Neoprene Rubber, Polyvinyl Chloride (PVC), Viton, Selection Category C).

*[Protective eyewear, which may include goggles, face shield and/or safety glasses, may be specified, if appropriate].

First Aid:

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

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.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". 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.

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.

4. For the purposes of registration, the CSF (dated 8/29/2006) for the proposed product may also have to be reviewed and accepted by the TRB Chemistry Team.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 22, 2007
Risk Manager: 23

STUDY TYPE: Acute Oral Toxicity (Up-and-Down Method) - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: GF-1883, Lot # E-2165:27, TSN105711, described as an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium. According to the certificate of analysis (p. 27) the density was 1.0527 g/mL; according to the laboratory (p. 13) it was 1.053 g/mL.

CITATION: Durando, J. (2006). GF-1883: Acute Oral Toxicity Up and Down Procedure in Rats. Eurofins/Product Safety Laboratories, Dayton, NJ. Laboratory Study No. 19754. Study completion date: August 22, 2006. MRID 46942403. 27 p. Unpublished.

SPONSOR: The Dow Chemical Company

SUBMITTER: Dow AgroSciences LLC

EXECUTIVE SUMMARY: In an acute oral toxicity up-and-down method study (MRID 46942403), GF-1883, Lot # E-2165:27, TSN105711, an amber liquid with a density of 1.053 g/mL containing 2.15% (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% (=169 g/L) triclopyr-triethylammonium, was orally administered to a total of 7 fasted (overnight) young (9-10 weeks) Fischer 344 albino rats (110-135 g; source: Charles River Laboratories, Stoneridge, NY). The test material was administered undiluted. Based on an estimated LD_{50} of 2500 mg/kg the default starting dose level was 790 mg/kg (1 rat); subsequent dose levels were 2500 mg/kg (3 rats) and 5000 mg/kg (3 rats).

All rats dosed at 790 and 2500 mg/kg survived, while all 3 rats dosed at 5000 mg/kg died within one day of dosage (two deaths occurred within 3 hours of dosage). The rat dosed at 790 mg/kg showed no signs of toxicity, while one of the three dosed at 2500 mg/kg showed piloerection at 1 hour post-dosing. Predeath signs of toxicity at 5000 mg/kg included hypoactivity, hunched posture and/or piloerection.

All surviving rats gained weight in the period from Day 0 to 7 and again from Day 7 to 14.

Following terminal sacrifice, rats dosed at 790 and 2500 mg/kg showed no abnormalities at gross necropsy. The 3 rats which died after dosage at 5000 mg/kg showed discoloured (red) intestines.

Estimated Oral LD_{50} (female rat) = 3752 mg/kg (95% confidence interval: 2500-5000 mg/kg).

Toxicity based on the oral LD_{50} value: 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 Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

The test material was administered undiluted.

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

Date/Time: Thursday, February 22, 2007, 4:06:08 PM
Data file name: GF-1883.dat
Last modified: 2/22/2007 4:06:07 PM

Test/Substance: GF-1883
Test type: Main Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): 2500
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 5000, 2500, 790, 250, 79, 25, 7.9, 2.5, 0.79

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	3101	790	O	O
2	3102	2500	O	O
3	3103	5000	X	X
4	3104	2500	O	O
5	3105	5000	X	X
6	3106	2500	O	O
7	3107	5000	X	X

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 5 reversals in 6 tests. LR criterion.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
790	1	0	1
2500	3	0	3
5000	0	3	3
All Doses	4	3	7

Statistical Estimate based on long term outcomes:

Estimated LD50 = 3752 (Based on an assumed sigma of 0.5).
Approximate 95% confidence interval is 2500 to 5000.

A. Mortality – All rats dosed at 790 and 2500 mg/kg survived, while all 3 rats dosed at 5000 mg/kg died within one day of dosage (two deaths occurred within 3 hours of dosage).

B. Clinical Observations – The rat dosed at 790 mg/kg showed no signs of toxicity, while one of the three dosed at 2500 mg/kg showed piloerection at 1 hour post-dosing. Predeath signs of toxicity at 5000 mg/kg included hypoactivity, hunched posture and/or piloerection.

All surviving rats gained weight in the period from Day 0 to 7 and again from Day 7 to 14.

C. Gross Necropsy - Following terminal sacrifice, rats dosed at 790 and 2500 mg/kg showed no abnormalities at gross necropsy. The 3 rats which died after dosage at 5000 mg/kg showed discoloured (red) intestines.

D. Reviewer's Conclusions: The estimated oral LD_{50} value is 3752 mg/kg. This defines an EPA Toxicity Category III for this formulation by the oral exposure route.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 22, 2007
Risk Manager: 23

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

TEST MATERIAL: GF-1883, Lot # E-2165:27, TSN105711, described as an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium. According to the certificate of analysis (p. 25) the density was 1.0527 g/mL; according to the laboratory report (p. 12) it was 1.053 g/mL.

CITATION: Durando, J. (2006). GF-1883: Acute Dermal Toxicity Study in Rats – Limit Test. Eurofins/Product Safety Laboratories, Dayton, NJ. Laboratory Study No. 19755. Study completion date: August 22, 2006. MRID 46942404. 25 p. Unpublished.

SPONSOR: The Dow Chemical Company

SUBMITTER: Dow AgroSciences LLC

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46942404), 5/sex Fischer 344 young (9 weeks) adult albino rats (males: 172-188 g; females: 125-130 g; source: Ace Animals, Inc., Boyertown, PA) were dermally exposed for 24 hours to a dosage of 5000 mg/kg GF-1883, Lot # E-2165:27, TSN105711, an amber liquid with a density of 1.053 g/mL containing 2.15% (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% (=169 g/L) triclopyr-triethylammonium. The test substance was applied to a dose area of approximately 2 inches x 3 inches (about 10% of the body surface). The gauze pad and entire trunk of each rat were wrapped with Durapore tape to avoid dislocation of the pad and to minimize loss of the test substance.

At the end of the 24-hour exposure period the tape and pads were removed and the test sites were cleansed of any residual test material. The rats were then observed for 14 days.

Dermal LD_{50} Males >5000 mg/kg bw (0/5 died)
Dermal LD_{50} Females >5000 mg/kg bw (0/5 died)
Dermal LD_{50} Combined >5000 mg/kg bw (0/10 died)

None of the rats died, and there were no signs of toxicity and no dermal irritation. All rats gained weight from Day 0 to 7 and again from Day 7 to 14.

Following terminal sacrifice, no gross abnormalities were noted at necropsy.

Based on the lack of deaths at 5000 mg/kg (indicating the dermal LD_{50} >5000 mg/kg), the formulation is in EPA Toxicity Category IV by this exposure route.

This acute dermal study is classified as 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 Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality – None.

B. Clinical observations – There were no signs of toxicity and there was no dermal irritation.

C. Gross Necropsy - Following terminal sacrifice, no gross abnormalities were noted at necropsy.

D. Reviewer's Conclusions: The acute dermal LD_{50} of GF-1883, Lot # E-2165:27, TSN105711, an amber liquid with a density of 1.053 g/mL containing 2.15% (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% (=169 g/L) triclopyr-triethylammonium, is greater than 5000 mg/kg in male and female rats. This defines an EPA Toxicity Category IV for this material in terms of dermal toxicity.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 22, 2007
Risk Manager: 23

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

TEST MATERIAL: GF-1883, containing 22.6 g/L (2.15 wt%) aminopyralid-triisopropanolammonium and 169 g/L (16.0% wt%) triclopyr-triethylammonium.

CITATION: Krieger, S.M. & Radtke, B.J. (2006). GF-1883: Acute Liquid Aerosol Inhalation Toxicity Study in F344/DUCRL Rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Co., Midland, MI. Laboratory Project Study ID 061105. Study completion date: August 17, 2006. MRID 46942405. 68 p. Unpublished.

SPONSOR AND SUBMITTER: Dow AgroSciences LLC

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46942405), a group of 5M and 5F young (12 weeks old) adult F344/DuCrl albino rats (M: 246.2-252.6 g; F: 150.5-169.4 g; source: Charles River Laboratories, Inc., Kingston, NY) received nose-only exposure (4-hours) to a time-weighted average concentration of 5.34 mg/L test material (GF-1883, Lot # E-2165:27, TSN105711, an amber liquid with a density of 1.053 g/mL containing 2.15% (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% (=169 g/L) triclopyr-triethylammonium). The MMAD and GSD values were 1.28 µm and 10.27. Approximately 65% of the particles by mass had an effective cutoff diameter of 3 µm or less.

There was no mortality. No clinical signs of toxicity were noted during exposure. Following exposure perineal soiling was observed in 1/5 males and 3/5 females, with all rats normal by day 3. All rats lost weight (losses from 2.7 to 6.3 g) in the 24-hour period following exposure, but 5/5M and 3/5F gained weight in the period from Day 1 (day of exposure) to 8, and all gained weight from Day 8 to 15.

LC_{50} Males	> 5.34 mg/L (0/5 died)
LC_{50} Females	> 5.34 mg/L (0/5 died)
LC_{50} Combined	> 5.34 mg/L (0/5 died)

Following terminal sacrifice, no gross abnormalities were noted at necropsy.

Toxicity based on the rat inhalation LC_{50} (> 5.34 mg/L): 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 compliance (p. 3), Quality Assurance (p. 5), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Gravi-metrie Conc. (mg/L)	MMAD µm	GSD	Mortality/Number Tested		
				Males	Females	Combined
9.25	5.34	1.28	10.27	0/5	0/5	0/10

Test Atmosphere / Chamber Deseription:

Exposure Chamber Volume:	42 L
Mean Airflow Rate:	~30 LPM
Temperature:	21 ± 0°C
Relative Humidity:	39.9 ± 4.1%
Time to 99% Target Concentration:	6.4 minutes

Test atmosphere concentration - From p. 14 of MRID 46942405: "The mass concentration of aerosol present in the chamber was determined gravimetrieally three times during the exposure period. Samples were taken by drawing air, at 1 L/minute, through a sampling probe located in the breathing zone of the animals... Aerosol particles were collected on 47 mm glass fiber filters... A substantial portion of the exposure chamber atmosphere consisted of vapour (primarily the solvent vehicle), therefore, vapour samples were collected using one charcoal and one silica sorbent tube in-line with the glass fiber filter. Background measurements of vapour in the chamber were taken 15 minutes after placing the animals on the chamber. After each atmosphere sampling, the filter and tubes were reweighed to obtain the total weight of the particles. The time-weighted average (TWA) exposure concentration was calculated from the gravimetric measurements..."

Particle size determination - From p. 14 of MRID 46942405: "The aerodynamic particle size was determined four times during the exposure period through a multi-stage cascade impactor... The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined for each sample as well as the average of four samples."

A. Mortality – There was no mortality.

B. Clinical observations - No clinical signs of toxicity were noted during exposure. Following exposure perineal soiling was observed in 1/5 males and 3/5 females, with all rats normal by day 3. All rats lost weight (losses from 2.7 to 6.3 g) in the 24-hour period following exposure, but 5/5M and 3/5F gained weight in the period from Day 1 (day of exposure) to 8, and all gained weight from Day 8 to 15.

C. Gross Necropsy - Following terminal sacrifice, no gross abnormalities were noted at necropsy.

D. Reviewer's Conclusions: Toxicity based on the rat inhalation LC_{50} (> 5.34 mg/L): EPA Toxicity Category IV.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 26, 2007
Risk Manager: 23

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

TEST MATERIAL: GF-1883, Lot # E-2165:27, TSN105711, described as an amber liquid with a pH between 7 and 8, containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium. According to the certificate of analysis (p. 30) the density was 1.0527 g/mL.

CITATION: Durando, J. (2006). GF-1883: Primary Eye Irritation Study in Rabbits. Eurofins/Product Safety Laboratories, Dayton, NJ. Laboratory Study No. 19753. Study completion date: August 22, 2006. MRID 46942406. 30 p. Unpublished.

SPONSOR: The Dow Chemical Company

SUBMITTER: Dow AgroSciences LLC

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46942406), 0.1 mL of GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium, was instilled into the right eye of each of three (2M, 1F) New Zealand albino rabbits (age: young adult; body weights: not reported; source: Robinson Services, Inc., Clemmons, NC). Rabbits were scored (Draize) for eye irritation at 1, 24, 48 and 72 hours, and at 4 and 7 days after instillation. Ophthalmic fluorescein sodium (2%) was also used to evaluate the extent or verify the absence of corneal opacity at 24 hours and at subsequent intervals if the previous reading was positive.

All three eyes showed corneal opacity at 24, 48 and 72 hours, and 2/3 eyes showed corneal opacity on day 4. Two eyes showed iritis at 1 hour, and one eye showed iritis at 24 and 72 hours. All three eyes were positive (score of 2) for conjunctival redness at 1, 24, 48 and 72 hours. One eye had completely cleared (all scores zero) on day 4, and the other two eyes had completely cleared by day 7.

In this study, GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium, caused positive irritation effects which were still present in 3/3 rabbit eyes at 72 hours, but which had completely cleared by day 7. This formulation is in EPA Toxicity Category III in terms of eye irritation potential.

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 Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Hours				Days	
	1	24	48	72	4	7
Corneal Opacity	0/3	3/3	3/3	3/3	2/3	0/3
Iritis	2/3	1/3	0/3	1/3	0/3	0/3
Redness*	3/3	3/3	3/3	3/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3	0/3	0/3
Discharge*	3/3	3/3.	2/3	1/3	0/3	0/3

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

A. Observations – All three eyes showed corneal opacity at 24, 48 and 72 hours, and 2/3 eyes showed corneal opacity on day 4. Two eyes showed iritis at 1 hour, and one eye showed iritis at 24 and 72 hours. All three eyes were positive (score of 2) for conjunctival redness at 1, 24, 48 and 72 hours. One eye had completely cleared (all scores zero) on day 4, and the other two eyes had completely cleared by day 7.

B. Reviewer's Conclusions: In this study, GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium, caused positive irritation effects which were still present in 3/3 rabbit eyes at 72 hours, but which had completely cleared by day 7. This formulation is in EPA Toxicity Category III in terms of eye irritation potential.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 26, 2007
Risk Manager: 23

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

TEST MATERIAL: GF-1883, Lot # E-2165:27, TSN105711, described as an amber liquid with a pH between 7 and 8, containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium. According to the certificate of analysis (p. 27) the density was 1.0527 g/mL.

CITATION: Durando, J. (2006). GF-1883: Primary Skin Irritation Study in Rabbits. Eurofins/Product Safety Laboratories, Dayton, NJ. Laboratory Study No. 19756. Study completion date: August 22, 2006. MRID 46942407. 27 p. Unpublished.

SPONSOR: The Dow Chemical Company

SUBMITTER: Dow AgroSciences LLC

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46942407), each of 3 (1M & 2F) young adult New Zealand albino rabbits (weights: not reported; source: Robinson Services, Inc., Clemmons, NC) was exposed to 0.5 mL undiluted GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium. This was applied to one 6-cm^2 intact dose site on each rabbit. After application, the site was then covered with a 1-inch x 1-inch, 4-ply gauze pad. The pad and entire trunk of each animal were then wrapped with semi-occlusive tape and Elizabethan collars were placed on the rabbits. After 4 hours of exposure, the pads and collars were removed and the test sites were cleansed of any residual test material.

Sites were scored (Draize) for dermal irritation at ½-1, 24, 48 and 72 hours and 7 days after patch removal.

All three sites scored "2" for erythema and "1" for edema at ½-1 hour after patch removal. Erythema scores were "1" or "2" at 24 hours, and edema scores were all "1." At 48 and 72 hours one site scored "1" for erythema; the other erythema and all edema scores were zero. On day 7 all sites were clear (all scores zero). The Primary Dermal Irritation Index (PDII) = 1.50.

In this study, GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium, was slightly irritating to the skin. This formulation is in EPA Toxicity Category IV in terms of dermal irritation potential.

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 Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal No.	Sex	Hours After Patch Removal				Days
		½-1	24	48	72	7
3501	F	2/1	1/1	0/0	0/0	0/0
3502	F	2/1	1/1	0/0	0/0	0/0
3503	M	2/1	2/1	1/0	1/0	0/0

A. **Observations** – Except for the dermal irritation, there were no signs of toxicity.

B. **Results** - All three sites scored "2" for erythema and "1" for edema at ½-1 hour after patch removal. Erythema scores were "1" or "2" at 24 hours, and edema scores were all "1." At 48 and 72 hours one site scored "1" for erythema; the other erythema and all edema scores were zero. On day 7 all sites were clear (all scores zero). The Primary Dermal Irritation Index (PDII) = 1.50.

C. **Reviewer's Conclusions**: In this study, GF-1883, Lot # E-2165:27, TSN105711, an amber liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium, was slightly irritating to the skin, with a PDII = 1.50 and with almost all irritation (average score: 0.33) gone by 72 hours. These results adequately define an EPA toxicity category IV classification in terms of dermal irritation potential for this formulation.

Reviewer: Byron T. Backus, Ph.D. **Date:** February 26, 2007
Risk Manager: 23

STUDY TYPE: Dermal Sensitization - CBA/J Mice; OPPTS 870.2600; OECD 429

TEST MATERIAL: GF-1883, Lot # E-2165:27, TSN105711, described as a yellow to orange liquid containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium.

CITATION: Woolhiser, M.R., Wiescinski, C.M., and Anderson, L.K. (2006). GF-1883: Local Lymph Node Assay in CBA/J Mice. Laboratory Project ID 061087. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. August 14, 2006. MRID 46942408. 27 p. Unpublished.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46942408) with GF-1833 (Lot # E-2165:27, TSN105711, a yellow to orange liquid containing 2.15% by weight [22.6 g/L] aminopyralid-triisopropanolammonium and 16.0% by weight [=169 g/L] triclopyr-triethylammonium), 6/group young adult female mice (Strain: CBA/J; Age: 9-12 weeks; Weight: 20.0-25.1 g; Source: Harlan, Indianapolis, IN) were tested using the Local Lymph Node Assay method. The test substance was prepared as a suspension in a diluting vehicle of Pluronic L92 surfactant (1% w/v) in water.

Following an irritation screen, six mice/group received one application (25 µL/ear) of test substance in 1% L92 in water to the dorsal surface of both ears at a concentration of 5%, 25% or 100% or 1% L92 (vehicle) once daily for three consecutive days. 30% (v/v) alpha-Hexylcinnamaldehyde (HCA) was run concurrently as the positive control substance.

On study day 6, the tail vein of each animal was injected with 250 µL of 20 µCi of ^{3}H-thymidine. The animals were sacrificed 5 hours later. The draining auricular lymph nodes of each ear were removed and disaggregated into a single cell suspension. The single cell suspensions were incubated overnight. On test day 7, the radioactivity was measured and reported as disintegrations per minute (dpm) per mouse. A stimulation index (SI) was derived for each experimental group by dividing the mean dpm of each experimental group by the mean dpm of the vehicle control group. Animals were weighed on days 1 and 6. Animals were observed for clinical signs daily throughout the study period. The mouse ears were evaluated for erythema.

The criterion for a positive response was a statistically significant increase in cell proliferation in the test concentration groups compared to the vehicle control group and/or SIs greater than or equal to 3.0.

No statistically significant differences in mean body weights and body weight gains compared to the vehicle control group were observed at any test concentration. There was no indication of any dermal irritation associated with exposure to the test material at any of the applied concentrations (5%, 25%, or 100%). There was no indication that the test substance induced a proliferative response as stimulation indices were 1.1, 1.2 and 0.9 (for 5%, 25% and 100%,

respectively) in comparison to the vehicle-treated mice. The test system was validated by the positive control HCA which elicited a stimulation index of 14.5.

In this study, GF-1833 (Lot # E-2165:27, TSN105711, a yellow to orange liquid containing 2.15% by weight [22.6 g/L] aminopyralid-triisopropanolammonium and 16.0% by weight [=169 g/L] triclopyr-triethylammonium), is **not** a **dermal sensitizer**.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 429) in the mouse.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

I. MATERIALS and METHODS

1. **Vehicle and positive control** - The vehicle for this study was Pluronic L92 surfactant (1%w/v) in water and the positive control used was HCA. (The study author explains the choice of vehicle stating that "Pluronic L92 surfactant (1% w/v) was selected based upon miscibility of GF-1834 while maintaining a solution suitable for application... Pluronic L92 provides good skin wetting properties for prolonged dermal contact and has been shown to yield positive LLNA results using a number of water-soluble dermal sensitizers. L92 surfactant should demonstrate improved compatibility with the test material when considering formulation properties, thus resulting in more realistic test conditions when compared with potential human exposure.").

2. **Treatment preparation and administration** - Six mice/group received one application (25 µL/ear) of test substance in an aqueous vehicle (containing 1% L92) to the dorsal surface of both ears at a concentration of 5%, 25% or 100% or 1% L92 (vehicle) once daily for three consecutive days. 30% (v/v) alpha-Hexylcinnamaldehyde (HCA) was run concurrently as the positive control substance.

On study day 6, the tail vein of each animal was injected with 250 µL of 20 µCi of ^{3}H-thymidine. The animals were sacrificed 5 hours later. The draining auricular lymph nodes of each ear were removed and disaggregated into a single cell suspension. The single cell suspensions were incubated overnight. On test day 7, the radioactivity was measured and reported as disintegrations per minute (dpm) per mouse. A stimulation index (SI) was derived for each experimental group by dividing the mean dpm of each experimental group by the mean dpm of the vehicle control group. Animals were weighed on days 1 and 6. Animals were observed for clinical signs daily throughout the study period. The mouse ears were evaluated for erythema.

II. RESULTS and DISCUSSION:

A. Disintegrations per Minute (group means) -

Concentration %	Animal Number	Individual Animal DPM	Group Mean DPM	Stimulation Index (SI)*
1% L92 Vehicle Control	1794	4.20	331.70	N/A
	1795	111.33		
	1796	179.97		
	1797	329.86		
	1798	977.22		
	1799	387.63		
5%	2849	206.32	360.17	1.1
	2850	632.01		
	2851	59.92		
	2852	257.57		
	2853	192.14		
	2854	813.03		
25%	2855	235.41	382.75	1.2
	2856	596.71		
	2857	535.78		
	2858	327.67		
	2859	393.83		
	2860	207.09		
100%	2861	392.51	411.94	1.3
	2862	1001.0		
	2863	200.19		
	2864	187.41		
	2865	504.39		
	2866	186.11		
30% HCA Positive control	1800	6527.2	4818.0	14.5
	1801	2629.1		
	1802	3362.1		
	1803	6089.3		
	1804	4800.1		
	1805	5500.0		

* SI = Group mean DPM ÷ Vehicle control mean DPM

B. Stimulation Index -

Sample Description Test or Control Group	Vehicle	Low	Medium	High	Positive Control
Stimulation Index (SI)	NA	1.1	1.2	1.3	14.5

C. Reviewer's Conclusions: In this study, GF-1833 (Lot # E-2165:27, TSN105711, a yellow to orange liquid containing 2.15% by weight [22.6 g/L] aminopyralid-triisopropanolammonium and 16.0% by weight [=169 g/L] triclopyr-triethylammonium), is not a dermal sensitizer.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D333097
2. **PC CODES:** 116002 (Triclopyr TEA: 16.22%); 005100 (Aminopyralid TIPA: 2.22%)
3. **CURRENT DATE:** 26 February 2007
4. **TEST MATERIAL:** GF-1883, Lot # E-2165:27, TSN105711, described as an amber liquid with a density of 1.0527 and with a pH between 7 and 8, containing 2.15% by weight (=22.6 g/L) aminopyralid-triisopropanolammonium and 16.0% by weight (=169 g/L) triclopyr-triethylammonium.

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat / Eurofins/Product Safety Laboratories / Lab Study No. 19754 / 22-AUG-2006	46942403	Up-and-down procedure: test material administered undiluted at 790 (1 rat), 2500 (3 rats) and 5000 mg/kg (3 rats). Initial dose based on estimated LD50 of 2500 mg/kg. All rats dosed at 790 and 2500 mg/kg survived; rats dosed at 5000 mg/kg all died within 24 hrs of dosage. One of 3 rats dosed at 2500 mg/kg showed piloerection at 1 hr postdosing. Predeath signs of toxicity at 5000 mg/kg included hypoactivity, hunched posture and/or piloerection. All survivivng rats gained weight from Day 0-7 and 7-14. Rats dosed at 790 & 2500 mg/kg showed no abnormalities at gross necropsy; rats dosed at 5000 mg/kg showed discolored (red intestines). LD50 = 3752 mg/kg with 95% C.I. 2500-5000 mg/kg.	III	A
Acute dermal toxicity / rat / Eurofins/Product Safety Laboratories /Lab Study No. 19755/ 22-AUG-2006	46942404	5M & 5F rats received 24-hr dermal exposure to 5000 mg/kg. No mortalities. Dermal LD50 > 5000 mg/kg. No signs of toxicity or dermal irritation. All gained wt Day 0-7 & 7-14. No abnormalities at gross necropsy.	IV	A

Acute inhalation toxicity / rat / Toxicology & Environmental Research & Consulting, Dow Chemical / Lab Project Study ID 061105 / 17-AUG-2006	46942405	A group of 5M & 5F rats received 4-hr nose-only exposure to 5.34 mg/L. MMAD = 1.28 µm; GSD = 10.27. No deaths. No clinical signs seen during exposure; post-exposure 1/5M & 3/5F showed perineal soiling, with all normal by day 3. All rats lost weight (losses from 2.7 to 6.3 g) in the 24-hr period after exposure, but 5/5M & 3/5F gained weight in the period from day 1 (day of exposure) to day 8, and all gained weight day 8-15. Following terminal sacrifice, no gross abnormalities were noted at necropsy. LC50 > 5.34 mg/L.	IV	A
Primary eye irritation / rabbit / Eurofins/Product Safety Laboratories / Lab Study No. 19753 / 22-AUG-2006	46942406	3/3 eyes had corneal opacity at 24, 48 & 72 hrs; 2/3 had corneal opacity on day 4. Two eyes showed iritis at 1 hr, and one eye showed iritis at 24 and 72 hrs. All eyes were positive (score of 2) for conjunctival redness at 1, 24, 48 & 72 hrs. One eye had completely cleared (all scores zero) by day 4 and the other two eyes had completely cleared by day 7.	III	A
Primary dermal irritation / rabbit / Eurofins/Product Safety Laboratories / Lab Study No. 19756 / 22-AUG-2006	46942407	All 3 sites scored "2" for erythema and "1" for edema at ½-1 hr. Erythema scores were "1" or "2" at 24 hrs and edema scores were all "1." At 48 & 72 hrs one site scored "1" for erythema; other erythema and all edema scores were zero. All scores zero on day 7. PDII=1.50.	IV	A
Dermal [LLNA] sensitization / CBA/J Mice/ Toxicology Research and Consulting, Dow Chemical / Laboratory Project ID 061087 / 14-AUG-2006	46942408	LLNA Protocol. Test material tested at 5, 25 and 100%; vehicle used was 1% L92 in water. No irritation seen following applications. SI values were 1.1, 1.2 & 1.3 for 5%, 25% and 100% groups respectively. SI for 30% HCA was 14.5; no indication test material is a dermal sensitizer.	Nega-tive	A

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