

US EPA ARCHIVE DOCUMENT



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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

04/FEB/2009

MEMORANDUM

Subject: Name of Pesticide Product: RF2042[CDSO]
EPA Reg. No. /File Symbol: 2724-TOA
DP Barcode: D357271
Decision No.: 399095
PC Codes: 128965 (etofenprox)
105402 (s-methoprene)
067501 (piperonyl butoxide)

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

E. McAndrew
M. H. ...
(To: Kevin Sweeney)

To: Kevin Sweeney, RM Team 13
Insecticide Branch
Registration Division (7505P)

Applicant: Wellmark International
1501 East Woodfield Road, Suite 200 West
Schaumburg, Illinois 60173

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt</u>
Etofenprox	30.0
S-Methoprene	3.6
Piperonyl Butoxide	5.0
<u>Inert Ingredient(s):</u>	<u>61.4</u>
Total:	100.0%

ACTION REQUESTED: Risk Manager requests: Please review attached acute toxicity studies. Note that the registrant has requested a waiver from the acute inhalation study.

BACKGROUND: Wellmark International has submitted acute oral, acute dermal, primary eye irritation, primary skin irritation and dermal sensitization studies to support the registration of the proposed product, RF2042[CDSO], EPA File Symbol 2724-TOA. The studies were conducted at Product Safety Laboratories, Dayton, New Jersey with assigned MRID numbers 475185-04 to -08. A CSF for a basic formulation dated August 15, 2008 is included in the submission.

The registrant is requesting a waiver from the requirement for an acute inhalation toxicity study (MRID 47518509). The waiver request rationale is as follows:

- All of the active ingredients have been tested for acute inhalation toxicity and are classified as EPA Toxicity Category IV.
- The inert ingredients are on the EPA list or Inert Ingredients Permitted for Use in Non-Food Use Pesticide Products (January 7, 2008).
- The manner which the product will be applied and the physical properties of the formulation do not have potential to produce an inhalation hazard.
- The product is packaged in single use individual applicators with directions to "hold applicator upright and snap tip back, away from face and body."

RECOMMENDATIONS: The five studies have been reviewed and are classified as acceptable. TRB agrees with the request for a waiver of the acute inhalation toxicity study.

The acute toxicity profile for RF2042[CDSO], EPA File Symbol 2724-TOA, is as follows:

Acute oral toxicity	IV	Acceptable	MRID 47518504
Acute dermal toxicity	IV	Acceptable	MRID 47518505
Acute inhalation toxicity	IV	Waived	MRID 47518509
Primary eye irritation	III	Acceptable	MRID 47518506
Primary skin irritation	IV	Acceptable	MRID 47518507
Dermal sensitization	Negative	Acceptable	MRID 47518508

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

PRODUCT ID #: 002724-00796

PRODUCT NAME: RF2042[CDSO]

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Causes moderate eye irritation. Avoid contact with eyes or clothing. [Wear protective eyewear.]* Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco.

*[Protective eyewear may be specified, if appropriate.]

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.

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

Reviewer: Eugenia McAndrew
Risk Manager (EPA): 13

Date: February 4, 2009

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

TEST MATERIAL: RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

CITATION: Lowe, C. (2008) RF2042[CDSO – Acute Oral Toxicity Up and Down Procedure in Rats. Study Number 22373. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. March 20, 2008. MRID 47518504.

SPONSOR: Wellmark International. 1501 E. Woodfield Road, Suite 200W. Schaumburg, IL 60173

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47518504), three fasted, young adult female Sprague-Dawley rats (age: 9-10 weeks; body weight: 174-220 g; source: Ace Animals, Inc., Boyertown, PA) were given a single dose of RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid) as received at a limit dose of 5000 mg/kg bw by gavage and observed for 14 days.

All animals survived, gained weight and appeared active and healthy throughout the study. No gross abnormalities were noted at necropsy.

LD₅₀ Females > 5000 mg/kg bw

RF2042[CDSO] is in EPA Toxicity Category IV.

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.

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
3102	F	5000	S
3103	F	5000	S
3103	F	5000	S

S = Survival, D = Death

- A. **Mortality**: All animals survived the study.
- B. **Clinical observations**: All animals gained weight and appeared active and healthy throughout the study.
- C. **Gross necropsy**: No gross abnormalities were noted.
- D. **Reviewer's conclusions**: This reviewer agrees with the study author regarding the acute oral LD₅₀.

RESULTS and DISCUSSION:

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

Date/Time: Wednesday, January 21, 2009, 11:50:18 AM
Data file name: work.dat
Last modified: 01/21/2009 11:50:16 AM

Test/Substance: RF2042[CDSO]
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	3101	5000	O	O
2	3102	5000	O	O
3	3103	5000	O	O

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
5000	3	0	3
All Doses	3	0	3

Statistical Estimates:

The LD₅₀ is greater than 5000 mg/kg.

Reviewer: Eugenia McAndrew
Risk Manager (EPA): 13

Date: February 4, 2009

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

TEST MATERIAL: RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

CITATION: Lowe, C. (2008) RF2042[CDSO] – Acute Dermal Toxicity Study in Rats – Limit Test. Study Number 22374. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. March 20, 2008. MRID 47518505.

SPONSOR: Wellmark International. 1501 E. Woodfield Road, Suite 200W. Schaumburg, IL 60173

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47518505), young adult Sprague-Dawley rats (5/sex; age: 8-9 weeks; body weight: males: 235-285 g and females: 168-195 g; source: Ace Animals, Inc., Boyertown, PA) were dermally exposed for 24 hours on an area of approximately 10% of the total body surface area on the clipped dorsal trunk to 5000 mg/kg bw RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid) as received. The test material was applied evenly over the dose area and covered with a gauze pad. The gauze pad and the trunk were wrapped with Durapore tape. The animals were observed for 14 days.

All animals survived, and gained weight and appeared active and healthy throughout the study. Dermal irritation (erythema and/or edema) was noted at 3/10 does sites on days 1-2. No gross abnormalities were noted at necropsy.

LD₅₀ Males > 5000 mg/kg bw
LD₅₀ Females > 5000 mg/kg bw
LD₅₀ Combined > 5000 mg/kg bw

RF2042[CDSO] 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:** All animals gained weight and appeared active and healthy throughout the study. Dermal irritation (erythema and/or edema) was noted at 3/10 does sites on days 1-2.

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

D. **Reviewer's conclusions:** This reviewer agrees with the study author regarding the acute dermal LD₅₀.

Reviewer: Eugenia McAndrew
Risk Manager (EPA): 13

Date: February 4, 2009

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

TEST MATERIAL: RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

CITATION: Lowe, C. (2008) RF2042[CDSO] – Primary Eye Irritation Study in Rabbits. Study Number 22375. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. March 20, 2008. MRID 47518506.

SPONSOR: Wellmark International. 1501 E. Woodfield Road, Suite 200W. Schaumburg, IL 60173

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47518506), 0.1 mL of undiluted RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid) was instilled as received into the conjunctival sac of the right eye of three female young adult New Zealand albino rabbits (source: Robinson Services, Inc., Clemmons, NC). The untreated eye served as a control. Prior to instillation, 2 drops of ocular anesthetic (Tetraicaine Hydrochloride Ophthalmic Solution, 0.5%) were placed into both the treated and control eye of each animal. The animals were observed for 72 hours.

Iritis and positive conjunctival irritation were noted on 3/3 animals one hour after test material instillation. No positive scores were noted at 48 hours and all eyes were free of irritation by 72 hours.

RF2042[CDSO] is classified as EPA Toxicity Category III 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			
Observations	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	3/3	2/3	0/3	0/3
Conjunctivae:				
Redness*	3/3	0/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3
Discharge**	3/3	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:** Iritis and positive conjunctival irritation were noted on 3/3 animals one hour after test material instillation. No positive scores were noted at 48 hours and all eyes were free of irritation by 72 hours.
- B. **Results:** RF2042[CDSO] was mildly irritating.
- C. **Reviewer's conclusions:** This reviewer agrees with the study author that the test material was mildly irritating and classified as EPA Toxicity Category III.

Reviewer: Eugenia McAndrew
Risk Manager (EPA): 13

Date: February 4, 2009

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

TEST MATERIAL: RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

CITATION: Lowe, C. (2008) RF2042[CDSO] – Primary Skin Irritation Study in Rabbits. Study Number 22376. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. March 20, 2008. MRID 47518507.

SPONSOR: Wellmark International. 1501 E. Woodfield Road, Suite 200W. Schaumburg, IL 60173

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47518507), three young adult female New Zealand albino rabbits (source: Robinson Services, Inc., Clemmons, NC) were dermally exposed to 0.5 mL of undiluted RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid) for 4 hours on a 6 cm² area of the clipped dorsal skin that was covered with a gauze pad. The pad and trunk were wrapped with semi-occlusive Micropore tape. Elizabethan collars were placed on the rabbits. The animals were observed and irritation was scored at 1, 24, 48, and 72 hours after patch removal.

Very slight erythema was noted on 3/3 rabbits 30-60 minutes after patch removal. All sites were free of irritation by 24 hours.

In this study, RF2042[CDSO] is classified as EPA Toxicity Category IV 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:

Erythema/Edema

Animal Number/Sex	Hours After Patch Removal				Days
	1	24	48	72	
3501/F	1/0	0/0	0/0	0/0	0/0
3502/F	1/0	0/0	0/0	0/0	0/0
3503/F	1/0	0/0	0/0	0/0	0/0

- A. Observations:** Very slight erythema was noted on 3/3 rabbits 30-60 minutes after patch removal. All sites were free of irritation by 24 hours.
- B. Results:** RF2042[CDSO] was slightly irritating. The Primary Irritation Index (PII) is 0.3.
- C. Reviewer's conclusions:** This reviewer agrees with the study author that the test material was slightly irritating.

Reviewer: Eugenia McAndrew
Risk Manager (EPA): 13

Date: February 4, 2009

STUDY TYPE: Dermal Sensitization – guinea pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

CITATION: Lowe, C. (2008) RF2042[CDSO – Dermal Sensitization Study in Guinea Pigs (Buehler Method). Study Number 22377. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. March 20, 2008. MRID 47518508.

SPONSOR: Wellmark International. 1501 E. Woodfield Road, Suite 200W. Schaumburg, IL 60173

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47518508) with RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid), 30 young adult Hartley albino guinea pigs (body weight: males: 356-423 g and females: 324-375 g; source: Elm Hill Breeding Labs, Chelmsford, MA) were tested using the Buehler Method. The test animals were induced with 0.4 mL of undiluted test material for six hours using occlusive 25 mm Hill Top Chambers that were secured and wrapped with non-allergenic adhesive tape. The procedure was repeated once each week for three consecutive weeks. Twenty-seven days after the first induction, the test animals were challenged with 0.4 mL of undiluted test material under occlusion to naive sites. The naive control animals were treated with 0.4 mL of undiluted test material under occlusion at challenge. Reactions were scored 24 and 48 hours after test material applications.

After three consecutive weekly inductions, no positive dermal reactions were noted from any animal after challenge.

Based on the results of this study, RF2042[CDSO] was not a dermal sensitizer

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

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

PROCEDURE:

- A. Induction:** The animals were induced and challenged according to the Buehler method. The dorsal and flank areas of 20 test guinea pigs were clipped prior to each treatment. For induction, 0.4 mL of undiluted test material was applied to the animal using an occlusive 25 mm Hill Top Chamber and secured with non-allergenic adhesive tape. The chamber was removed after six hours and excess test material removed. The procedure was repeated once each week for three consecutive weeks. Reactions were scored 24 and 48 hours after the induction applications.
- B. Challenge:** Twenty-seven days after the first induction, the test animals were challenged with 0.4 mL of undiluted test material under occlusion to naive sites for 6 hours. Reactions were scored 24 and 48 hours after challenge application.
- C. Naive control:** The dorsal and flank areas of 10 naive control animals were clipped prior to treatment. At challenge, the naive control group was treated with 0.4 mL of undiluted test material for 6 hours. Reactions were scored 24 and 48 hours following challenge application.

RESULTS and DISCUSSION:

- A. Reactions and durations:** Very faint usually non-confluent erythema (0.5) was noted on 17/20 test animals over the course of three inductions. Very faint usually non-confluent erythema was noted on 11/20 test animals at 24 hours and on 4/20 test animals at 48 hours after challenge. Very faint usually non-confluent erythema was noted on 4/10 naive control animals 24 hours after challenge persisting at one site at 48 hours. The test material was not a dermal sensitizer.
- B. Positive control:** The report included the results of a positive control (alpha-hexylcinnamaldehyde) study # 21953 conducted within six months of the current study; the results were appropriate.
- C. Reviewer's conclusion:** This reviewer agrees with the study author that the test material was not a dermal sensitizer.

1. **DP BARCODE:** DP357271
2. **PC CODES:** 128965, 105402, 067501
3. **CURRENT DATE:** February 4, 2009
4. **TEST MATERIAL:** RF2042[CDSO](Lot # 495-97; 30.0% etofenprox, 3.60% methoprene and 5.00% piperonyl butoxide; oily yellowish liquid)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Eurofins/Product Safety Laboratories 22373/March 20, 2008	47518504	LD ₅₀ > 5000 mg/kg bw females	IV	A
Acute dermal toxicity/rat Eurofins/Product Safety Laboratories 22374/March 20, 2008	47518505	LD ₅₀ > 5000 mg/kg bw males, females combined	IV	A
Acute inhalation toxicity waiver request 3474/August 12, 2008	47518509	Waived	IV	W
Primary eye irritation/rabbit Eurofins/Product Safety Laboratories 22375/March 20, 2008	47518506	Mildly irritating	III	A
Primary dermal irritation/rabbit Eurofins/Product Safety Laboratories 22376/March 20, 2008	47518507	Slightly irritating	IV	A
Dermal sensitization/Guinea pig Eurofins/Product Safety Laboratories 22377/March 20, 2008	47518508	Not sensitizing	-	A

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