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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

NOV 26, 2007

MEMORANDUM

Subject:	EPA File Symbol:	62719-LIR **GF-1847**
	DP Barcode:	341266
	Decision No:	380436
	PC Code:	108702
	Action Code	R31

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505C)

MH
Byron T. B
11-26-2007

To: James Stone, RM Team 25
Herbicide Branch
Registration Division

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

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Pyroxsulam	4.31
Inert Ingredients	95.69
Total:	100.00

ACTION REQUIRED: The Risk Manager requested a review of the acute toxicity data for the File Symbol #62719-LIR.

BACKGROUND: A pack of six acute toxicity studies was submitted by Dow AgroSciences to support the registration of GF-1847, File Symbol #62719-LIR. The acute toxicity studies were conducted by Product Safety Laboratories, Dayton, NJ. An Agency Contractor, Oak Ridge National Laboratory (ORNL), performed the primary review of these studies. TRB made necessary changes.

RECOMMENDATIONS: Each of the six studies (MRID 47158703-08) is in compliance with Sub-Division F guidelines.

The toxicology profile for #62719-LIR is as follows:

acute oral toxicity	III	acceptable	MRID 47158703
acute dermal toxicity	IV	acceptable	MRID 47158704
acute inhalation study	III	acceptable	MRID 47158705
primary eye irritation	II	acceptable	MRID 47158706
primary dermal irritation	III	acceptable	MRID 47158707
dermal sensitization	pos.	acceptable	MRID 47158708

Note: Additional data (MRIDs 47158709-14) are the summaries of the above studies.

LABELING:

PRODUCT ID #: **062719-00581**

PRODUCT NAME: **GF-1847**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **WARNING**

SPANISH SIGNAL WORD: AVISO

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.)

Hazards to Humans and Domestic Animals:

Contains Petroleum Distillate.

Prolonged or repeated use of the product may cause allergic reactions in some individuals.

Causes substantial but temporary eye injury. Harmful if inhaled. 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). Wash thoroughly with soap and water after handling and before eating, drinking,

chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse. Avoid breathing spray mist. Wear long-sleeved shirt and long pants, socks, shoes, and gloves.

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 inhaled:
-Move the person to fresh air.
-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
-Call a poison control center or doctor for further treatment advice.

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 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: May pose an aspiration pneumonia hazard. Contains petroleum distillate. 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.

DATA EVALUATION RECORD

PYROXSULAM AND CLOQUINTOCET-MEXYL
(GF-1847)

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 425]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - GUINEA PIG [OPPTS 870.2600; OECD 429]

Summaries → **MRID 47158703, 47158704, 47158705, 47158706, 47158707, and 47158708; 47158709, 47158710, 47158711, 47158712, 47158713, and 47158714**

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 1-7

Primary Reviewer:
Susan Chang, M.S. — Signature: — Date: NOV 08

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T. — Signature: — Date: NOV 08

Robert H. Ross, M.S., Group Leader — Signature: — Date: NOV 08

Quality Assurance:
Kimberley G. Slusher, M.S. — Signature: — Date: NOV 08

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

CITATION: Durando J. (2007) GF-1847 – Acute Oral Toxicity Up and Down Procedure in Rats. Study Number 21573. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. May 1, 2007. MRID 47158703.

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences LLC, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47158703), six fasted, young adult female Fischer 344 rats (age: 9-10 weeks old; body weight: 111-141 g; source: Charles River Laboratories, Stoneridge, NY) were given a single dose of GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901] as received at doses of 175, 550 (dosed as 20% w/w test material in corn oil), or 2000 mg/kg bw by gavage and observed for 14 days.

One 2000 mg/kg animal was dosed for the limit test and died on day 2. All five animals including 3 dosed at 2000 mg/kg in the main test survived the study. Hypoactivity, hunched posture, piloerection, reduced fecal volume, anogenital staining, and/or ocular discharge were noted from all 550 and 2000 mg/kg animals. The surviving animals recovered by day 6 or earlier and appeared active and healthy thereafter. The 175 mg/kg animal appeared active and healthy throughout the study. The decedent revealed moderate red lungs and extremely red intestines. No gross abnormalities were noted from any survivor at necropsy.

LD_{50} Females > 2000 mg/kg bw

GF-1847, based on the oral LD_{50} in rats is in EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements 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:

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

Date/Time: Thursday, October 25, 2007, 9:06:26 AM
Data file name: work.dat
Last modified: 10/25/2007 9:06:24 AM

Test/Substance: GF-1847
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD_{50} (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	1	175	O	O
2	2	550	O	O
3	3	2000	O	O
4	4	2000	O	O
5	5	2000	O	O

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 3 at Limit Dose.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	1	0	1
550	1	0	1
2000	3	0	3
All Doses	5	0	5

Statistical Estimate based on long term outcomes:

The LD_{50} is greater than 2000 mg/kg.

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
3101	F	2000	D
3102	F	175	S
3103	F	550	S
3104	F	2000	S
3105	F	2000	S
3106	F	2000	S

S = Survival, D = Death

A. Mortality: One 2000 mg/kg animal was dosed for the limit test and died on day 2. All five animals in the main test survived the study.

B. Clinical observations: Hypoactivity, hunched posture, piloerection, reduced fecal volume, anogenital staining, and/or ocular discharge were noted on all 550 and 2000 mg/kg animals. The surviving animals recovered by day 6 or earlier and appeared active and healthy thereafter. The 175 mg/kg animal appeared active and healthy throughout the study.

C. Gross necropsy: The decedent had moderate red lungs and extremely red intestines. No gross abnormalities were noted from any survivor at necropsy.

D. Reviewer's conclusions: This reviewer agrees with the study author that the acute oral LD_{50}>2000 mg/kg. The formulation is in EPA Tox Category III for oral toxicity.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

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

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

CITATION: Durando, J. (2007) GF-1847 – Acute Dermal Toxicity in Rats –Limit Test. Study Number 21574. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. April 19, 2007. MRID 47158704.

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences LLC, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47158704), groups of young adult Fischer 344 rats (5/sex; body weight, males: 200-236 g and females: 137-153 g; source, Charles River Laboratories, Stoneridge, NY) were dermally exposed for 24 hours on an area of approximately 2 inches x 3 inches (approximately 10% of the total body surface area) on the clipped dorsal trunk to 5000 mg/kg bw GF-1847 (44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; pH not reported) as received. The test material was applied evenly over the dose area and covered with a gauze pad. The gauze and the trunk were wrapped with Durapore tape. The animals were observed for 14 days.

All animals survived the study. Erythema and edema were noted at dose site of all animals from days 1-4. Mechanical damage around dose site due to unwrapping was noted on all animals on days 1-7, 1-8, 1-11, or 1-12. All animals appeared active and healthy. No gross abnormalities were noted at necropsy.

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

Based on the dermal LD_{50} in rats (>5000 mg/kg), the formulation is in EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirements 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:

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

A. Mortality: All animals survived the study.

B. Clinical observations: Erythema and edema were noted at dose sites of all animals from days 1-4. Mechanical damages around dose site due to unwrapping were noted on all animals on days 1-7, 1-8, 1-11, or 1-12. All animals appeared active and healthy thereafter.

C. Gross necropsy: No gross abnormalities were noted at necropsy.

D. Reviewer's conclusions: The dermal LD_{50}>5000 mg/kg, the product is classified in EPA Tox Category IV.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

STUDY TYPE: Acute Inhalation Toxicity – Rat (Fischer 344/DuCrl; age: approximately 12 weeks old; body weight: males: 245.7-270.3 g and females: 146.8-170.0 g; source, Charles River Laboratories, Kingston, NY); OPPTS 870.1300; OECD 403

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

SYNONMS: A mixture of N-(5,7-dimethoxy(1,2,4)trianolo(1,5-a)pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pryridinesulfonamide (XDE-742, pyroxsulam) and ((5-chloro-8-quinolinyl)oxy)-acetic acid 1-methylhexyl ester (cloquintocet-mexyl)

CITATION: Krieger, S. and B. Radtke (2007) GF-1847 – Acute Liquid Aerosol Inhalation Toxicity Study in F344/DuCrl Rats. Laboratory Project Study ID 071001. Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. April 18, 2007. MRID 47158705.

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

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47158705), groups of young adult Sprague-Dawley rats (5/sex; body weight, males: 245.7-270.3 g and females: 146.8-170.0 g) were exposed by nose-only inhalation to GF-1847 (44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901) for 4 hours and 1 minute at a concentration of 1.1 mg/L (the highest attainable respirable exposure chamber concentration). The animals were observed for 14 days. The MMAD was 3.39 μm and the GSD 1.71.

All animals survived the study. No clinical effects were noted during exposure. Noisy and/or labored respiration, and perioral and/or perineal soiling were noted post-exposure with recovery by day 3. All animals gained weight by the end of the study. No treatment-related visible lesions were noted in any animal at necropsy.

LC_{50} Males > 1.1 mg/L
LC_{50} Females > 1.1 mg/L
LC_{50} Combined > 1.1 mg/L

GF-1847 based on its LC_{50} is classified in EPA Toxicity Category III for inhalation toxicity.

This study is classified as acceptable. It does satisfy the guideline requirements 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 Conc. (mg/L)	Gravimetric Conc. (mg/L)	MMAD µm	GSD	Mortality/Number Tested		
				Males	Females	Combined
1.36	1.1	3.39	1.71	0/5	0/5	0/10

Test Atmosphere / Chamber Description: A liquid aerosol of the test material was generated by metering the test material with a FMI pump (Fluid Metering, Inc., Oyster Bay, NY) into a stainless steel ¼-J spray nozzle (Spraying Systems Co., Wheaton, IL). The test material was mixed with compressed filtered air in the spray nozzle and the aerosol was sprayed into the exposure chamber (Dow-modified ADG nose-only exposure chamber, 30 cm in diameter by 60 cm high).

Gravimetric Conc. (mg/L):	**1.1**
Chamber Volume (L):	**42**
Total Airflow (L/min):	**30**
Temperature	**20.5±0.3°C**
Relative Humidity	**35.1±0.7%**
Time to equilibrium:	**6.4 minutes**

Test atmosphere concentration: During exposure, gravimetric samples were collected six times from the breathing zone of the animals, using polytetrafluoroethylene filters. Vapor samples were collected using two charcoal sorbent tubes in-line with the polytetrafluoroethylene filters. Background measurements of vapor in the chamber were taken 20 minutes after placing the animals on the chamber and the addition of humidified air. Filters and tubes were weighed before and after collection to determine the mass collected. The time-weighted average exposure concentration was calculated from gravimetric measurements, after subtraction of the background measurements.
Particle size for each exposure concentration was determined twice using a multi-stage cascade impactor. The mass median aerodynamic diameter and geometric standard deviation were determined.

A. **Mortality:** All animals survived the study.

B. **Clinical observations:** No clinical effects were noted during exposure. Noisy and/or labored respiration, and perioral and/or perineal soiling were noted post-exposure with recovery by day 3. Most animals lost weight in the first few days, but all animals gained weight by day 8 and the second week.

C. **Gross necropsy:** No treatment-related visible lesions were noted in any animal at necropsy.

D. **Reviewer's conclusions:** This reviewer agrees with the study author that the acute inhalation LC_{50} (1.1 mg/L), the product is in EPA Tox Category III.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

STUDY TYPE: Primary Eye Irritation – Rabbit (New Zealand White; young adult; source, Robinson Services, Inc., Clemmons, NC); OPPTS 870.2400; OECD 405

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

CITATION: Durando, J. (2007) GF-1847 – Primary Eye Irritation Study in Rabbits. Study Number 21575. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. April 12, 2007. MRID 47158706.

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences LLC, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47158706), 0.1 mL of undiluted GF-1847 (44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; pH not reported) was instilled into the conjunctival sac of the right eye of three male young adult New Zealand White rabbits. The untreated eye served as a control. The animals were observed for 14 days and ocular irritation was scored at 1, 24, 48, 72 hours and at 4, 7, 10, and 14 days.

Corneal opacity was noted on 3/3 rabbits 24 hours through day 10 after test material instillation with clearance by day 14. Iritis was noted on 3/3 rabbits one hour through day 7 after test material instillation with clearance by day 10. Positive conjunctival irritation was noted on 3/3 rabbits one hour through day 7 after test material instillation with clearance on two rabbits by day 10 and on one rabbit by day 14. The highest maximum mean total score was 37.0, recorded one hour after test material instillation.

In this study, the formulation GF-1847 is classified as EPA Toxicity Category II for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements 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 treated							
	Hours				days			
Observations	**1**	**24**	**48**	**72**	**4**	**7**	**10**	**14**
Corneal Opacity	0/3	3/3	3/3	3/3	3/3	3/3	3/3	0/3
Iritis	3/3	3/3	3/3	3/3	3/3	3/3	0/3	0/3
Conjunctivae:								
Redness*	3/3	3/3	3/3	3/3	3/3	3/3	1/3	0/3
Chemosis*	3/3	3/3	2/3	2/3	2/3	0/3	0/3	0/3
Discharge**	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3

* Score of 2 or more required to be considered "positive"
** Discharge is not a positive effect according to the grading scale

A. **Observations:** Corneal opacity was noted on 3/3 rabbits 24 hours through day 10 after test material instillation with clearance by day 14. Iritis was noted on 3/3 rabbits one hour through day 7 after test material instillation with clearance by day 10. Positive conjunctival irritation was noted on 3/3 rabbits one hour through day 7 after test material instillation with clearance on two rabbits by day 10 and on one rabbit by day 14.

B. **Results:** Exposure to GF-1847 cause eye irritation which was still present of day 10 and cleared by day 14. The highest maximum mean total score was 37, recorded 24 hours after test material instillation.

C. **Reviewer's conclusions:** TRB classifies the test material in EPA Tox Category II for eye irritation study.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

STUDY TYPE: Primary Dermal Irritation – Rabbit (New Zealand White; young adult; source, Robinson Services, Inc., Clemmons, NC) OPPTS 870.2500; OECD 404

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

CITATION: Durando, J. (2007) GF-1847 – Primary Skin Irritation Study in Rabbits. Study Number 21576. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. April 30, 2007. MRID 47158707.

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences LLC, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47158707), three female young adult New Zealand White rabbits were dermally exposed to 0.5 mL of undiluted GF-1847 (44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; pH not reported) for 4 hours on a 6 cm^2 area of the clipped dorsal skin that was covered with a gauze patch. The patch and trunk were wrapped with semi-occlusive Micropore tape. The animals were observed and irritation was scored at 1, 24, 48, and 72 hours and on days 7, 10, and 14.

Well defined erythema and slight edema was noted on all rabbits 30-60 minutes through 24 hours after patch removal. All rabbits had moderate erythema and moderate edema by 48 hours. The moderate erythema persisted on all rabbits through 72 hours and reduced to well defined by day 7 and through day 10 then reduced to very slight by day 14. The moderate edema reduced to slight then to very slight with clearance on one rabbit by day 10 and on two rabbits by day 14.

In this study, the formulation has the Primary Irritation Index (PII) of 4.8, and a mean score of 5 at 72 hours, therefore, GF-1847 is classified as EPA Toxicity Category III for primary dermal irritation.

This study is classified as acceptable. It does satisfy the guideline requirements 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:

Animal Number	Sex	Hours				Days		
		1	24	48	72	7	10	14
3501	F	2/2[a]	2/2	3/3	3/2	2/1	2/0	1/0
3502	F	2/2	2/2	3/3	3/2	2/2	2/1	1/0
3503	F	2/2	2/2	3/3	3/2	2/2	2/1	1/0
Severity of Irritation – Mean Score		4.8						

[a] Erythema/edema

A. Observations: Well defined erythema and slight edema was noted on all rabbits 30-60 minutes through 24 hours after patch removal. All rabbits had moderate erythema and moderate edema by 48 hours. The moderate erythema persisted on all rabbits through 72 hours and reduced to well defined by day 7 and through day 10 then reduced to very slight by day 14. The moderate edema reduced to slight then to very slight with clearance on one rabbit by day 10 and on two rabbits by day 14.

B. Results: GF-1847 was moderately irritating. The Primary Irritation Index (PII) is 4.8 (calculated by the reviewer).

C. Reviewer's conclusions: This reviewer classifies the test material as Tox Category III for primary dermal irritation study in rabbits.

Reviewer: ORNL **Date:** October 24, 2007
Risk Manager (EPA): 25

STUDY TYPE: Dermal Sensitization – mouse (CBA/J; age: approximately 9-12 weeks old; body weight: 17.4-20.4 g; Harlan, Indianapolis, IN); OPPTS 870.2600; OECD 429

TEST MATERIAL: GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

SYNONMS: A mixture of N-(5,7-dimethoxy(1,2,4)trianolo(1,5-a)pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pryridinesulfonamide (XDE-742, pyroxsulam) and ((5-chloro-8-quinolinyl)oxy)-acetic acid 1-methylhexyl ester (cloquintocet-mexyl)

CITATION: Woolhiser, M., C. Wiescinski, and L. Sosinski (2007) GF-1847 – Local Lymph Node Assay in CBA/J Mice. Laboratory Project Study ID 061197. Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. April 2, 2007. MRID 47158708.

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences LLC, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47158708) with GF-1847 (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901), 30 female young adult CBA/J mice (body weight: 17.4-20.4 g) were tested using the Local Lymph Node Assay. Groups of six female mice were treated with 25 µL vehicle (1% L92), 1%, 5%, and 25% test material in vehicle, or positive control (30% HCA in vehicle) on the ear. Erythema on the ears was evaluated on days 2, 3, and 6. All mice were weighed on days 1 and 6. On day 6, all mice received a 250 µL i.v. injection via the lateral tail vein containing 20 µCi of ^{3}H-thymidine (specific activity 2 Ci/mmol) diluted in phosphate-buffered saline (PBS). The mice were sacrificed five hours later and the auricular lymph nodes located at the bifurcation of the jugular veins were excised and placed in PBS. A single cell suspension of the auricular lymph nodes from one mouse was prepared. The cells were washed twice and were suspended in 3 mL of 5% trichloroacetic acid (TCA) for approximately 18 hours. The precipitates were centrifuged and reconstituted in 5% TCA and counted in Aquasol-2 scintillation cocktail using a β–scintillation counter and reported as disintegrations per minute (dpm) per mouse. The mean SI ±SD (absolute dpm for each mouse/mean dpm from the vehicle control mouse) was calculated for each group. The test material produces a SI of ≥3 in the LLNA should be considered "positive" for contact sensitization.

Erythema was not noted on the mice treated with 1% and 5% test material, but slight erythema was noted on the mice treated with 25 % test material with resolution by day 6. The mice treated with 1% or 5% test material had normal body weight gain, but the mice treated with 25% test material lost weight slightly. The group mean dpm of vehicle (1% L92), 1% GF-1847, 5% GF-1847, 25% GF-1847, and 30% HCA were 626.81, 1076.4, 1551.0, 2083.4, 5463.3, respectively. The test material elicited proliferative responses with Stimulation Indices for the low, medium, and high test concentrations of 1.7, 2.5, and 3.3, respectively, and the response for the vehicle

and the positive control were 1.0 and 8.7, respectively. The concentration that would cause a 3-fold increase in proliferation (EC_3) was calculated to be 17.5% which is consistent with weak dermal sensitization potential.

Based on the results of this study, GF-1847 was a weak dermal sensitizer.

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

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

MATERIALS AND METHODS:

A. **Vehicle and positive control**: The block copolymer Pluronic L92 surfactant (1% w/v) in water was used as the vehicle. α–Hexylcinnamaldehyde (HCA) was diluted to 30% v/v in 1% L92 was the positive control.

B. **Treatment preparation and administration**: Prior to the LLNA study, the test material was evaluated/screened for irritation potential as measured by erythema on the ears. Based on the results of the screen, the test material was combined with 1% L92 to obtain concentrations of 1%, 5%, and 25% daily just prior to dosing. The test material (25 µL/ear) at concentrations of 1%, 5%, or 25% was applied on the dorsal surface of both ears of six female CBA/J mice once for three consecutive days. The vehicle (1% L92) or positive control (30% v/v in vehicle) was run concurrently of the test material solutions. Erythema on the ears was evaluated on days 2, 3, and 6. All mice were weighed on days 1 and 6. On day 6, all mice received a 250 µL i.v. injection via the lateral tail vein containing 20 µCi of ^{3}H-thymidine (specific activity 2 Ci/mmol) diluted in phosphate-buffered saline (PBS). The mice were sacrificed five hours later and the auricular lymph nodes located at the bifurcation of the jugular veins were excised and placed in PBS. A single cell suspension of the auricular lymph nodes from one mouse was prepared. The cells were washed twice and were suspended in 3 mL of 5% trichloroacetic acid (TCA) for approximately 18 hours. The precipitates were centrifuged and reconstituted in 5% TCA and counted in Aquasol-2 scintillation cocktail using a β–scintillation counter and reported as disintegrations per minute (dpm) per mouse. The mean SI ±SD (absolute dpm for each mouse/mean dpm from the vehicle control mouse) was calculated for each group.

If the test material produces a SI of ≥3 in the LLNA should be considered "positive" for contact sensitization. The determination of EC_3 values (estimated concentrations resulting in a 3-fold SI) can compare relative sensitization potency of test materials; and the contact allergens can be categorized as weak (≥10% - ≤100%), moderate (≥1% - <10%), and strong (≥0.1% - < 1%), and extreme (<0.1%).

RESULTS AND DISCUSSION:

A. Disintegrations per Minute (group means):

Concentration %	Animal Number	Individual Animal DPM	Group Mean DPM	Stimulation Index (SI)*
Vehicle (1% L92)	7301	268.08	626.81±255.58	1.0[a]± 0.4
	7302	612.02		
	7303	477.35		
	7304	1001.4		
	7305	591.34		
	7306	810.63		
1% GF-1847	7313	913.87	1076.4±267.85	1.7[a] ±0.4
	7314	1359.7		
	7315	1367.3		
	7316	729.10		
	7317	894.67		
	7318	1193.9		
5% GF-1847	7319	1880.8	1551.0*±649.24	2.5[a] ±1.0
	7320	1053.9		
	7321	1781.0		
	7322	1770.3		
	7323	2307.5		
	7324	512.49		
25% GF-1847	7325	2390.4	2083.4*±259.10	3.3[a] ±0.4
	7326	1707.8		
	7327	2195.4		
	7328	2013.7		
	7329	1893.2		
	7330	2299.6		
30% HCA	7307	7015.2	5463.3*±1222.8	8.7[a] ±2.0
	7308	4430.4		
	7309	4481.4		
	7310	6750.2		
	7311	4329.8		
	7312	5772.7		

SI = Group Mean DPM ÷ Vehicle Control Mean DPM
[a] Indicates no statistical comparison of means
* Statistically different from control by Dunnett's test, alpha = 0.05.

B. Stimulation Index:

Sample Description Test or Control	Vehicle	Low	Medium	High	Positive Control
Stimulation Index	1.0 ± 0.4	1.7± 0.4	2.5 ± 1.0	3.3 ± 0.4	8.7 ± 2.0

The study author calculated the concentration that would cause a 3-fold increase in proliferation (EC_3) to be 17.5% which is consistent with weak dermal sensitization potential.

C. **Reviewer's conclusion**: This reviewer agrees with the study author that the test material was a weak dermal sensitizer.

1. **DP BARCODE:** DP341266

2. **PC CODE:** 108702

3. **CURRENT DATE:** October 29, 2007

4. **TEST MATERIAL:** GF-1847 [44 g/L pyroxsulam (wt. % pyroxsulam = 4.2), 91 g/L cloquintocet-mexyl (wt. % cloquintocet-mexyl = 8.7); Lot No. E2154-73, TSN 105901; dark brown liquid; density 1.0458 g/mL at 20°C; emulsifiable in water, soluble in ethanol and acetone, dispersible in corn oil and mineral oil]

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Eurofins/Product Safety Laboratories 21573/May 1, 2007	47158703	LD_{50} Females > 2000 mg/kg bw	III	A
Acute dermal toxicity/rat Eurofins/Product Safety Laboratories 21574/April 19, 2007	47158704	LD_{50} Males > 5000 mg/kg bw LD_{50} Females > 5000 mg/kg bw LD_{50} Combined > 5000 mg/kg bw	IV	A
Acute inhalation toxicity/rat Toxicology and Environmental Research and Consulting, The Dow Chemical Company 071001/April 18, 2007	47158705	LC_{50} Males > 1.1 mg/L LC_{50} Females > 1.1 mg/L LC_{50} Combined > 1.1 mg/L	III	A
Primary eye irritation/rabbit Eurofins/Product Safety Laboratories 21575/April 12, 2007	47158706	Severely irritating	II	A
Primary dermal irritation/rabbit Eurofins/Product Safety Laboratories 21576/April 30, 2007	47158707	Moderately irritating	III	A
Dermal sensitization/guinea pig Toxicology and Environmental Research and Consulting, The Dow Chemical Company 061197/April 2, 2007	47158708	Sensitizer	-	A

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