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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

13/AUG/2007

MEMORANDUM

Subject:	Name of Pesticide Product:	GF-1674
	EPA File Symbol:	62719-LAI
	DP Barcode:	D332133
	Decision No.:	369827
	PC Code:	108702 Pyroxsulam

From: Eugenia McAndrew, Biologist
Technical Review Branch (TRB)
Registration Division (7505P)

To: James Stone, RM Team 23
Herbicide Branch
Registration Division (7505P)

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

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
108702	Pyroxsulam (XDE-742) [CAS No. 422556-08-9]	2.87%
	Inert Ingredient(s):	97.13.%
	Total:	100.00%

ACTION REQUESTED: The Risk Manager requests:

"Review acute toxicity data submitted to support registration of formulation with a new active ingredient."

BACKGROUND: The registrant, Dow AgroSciences LLC, has submitted five acute toxicity studies (MRID Nos. 46908338, 46908340, 46908344, 46908346 and 46908348) and a waiver request for the acute inhalation study (MRID No. 46908342) to support the registration of GF-1674, EPA File Symbol 62719-LAI. The registrant has also submitted Study Profile Templates (SPT) for each of the acute toxicity studies (MRID Nos. 46908539, 46908541, 46908543, 46908545 and 46908547). Four of the acute toxicity studies were conducted at Product Safety Laboratories, Dayton, New Jersey. The dermal sensitization study was conducted at Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan.

The proposed product is an end use formulation containing 2.87% of the active ingredient pyroxsulam. The Registrant states that the active ingredient may be identified in studies as XDE-742, XR-742 or DE-742.

COMMENTS AND RECOMMENDATIONS:

1. The acute oral toxicity, acute dermal toxicity, primary eye irritation, primary dermal irritation and dermal sensitization studies have been reviewed and are classified as acceptable.

2. TRB reviewed the registrant's waiver request for the acute inhalation study. The waiver request is denied. An acute inhalation toxicity study should be conducted and submitted. The decision to deny the waiver request was vetted through Canada and Australia as part of the Global review process for this new AI. All countries agree on the waiver denial (memos sent by Deborah Ramsingh dated 7-19-07, and Julian O'Dea, 7-22-07).

3. Based on the reviewed acute toxicity studies, the acute toxicity profile for GF-1674, EPA File Symbol 62719-LAI is as follows:

Acute oral toxicity	III	Acceptable	MRID 46908338, 46908539
Acute dermal toxicity	IV	Acceptable	MRID 46908340, 46908541
Acute inhalation toxicity	---	Unacceptable	MRID 46908342
Primary eye irritation	II	Acceptable	MRID 46908344, 46908543
Primary skin irritation	III	Acceptable	MRID 46908346, 46908545
Dermal sensitization	Positive	Acceptable	MRID 46908348, 46908547

LABELING: A label was not generated at this time. When the acute inhalation toxicity study is submitted a label will be generated.

Reviewer: Eugenia McAndrew **Date:** Aug 13, 2007
Risk Manager: James Stone, RM Team 23

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

TEST MATERIAL: GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid; density - 1.042 g/mL)

CITATION: Durando, J. (2006) GF-1674 - Acute Oral Toxicity Up and Down Procedure in Rats. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. Laboratory Study Number 18346. February 14, 2006. MRID No. 46908338

Durando, J. (2006) Study Profile Template (SPT) for GF-1674: Acute Oral Toxicity Up and Down Procedure in Rats. Laboratory Study Number: 18346.SPT. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. February 14, 2006. MRID No. 46908539

SPONSOR: The Dow Chemical Company, Midland, Michigan for Dow AgroSciences LLC, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46908338 and 46908539), nine female Fischer 344 young adult rats (age: 8-12 weeks; source: Charles River Laboratories, Raleigh, NC; 117-147 g) were given a single oral dose of GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid; density - 1.042 g/mL) using the Up and Down Procedure. A limit dose of 5000 mg/kg of the test substance was administered to one healthy female rat by oral gavage. This animal died so eight additional females were dosed at levels of 175, 550, 1750 or 5000 mg/kg. Individual body weights were recorded prior to test material administration and again on Days 7 and 14 (termination) following dosing. Animals were observed for clinical signs of toxicity and mortality at least once daily for 14 days after dosing. A gross necropsy examination was performed on all animals at scheduled euthanasia.

Oral LD_{50} Females = 3129 mg/kg bw [95% C.L. 1750 (lower) to 5000 (upper)]

At the 175, 550 and 1750 dose levels, all animals survived and gained weight. No clinical signs were observed. At the 5000 mg/kg dose level, the three animals died within two days of test substance administration. Prior to death toxic signs observed included hypoactivity, hunched posture, reduced fecal volume, piloerection, clear ocular discharge and ano-genital staining. No gross abnormalities were noted in any of the animals at the 175, 550 and 1750 dose levels. Gross necropsy of the animals dosed at 5000 mg/kg revealed discoloration of the intestines.

Toxicity based on the calculated LD_{50}. 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:

Limit Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	Short Term Outcome	14 Day Outcome
1	5528	5000	D	D

Main Test

Dosing Sequence	Animal No.	Dose level (mg/kg)	Short Term Outcome	14 Day Outcome
1	5792	175	S	S
2	5843	550	S	S
3	5876	1750	S	S
4	5886	5000	D	D
5	5913	1750	S	S
6	5945	5000	D	D
7	5994	1750	S	S
8	6038	5000	D	D

S = survival D = death

Statisitics - The Acute Oral Toxicity (Guideline 425) Statistical Program (Westat, version 1.0, May 8001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} confidence limit calculations.

A. Mortality - Three females dosed at 5000 mg/kg died within two days of test substance administration.

B. Clinical observations: At the 175, 550 and 1750 dose levels, all animals survived and gained weight. No clinical signs were observed. At the 5000 mg/kg dose level, the three animals died within two days of test substance administration. Prior to death toxic signs observed included hypoactivity, hunched posture, reduced fecal volume, piloerection, clear ocular discharge and ano-genital staining.

C. Gross Necropsy: No gross abnormalities were noted in any of the animals at the 175, 550 and 1750 dose levels. Gross necropsy of the animals dosed at 5000 mg/kg revealed discoloration of the intestines.

D. Reviewer's Conclusions: TRB agrees with study author's conclusions that under the conditions of this study the acute oral LD_{50} of GF-1674 is estimated to be 3129 mg/kg body weight in female rats with an approximate 95% confidence interval of 1750 mg/kg (lower) to 5000 mg/kg (upper).

E. Deficiencies - Due to a technician error, the clinical observations for animal # 5994 were not recorded on day 9. The observations recorded on days 8 and 10 were the same. This deviation did not affect the outcome of the study.

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

Date/Time: Friday, April 20, 2007, 11:11:54 AM
Data file name: GF-1674.dat
Last modified: 4/20/2007 11:11:50 AM

Test/Substance: GF-1674
Test type: Limit Test
Limit dose (mg/kg): **5000**
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	5528	5000	X	X

(X = Died, O = Survived)

Dose Recommendation: Stop the limit test and conduct a main test at 175 mg/kg.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
5000	0	1	1
All Doses	0	1	1

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

Date/Time: Friday, April 20, 2007, 11:13:58 AM
Data file name: GF-1674 Main.dat
Last modified: 4/20/2007 11:13:56 AM

Test/Substance: GF-1674 Main
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	5792	175	O	O
2	5843	550	O	O
3	5876	1750	O	O
4	5886	5000	X	X
5	5913	1750	O	O
6	5945	5000	X	X
7	5994	1750	O	O
8	6038	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
175	1	0	1
550	1	0	1
1750	3	0	3
5000	0	3	3
All Doses	5	3	8

Statistical Estimate based on long term outcomes:

Estimated LD50 = 3129 (Based on an assumed sigma of 0.5).
Approximate 95% confidence interval is 1750 to 5000.

Reviewer: Eugenia McAndrew **Date:** Aug 13, 2007
Risk Manager: James Stone, RM Team 23

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

TEST MATERIAL: GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid)

CITATION: Durando, J. (2006) GF-1674 - Acute Dermal Toxicity in Rats - Limit Test. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. Laboratory Study Number 18347. February 14, 2006. MRID No. 46908340

Durando, J. (2006) Study Profile Template (SPT) for GF-1674: Acute Dermal Toxicity Study in Rats. Laboratory Study Number: 18347.SPT. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. February 14, 2006. MRID No. 46908541

SPONSOR: The Dow Chemical Company, Midland, Michigan for Dow AgroSciences LLC, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46908340 and 46908541) five/sex young adult Fischer 344 rats (age: 12 weeks; source: Charles River Laboratories, Raleigh, NC; 240-258 g males and 140-156 g females) were exposed to a single dermal application of GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid) for 24 hours.

Five thousand mg/kg of body weight of the shaken test substance was applied to a dose area of approximately 2 inches by 3 inches (approximately 10% of the body surface) and covered with a gauze pad. The pad and entire trunk of each animal were wrapped with tape. After 24 hours of exposure, the pads were removed and the test sites were gently cleansed (with water or appropriate solvents) using clean towels to remove residual test substance. Individual body weights were recorded prior to test substance application and again on Days 7 and 14 (termination) following dosing. Animals were observed for clinical signs of toxicity and mortality several times on the day of dosing and at least once daily thereafter for 14 days after dosing. A gross necropsy examination was performed on all animals at scheduled euthanasia.

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

Based on no deaths at the limit dose, GF-1674 is classified as EPA Toxicity Category IV.

All animals survived and gained body weight during the study. Dermal irritation was noted at the dose site of all animals between days 1 and 14. Erythema and edema were noted for approximately the first 4 days, followed by hyperkeratosis for 1-2 days, and then eschar for the remainder of the observation period. No other clinical signs were observed. No gross abnormalities were observed at necropsy.

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:

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

A. Mortality: None

B. Clinical observations: All animals survived and gained body weight during the study. Dermal irritation was noted at the dose site of all animals between days 1 and 14. Erythema and edema were noted for approximately the first 4 days, followed by hyperkeratosis for 1-2 days, and then eschar for the remainder of the observation period. No other clinical signs were observed.

C. Gross Necropsy: No gross abnormalities were observed

D. Reviewer's Conclusions: TRB agrees with study author's conclusion under the conditions of this study the single dose acute dermal LD_{50} of GF-1674 is greater than 5000 mg/kg body weight in male and female rats.

E. Deficiencies: None.

Reviewers: John Redden and John Whalan **Date:** Aug 13, 2007
Risk Manager: James Stone, RM Team 23

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

TEST MATERIAL: GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid)

CITATION: Mehta, J. (2006) Waiver Rationale for GF-1634 Acute Inhalation Study. Project Number: JM06003. Unpublished study prepared by Dow AgroSciences LLC. July 25, 2006. MRID No. 46908342

SPONSOR: Dow AgroSciences LLC, European Development Centre, 3 Milton Park, Abingdon, OX14 4RN, United Kingdom

EXECUTIVE SUMMARY: The registrant has submitted a waiver rationale (MRID No. 46908342) for the acute inhalation study. By consensus agreement with Canada and Australia, TRB recommends the denial of this waiver request because: 1) An aerosol is formed when sprayed (potential inhalation exposure). Particles 100 micrometers and larger can be inhaled. Most large particles will be captured in the nose. The Agencies cannot rule out that some of these particles will not be absorbed in the nose; 2) Particle size, with evaporation, will make the particles more respirable. When aqueous 30 micrometers particle are sprayed, the water quickly evaporates as the particles fall. This will result in smaller particles that contain a higher concentration of the a.i. Many of these shrinking particles will become respirable; 3) The 3 Rs do not apply here because there is no available inhalation protocol (yet) that **R**educes the number of animals, **R**efines the inhalation procedure or **R**eplaces the inhalation test; and 4) Although not corrosive but moderately irritating to the skin, therefore it can not be determined if this product will be a respiratory irritant.

Reviewer: Eugenia McAndrew **Date:** Aug 13, 2007
Risk Manager: James Stone, RM Team 23

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

TEST MATERIAL: GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid)

CITATION: Durando, J. (2006) GF-1674 - Primary Eye Irritation Study in Rabbits. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. Laboratory Study Number 18348. February 14, 2006. MRID No. 46908344

Durando, J. (2006) Study Profile Template (SPT) for GF-1674: Primary Eye Irritation Study in Rabbits. Laboratory Study Number: 18348.SPT. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. February 14, 2006. MRID No. 46908543

SPONSOR: The Dow Chemical Company, Midland, Michigan for Dow AgroSciences LLC, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46908344 and 46908543), 0.1 ml of GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid) was instilled into the lower conjunctival sac of the right eye of three (2 male and 1 female) young adult New Zealand albino rabbits (source: Robinson Services Inc., Clemmons, NC). The left eye served as the untreated control. The study was conducted in a stepwise fashion. Initially, one rabbit was placed on test. Since irritation cleared from the eye of the first animal treated by day 14, two additional animals were placed on test. Ocular irritation was assessed by the method of Draize at approximately 1, 24, 48, 72 hours and on 4, 7, 10, 14 and 17 days post-instillation.

All treated eyes exhibited corneal opacity, iritis and conjunctivitis from 24 hours through day 4. The corneal opacity persisted in 2/3 eyes and the iritis persisted in 1/3 eyes through day 14. A white discharge was noted in all eyes between 24 hours and day 4. All irritation was resolved by day 17.

In this study, GF-1674 is severely irritating to the eye. EPA Toxicity Category II.

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
Corneal Opacity	0/3	3/3	3/3	3/3	3/3	3/3	3/3	2/3	0/3
Iritis	2/3	3/3	3/3	3/3	3/3	2/3	2/3	1/3	0/3
Conjunctivae:*									
Redness*	3/3	3/3	3/3	3/3	3/3	1/3	0/3	0/3	0/3
Chemosis*	1/3	3/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3
Discharge*	3/3	3/3	3/3	3/3	3/3	1/3	0/3	0/3	0/3

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

A. <u>Observations</u>: All treated eyes exhibited corneal opacity, iritis and conjunctivitis from 24 hours through day 4. The corneal opacity persisted in 2/3 eyes and the iritis persisted in 1/3 eyes through day 14. A white discharge was noted in all eyes between 24 hours and day 4. All irritation was resolved by day 17.

B. <u>Reviewer's Conclusions</u>: TRB agrees with the study author's conclusion that under the conditions of this study, GF-1674 caused corneal opacity, iritis and conjunctival irritation clearing by day 17.

C. <u>Deficiencies</u>: None

Reviewer: Eugenia McAndrew **Date:** Aug 13, 2007
Risk Manager: James Stone, RM Team 23

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

TEST MATERIAL: GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid)

CITATION: Durando, J. (2006) GF-1674 - Primary Skin Irritation Study in Rabbits. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. Laboratory Study Number 18349. February 14, 2006. MRID No. 46908346

Durando, J. (2006) Study Profile Template (SPT) for GF-1674: Primary Skin Irritation Study in Rabbits. Laboratory Study Number: 18349.SPT. Unpublished study prepared by Product Safety Laboratories, Dayton, New Jersey. February 14, 2006. MRID No. 46908545

SPONSOR: The Dow Chemical Company, Midland, Michigan for Dow AgroSciences LLC, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46908346 and 46908545), 0.5 mL of GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid) was applied to the skin of three young adult New Zealand albino rabbits (1 male and 2 female; source: Robinson Services, Inc., Clemmons, NC). The test material was applied in a single dose to the intact untreated skin (6 cm^2) and covered with a gauze pad. The pad and entire trunk of each animal were wrapped with semi-occlusive tape. After 4 hours of exposure, the pads were removed and the test sites were gently cleansed (with water or appropriate solvents) using clean towels to remove residual test substance. Individual dose sites were scored at 1, 24, 48, 72 hours and at 7, 10 and 14 days after patch removal.

In this study, GF-1674 is moderately irritating. EPA Toxicity Category III.

Primary Dermal Irritation Index (PDII) = 4.6 Well defined erythema (score 2) and slight edema (score 2) were observed in all animals 1 hour after removal of the patch. From 24 to 72 hours, all sites exhibited well defined to moderate/severe erythema (score 2-3) and slight edema. The irritation decreased with time. Brown areas and/or desquamation were noted at all dose sites between 24 hours and day 14. Very slight erythema persisted at one site through day 14 (study termination).

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:

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

	Time after patch removal						
	Hours				**Days**		
Animal Number/Sex	1	24	48	72	7	10	14
3501/F	2/2	3/2	2/2	2/2	2/1	1/0	0/0
3502/M	2/2	3/2	3/2	3/2	2/1	1/0	0/0
3503/F	2/2	3/2	3/2	3/2	2/2	2/1	1/0

A. Observations: Well defined erythema (score 2) and slight edema (score 2) were observed in all animals 1 hour after removal of the patch. From 24 to 72 hours, all sites exhibited well defined to moderate/severe erythema (score 2-3) and slight edema. The irritation decreased with time. Brown areas and/or desquamation were noted at all dose sites between 24 hours and day 14. Very slight erythema persisted at one site through day 14 (study termination).

B. Results: Primary Dermal Irritation Index (PDII) = 4.6

C. Reviewer's Conclusions: TRB agrees with the study author's conclusion that under the conditions of this study, GF-1674 caused very slight to moderate/severe erythema and very slight to slight edema.

D. Deficiencies: None

EPA Reviewer: Eugenia McAndrew **Date:** Aug 13, 2007
Risk Manager: James Stone, RM 23

STUDY TYPE: Dermal Sensitization - BALB/cAnNCrl Mice; OPPTS 870.2600; OECD 429

TEST MATERIAL: GF-1674 (Lot # 190/65-A; 29 g/l XDE-742; green to brown liquid; oil dispersion)

CITATION: Durando, J. (2005) GF-1674: Local Lymph Node Assay in BABL/cAnNCrl Mice. Unpublished study prepared by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory Project Study Number 051168. December 2, 2005. MRID No. 46908348

Woolhiser, M.R. (2006) Study Profile Template (SPT) for GF-1674: Local Lymph Node Assay in BABL/cAnNCrl Mice. Laboratory Project Study Number: 051168.SPT. Unpublished study prepared by Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. February 23, 2006. MRID No. 46908547

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

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46908348) with GF-1674 (Lot # 190/65-A; 29 g/l XDE-742; green to brown liquid; oil dispersion), 6/group young adult female mice (strain: BALB/cAnNCrl; age: 8-12 weeks; weight: 17.5 - 20.3 g; source: Charles River Laboratories, Inc., Kingston, NY) 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 2%, 10% or 50% or 1% L92 (vehicle) once daily for three consecutive days. 30% alpha-Hexylcinnamaldehyde (HCA) in vehicle 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.

In the 2% GF-1634 dose group, erythema was absent throughout the study period. Test animals in the 10% and 50% GF-1634 dose groups showed slight to well defined erythema on day 3. On

day 6, erythema had resolved in the 10% group but persisted in all animals in the 50% group. Animals in the 2% group gained 0.6 grams of body weight while the animals in the 10% group lost 0.1 grams and those in the 50% group lost 0.6 grams.

Topical applications of 2%, 10% or 50% (v/v) elicited stimulation indexes (SI) that were respectively 1.4, 4.1 or 11.7 fold greater than vehicle controls. The test system was validated by the positive control HCA which elicited a stimulation index of 12.0.

In this study, GF-1634 **is 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, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS and METHODS

A. Vehicle and positive control - The vehicle used for this study was Pluronic L92 surfactant (1% w/v) in water and the positive control used was 30% HCA.

The study authors explain the choice of vehicle stating: "Pluronic L92 surfactant (1% w/v) was selected based upon miscibility of GF-1674 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."

B. Treatment preparation and administration - 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 2%, 10% or 50% or 1% L92 (vehicle) once daily for three consecutive days. 30% alpha-Hexylcinnamaldehyde (HCA) in vehicle 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.

Note: The study authors explain the choice of BALB/cAnNCrl strain of mice stating: "Because this strain of mouse (CBA/Ca) was not readily available from commercial supplies, BALB/c mice were selected because of their general acceptance and suitability for toxicity testing, and availability of historical background data in this laboratory. BALB/cAnNCrl mice have been

successfully used by other laboratories in LLNA protocols (Woolhiser *et al*., 1998; van't Erve *et al*., 1999; Ehling *et al*., 2005) and have been shown to be equivalent with CBA mice when simultaneously evaluating the LLNA response towards known chemical sensitizers (Woolhiser *et al*., 2000).

II. RESULTS and DISCUSSION:

A. Disintegrations per Minute (group means) -

Dose % GF-1634	Animal Number	Individual Animal DPM	Group Mean DPM	Stimulation Index (SI)*
1% L92 Vehicle Conrol	7268	335.27	241.09	N/A
	7269	251.24		
	7270	100.36		
	7271	408.97		
	7272	169.63		
	7273	181.09		
2%	7280	100.55	344.86	1.4
	7281	187.52		
	7282	702.93		
	7283	211.71		
	7284	433.92		
	7285	432.55		
10%	7286	1382.3	974.78	4.1
	7287	1827.5		
	7288	840.31		
	7289	836.04		
	7290	534.59		
	7291	428.00		
50%	7292	2710.7	2820.5	11.7
	7293	2193.1		
	7294	2854.9		
	7295	3520.4		
	7296	2784.4		
	7297	2859.4		
30% HCA	7274	1784.1	2893.8	12.0
	7275	3520.7		
	7276	2810.7		
	7277	4574.3		
	7278	1556.6		
	7279	3115.5		

***** 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	1.4	4.1	11.7	12.0

C. Reviewer's Conclusions - TRB agrees with the study author that GF-1674 is a dermal sensitizer.

D. Deficiencies: None

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D332133
2. **PC CODE:** 108702 Pyroxsulam
3. **CURRENT DATE:** 08/MAY/2007
4. **TEST MATERIAL:** GF-1674 (XR-742 (Pyroxsulam); Lot # 190-65/A; TSN105329; Purity: 29 g/L; green opaque liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Product Safety Labs 18346/02-14-2006	46908338 46908539	LD_{50} = 3129 mg/kg (females)	III	A
Acute dermal toxicity / rat Product Safety Labs 18347/02-14-2006	46908340 46908541	LD_{50} > 5000 mg/kg (males and females)	IV	A
Acute inhalation toxicity / rat JM06003 / 07-25-2006	46908342	Waiver request denied	---	U
Primary eye irritation / rabbit Product Safety Labs 18348/02-14-2006	46908344 46908543	Corneal opacity, iritis and conjunctivitis from 24 hours through day 4. Corneal opacity persisted in 2/3 eyes and the iritis persisted in 1/3 eyes through day 14. All irritation was resolved by day 17.	II	A
Primary dermal irritation / rabbit Product Safety Labs 18349/02-14-2006	46908346 46908545	PDII = 4.6 Well defined erythema and slight edema at all sites at 1 hour. Well defined to moderate/severe erythema and slight edema at all sites from 24 to 72 hours. Very slight erythema at one site through day 14 (study termination).	III	A
Dermal sensitization /mouse Toxicology & Environmental Research and Consulting - Dow 051168/12-02-20	46908348 46908547	A sensitizing effect	---	A

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