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

010940

APR 29 1994

APR 29 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Registration of Technical Methyl Anthranilate (REJEX-IT MA, File Symbol 58035-I), and Two End-Use Products (REJEX-IT AP-50, File Symbol 58035-A; REJEX-IT TP-40, File Symbol 58035-T). Product Chemistry and Mammalian Toxicology Data (Case # 015580; Chemical # 128725; Submission # S439068; DP Barcode # D192325)

TO: Robert Forrest, Product Manager (PM-14)
Daniel Peacock, Reviewer (PM-14)
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: Sheryl K. Reilly, Ph.D., Biological Section
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: William L. Burnam, Branch Chief
Science Analysis Branch
Health Effects Division (7509C)

and

Roy D. Sjoblad, Ph.D., Section Head
Biological Section, Science Analysis Branch
Health Effects Division (7509C)

ACTION REQUESTED: PMC Specialties Group, Inc. has submitted a registration application for REJEX-IT™ MA, technical methyl anthranilate, and two end-use products, REJEX-IT™ AP-50 (50% a.i.) and REJEX-IT™ TP-40 (40% a.i.). Methyl anthranilate is a biochemical pesticide, and its end-use products are to be used as a bird repellant in tailing ponds, impoundments, landfills, and temporary pools of standing water at airports. Methyl anthranilate is considered GRAS under 21 CFR 182.60, and is used as a flavoring agent in foods (alcoholic and nonalcoholic beverages, ice cream, candy, baked goods, gelatins and puddings, chewing gum, and is also a component of perfumes.

CONCLUSIONS: The registrant did not submit a list of impurities, their percentages, or reasons for occurrence (Guideline Reference Number 151-12). No data were submitted to indicate the efficacy of

Recycled/Recyclable
Printed with Soy/Canola Ink on paper that contains at least 50% recycled fiber

the methodologies used to detect MA for identifying or quantitating impurities. Most of the studies submitted for acute mammalian toxicology were graded Supplementary. All of these studies are upgradeable, provided the lot number of the test material used in these studies and its purity (e.g., if it was technical grade, 97-100% pure, etc.) are specified.

DETAILED CONSIDERATIONS:

A. Product Characterization

The following product data are required under 40 CFR § 158 Subpart C, in accordance with Subdivision M § 151-10 to -18 of the Pesticide Assessment Guidelines:

1. Guideline 151-10: Identity of the Active Ingredient

Product Identity

REJEX-IT™ MA (Technical, 97-100% a.i.)
REJEX-IT™ AP-50 (end-use product, 50% a.i.)
REJEX-IT™ TP-40 (end-use product, 40% a.i.)

Confidential Statement of Formula (CSF)

The registrant has provided the CSF for the technical and two end-use products; photocopies are located in the attached Confidential Appendix.

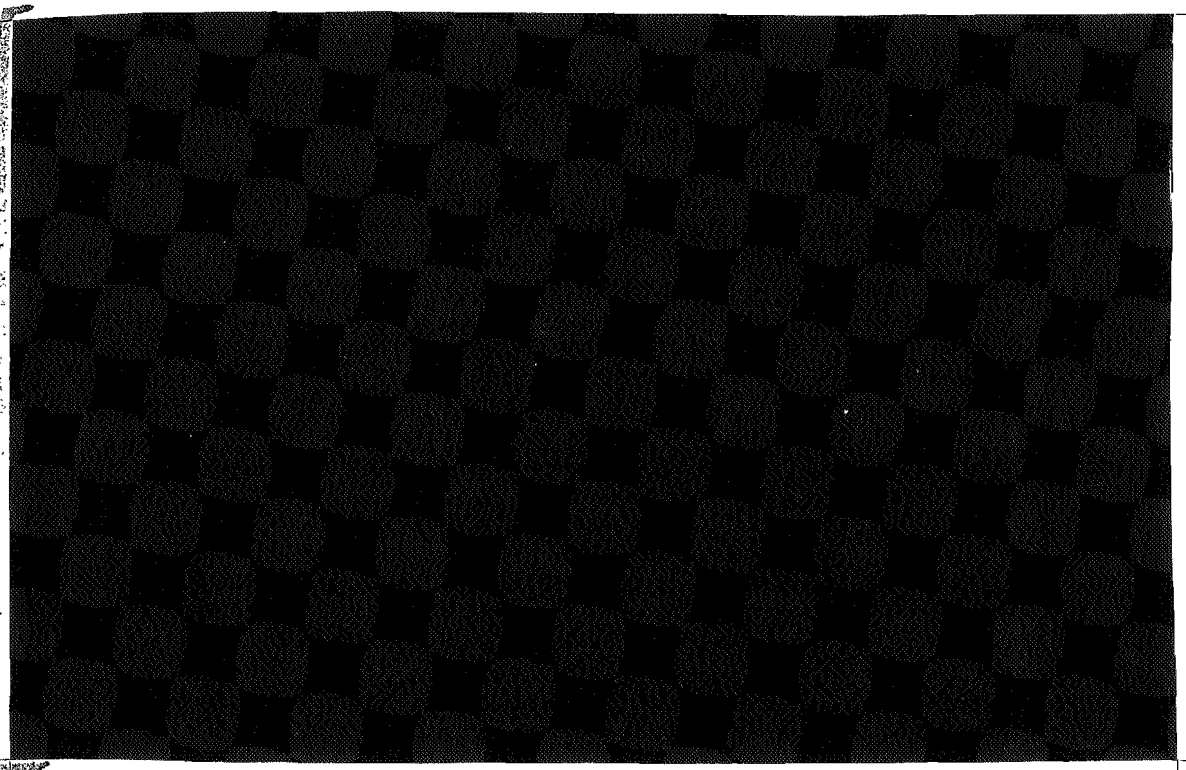
Information on Active Ingredient

The following table summarizes information submitted regarding the active ingredient:

Chemical Name	methyl 2-aminobenzoate
CAS Registry No.	134-20-3
Common Name	Methyl Anthranilate (MA)
Empirical Formula	$C_8H_9NO_2$
Molecular Formula	$COOCH_3-C_6H_4-NH_2$
Molecular Weight	151.17
Source of biochemical	grape varieties, flower oils, synthetic process (see below)
Mode of Action	Bird repellant; presumably by taste or irritation owing to the aromatic nature of MA

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

2. Guideline 151-11: Manufacturing Process



This information on manufacturing process may not have to have been supplied, provided the MA is food-grade material.

3. Guideline 151-12: Discussion of the Formation of Unintentional Ingredients

The petitioner did not submit a list of impurities, their percentages, or reasons for occurrence. The HPLC methodology showed only one peak of significance (i.e., MA), but no data were submitted to indicat the efficacy of the method for determining impurities. Gas chromatography methodology for detecting MA was also submitted, which indicated it was "suitable for determination not only of the purity of methyl anthranilate but also the probable impurities." No data were submitted to support whether this method was useful in detecting impurities.

4. Guideline 151-13: Analysis of Samples

Method Validation:

REJEX-IT™ AP-50 Lot/batch/ID # MC 23005
REJEX-IT™ TP-40: Lot/batch/ID # 41092

Analytical Standard (>99% pure): REJEX-IT™ MA

HPLC Column: HP C-18 (200 x 4.6 mm x 5.0 μm)
Column Temperature: 40°C
Mobile phase: 50% acetonitrile/50% deionized H_2O
Flow rate: 0.75 mg/min
UV Detector: 230 nm
Limits of detection: 57.4 ± 0.4 μg/ml
Retention Time: 5.98 minutes

Linearity: Coefficient of correlation = 0.999603 for concentrations 58.5, 93.6, 117.0 140.0 and 176.0 μg/ml

Precision: Relative standard deviation (%) for 40% and 50% standard solutions was 0.13 and 0.14, respectively

Recovery: 100.5% for the 40% standard, 101.0% for the 50% standard

5. Guideline 151-15: Certification of Ingredient Limits

The Certifications of Ingredient Limits for technical MA and REJEX-IT™ AP-50 are provided in the attached Confidential Appendix. The certified limits (upper and lower) are found in column 14 of the CSFs. The petitioner did not send in 5-batch analysis data.

6. Guideline 151-16: Analytical Methods for Certified Limits

As mentioned previously (see Manufacturing Process, above), the petitioner submitted HPLC and GC methodology for assaying MA and impurities.

7. Guideline 151-17: Physical and Chemical Characteristics

The following table summarizes the data that satisfy the requirements of 40 CFR § 158.190:

Guideline No.	Characteristics	MA	AP-50	TP-40
63-2	Color	Pale Yellow	White	Clear Blue
63-3	Physical State	liquid or crystals	granular	liquid
63-4	Odor	orange blossoms; grapes	grapes	grapes
63-5	Melting Point	23.5-25°C	NR	NR
63-6	Boiling Point (760 mm Hg)	256°C	NR	208°C
63-7	Density (20-25°C)	1.2*	432 g/l	949 g/l
63-8	Water Solubility: (g/100 ml)	0.29	0.27	0.18
63-9	Vapor Pressure	0.012 mm @ 20°C	NR	NR
63-10	Dissociation Constant	K(25°C): 1.7 x 10-[illegible]	NR	NR
63-11	Octanol/Water Partition Coefficient: Water Octanol	42±11.6 0.03 mg/ml 1.20 mg/ml	NR	NR
63-12	pH (24°C):	Waived	Waived	Waived
63-13	Stability	Waived	NR	NR
63-15	Flammability	Waived	Waived	Waived
63-16	Explodability	Waived	NR	Waived
63-17	Storage Stability**	100%	56.2%	35.8%
63-18	Viscosity	NR	NR	16 cps @ 25°C
63-19	Miscibility	NR	Waived	Waived
63-20	Corrosion Characteristics	None	None	None

* Relative density is reported for MA; bulk density for end-use products.

** Thirty days @ 50°C; accountability in % Total. NOTE: Storage stability currently is not required for end-use products.

NR = Not required

8. Data Waivers

a. pH - These data are waived because there were no acute toxicity concerns (all acute mammalian toxicity categories were III or IV).

b. Flammability - The waiver request for flammability is granted because the product does not contain combustible liquids.

c. Stability - This data requirement can be waived for the TGAI because manufacturing process indicates MA is stable at high distillation temperatures; also, the registrant submitted storage stability data which indicated the product is stable for at least 30 days at elevated temperatures (50°C).

d. Explodability - SAB accepts the rationale that this requirement be waived because the flash point is over 248°F.

e. Miscibility - The waiver request for miscibility is granted because the product is not an emulsifiable liquid which is to be diluted with petroleum solvents.

9. Data Gaps: The following product chemistry data gap exists for this petition:

Guideline	
151-12:	Discussion of the Formation of Unintentional Ingredients for the technical and both end-use products

6

B. Human Health Assessment

1. Mammalian Toxicology Data Base

Acute and subchronic mammalian toxicology studies have been submitted and **do not** satisfy the requirements as set forth in 40 CFR 158.690. The tables below summarize the toxicology studies:

a. TOXICOLOGY DATA BASE FOR REJEX-IT™ MA (TECHNICAL)

STUDY (Species)	MRID No.	RESULTS	TOX. CATEGORY	COREGRADE
Acute Oral Toxicity (rat)	42608802	LD_{50} = 3288 mg/kg[1]	III	S
Acute Dermal Toxicity (rabbit)	42608803	LD_{50} > 2 g/kg	III	S
Acute Inhalation Toxicity (rat)	Waived			
Eye Irritation (rabbit)	42608804	Moderate Irritant[2]	III	S
Dermal Irritation (rabbit)	42608805	nonirritating	IV	S
Dermal Sensitization - modified Buehler (guinea pig)	42608806	Not a sensitizer	N/A	S
Immune Response	Waived			

[1] LD50 ♂/♀ (estimated) = 3633/3000 mg/kg; toxic signs included prostrating, staggered gait, absence of righting reflex; resolved by day 2.

[2] Corneal epithelial peeling, blanching, and clear conjunctival discharge; all signs cleared at 72 hours.

(S = Supplementary)

7

010940

b. TOXICOLOGY DATA BASE FOR REJEX-IT™ AP-50

STUDY (Species)	MRID No.	RESULTS	TOX. CATEGORY	Coregrade
Acute Oral Toxicity (rat)	42608702	LD_{50} > 5g/kg	IV	S
Acute Dermal Toxicity (rabbit)	42608703	LD_{50} > 2 g/kg	III	G
Acute Inhalation Toxicity (rat)	Waived			
Eye Irritation (rabbit)	42608704	Moderate-severe conjunctival irritant[1]	II	S
Dermal Irritation (rabbit)	42608705	Slight irritant[2]	IV	G
Dermal Sensitization - modified Buehler (guinea pig)	42608706	Not a sensitizer	N/A	S
Immune Response	Waived			

[1] Scattered, diffuse corneal opacity and circumcorneal injection; all signs cleared within 14 days.

[2] Average Draize score = 0.1 @ 72 hour.

G = Guideline)

8

c. TOXICOLOGY DATA BASE FOR REJEX-IT™ TP-40

STUDY (Species)	MRID No.	RESULTS	TOX. CATEGORY	Coregrade
Acute Oral Toxicity (rat)	42608902	LD_{50} > 5g/kg[1]	IV	S
Acute Dermal Toxicity (rabbit)	42608903	LD_{50} > 2 g/kg[2]	III	S
Acute Inhalation Toxicity (rat)	Waived			
Eye Irritation (rabbit)	42608904	Minimal irritant[3]	IV	S
Dermal Irritation (rabbit)	42608905	Slight irritant[4]	IV	S
Dermal Sensitization - modified Buehler (guinea pig)	42608906	Not a sensitizer	N/A	S
Immune Response	Waived			

[1] Minimal signs of toxicity (soft stool, hypoactivity) resolved by day 2; no mortality.

[2] Moderate to severe erythema (Draize scores 2-3 through day 7), slight to severe edema (Draize scores 1-3), no mortality or signs of toxicity.

[3] Slight conjunctival irritation clearing within 24 hours (avg. Draize score 3.3 @ 1 hour).

[4] Slight to severe erythema and very slight edema, resolved by day 7; desquamation observed at day 7.

2. Data Waivers:

a. **Guideline Ref. No. 81-3** - The registrant requested a waiver for acute inhalation studies since the label will require the wearing of a respirator as protective clothing.

SAB does not support this waiver request for the studies solely on the basis of the "product will not result in repeated inhalation exposure at concentrations likely to be toxic. No exposure data were submitted to support this claim. SAB believes that pulmonary exposure will not result at a toxic concentration only because of the label specification that a respirator should be worn by applicators. The type of respirator that is required for this use is a dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C; personal communication with A. Nielson, Occupational and Residential Exposure Branch).

b. **Guideline Ref. No. 152-18** - The immune response waiver requested because product is an FDA GRAS list material, widely consumed for many years, etc. is not supported by SAB for the reasons presented by the petitioner; however, SAB will support

9

a waiver of 152-18 because the use patterns and protective clothing as proposed is not likely to increase exposure to that which already occurs via the diet.

3. Data Gaps:

All of the mammalian toxicology studies which were coregraded supplementary are upgradeable, pending receipt of information on the lot number of the test material used in these studies, its purity (e.g., if it was technical grade, 97-100% pure, etc.) are specified.

Attachments:

1. Data Evaluation Reports for Acute Toxicity Studies (series 81-1, -2, -4, -5 and -6) for REJEX-IT™ MA, REJEX-IT™ AP-50, and REJEX-IT™ TP-40

2. Confidential Appendix

CONFIDENTIAL APPENDIX

METHYL ANTHRANILATE

Page_____ is not included in this copy.

Pages 12 through 16 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

X The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

010940

FINAL

DATA EVALUATION REPORT

Rejex-it AP-50

Study Type: Acute Oral Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date 1/13/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3.36
Clement Number: 154
Project Officer: Caroline Gordon

17 V

Guideline Series 81-1: Acute Oral Toxicity in Rats

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: R D. Sjoblad
Date: 4/15/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-1; acute oral toxicity in rats
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426087-02
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it AP-50
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305696
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Acute Oral Toxicity Study of Rejex-it AP-50 in Rats
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 7, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 7, 1992, was submitted.
CONCLUSIONS:	Estimated acute oral LD_{50} for males: >5000 mg/kg body weight Estimated acute oral LD_{50} for females: >5000 mg/kg body weight
CORE CLASSIFICATION:	Core Supplementary. This study satisfies the guideline requirements (81-1) for an acute oral toxicity study in rodents. However, insufficient

data were reported about the test material, i.e., lot number, stability, and purity were not provided. This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it AP-50
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	White powder
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	Corn oil
Concentration in vehicle:	0.25 g/mL
Dose level:	5000 mg/kg body weight
Dose volume:	20 mL/kg body weight (4.7-5.8 mL, males; 4.3-4.6 mL, females)

Note: The guidelines (81-1) recommend that the dose volume should not exceed 10 mL/kg for non-aqueous solutions.

Controls

There were no controls.

Test Animals

Species:	Albino rat
Strain:	Crl:CD®BR
Source:	Charles River Laboratories, Inc., Portage, MI
Sex:	5 males and 5 females
Age:	Young adult
Initial body weights (fasted):	214-230 g for males; 234-290 g for females
No. animals:	5/sex/dose
Temperature:	22-27°C
Relative humidity:	39-54%
Photoperiod:	12-hour light/dark cycle
Feeding:	Purina Certified Rodent Chow #5001, *ad libitum*
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	5/cage; sexes separate
Identification:	Ear tags
Selection:	Healthy animals within unspecified weight limits were selected

B. **TEST PERFORMANCE**

Method of administration:	Oral gavage
Animals fasted:	food was withheld 17-20 hours before dosing
Dosing:	Once __x__; Other _____ (describe)
Observation period:	14 days
Observation frequency:	Clinical observations and mortality checks were conducted 1, 2.5, and 4 hours after dosing. Clinical observations were econducted daily and mortality checks were made twice daily thereafter for 14 days.
Body weight interval:	Body weights were measured day 0 (before dosing), day 7, and day 14 (study termination).
Gross pathology:	Yes
Histopathology:	No

C. RESULTS

Mortality

There were no deaths during the study.

Clinical observations

Clinical signs of toxicity included yellow-stained urogenital areas in 3/5 males at days 1 and 2, and soft stool in 1/5 females 4 hours post-treatment.

Body weights

All rats gained weight by the end of the 14-day observation period.

Gross necropsy

No compound-related changes were observed in any rats.

LD_{50} determination

The estimated acute oral LD_{50} for male and female rats was >5000 mg/kg body weight.

D. REVIEWERS' COMMENTS

Under these study conditions, the estimated acute oral LD_{50} for both male and female rats administered Rejex-it AP-50 was greater than 5000 mg/kg body weight. Clinical signs of toxicity included yellow-stained urogenital areas (3 rats) and soft stool in 1 rat. These effects may have been due to the large volume of corn oil that was administered. This LD_{50} corresponds to Toxicity Category IV (Cauti...

Guideline Series 81-1: Acute Oral Toxicity in Rats

C10940

The study was done at the limit dose (5 g/kg) specified in guideline series 81-1.

21

010940

FINAL

DATA EVALUATION REPORT

Rejex-it AP-50

Study Type: Acute Dermal Toxicity in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz ~~M.P.~~H.	Date 1/13/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 155
Project Officer: Caroline Gordon

33 U

010940

Guideline Series 81-2: Acute Dermal Toxicity in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: R D Sjoblad
Date: 2/15/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-2; acute dermal toxicity in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426087-03
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it AP-50
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305700
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Acute Dermal Toxicity Study of Rejex-it AP-50 in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 7, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 7, 1992, was submitted.
CONCLUSIONS:	Estimated acute dermal LD_{50} for males: >2000 mg/kg body weight Estimated acute dermal LD_{50} for females: >2000 mg/kg body weight
CORE CLASSIFICATION:	Core Guideline. This study satisfies the guideline requirements (81-2) for an acute dermal toxicity study in rabbits.

23

TOXICITY CATEGORY: III (Caution)

010940

A. MATERIALS

Test Compound

Test material:	Rejex-it AP-50
Lot no.:	56-612-69-02
Purity:	Determined by sponsor
Physical description:	White powder
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	The test material was moistened with an unspecified amount of 0.9% saline
Dose level:	2000 mg/kg body weight (limit dose)

Controls

None.

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo, MI
Sex:	5 males and 5 females
Age:	Young adult
Initial body weights:	2114-2364 g for males; 2016-2262 g for females
No. animals:	5/sex/dose
Temperature:	20-25°C
Relative humidity:	36-65%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals within unspecified weight limits were selected

B. TEST PERFORMANCE

Application

The hair on the back of each rabbit (approximately 10% of the total body surface area) was clipped on the day before dosing. The test material (2000 mg/kg body weight) was moistened with an unspecified amount of 0.9% saline and applied to the intact skin of each rabbit. The area of application was covered with a 10 cm X 10 cm gauze patch, secured with paper tape, and wrapped with Saran Wrap and Elastoplast tape. After 24 hours the wrappings were removed. Excess test material was washed from the test site with tap water and paper towels.

24

Observation period

Observations for clinical signs of toxicity were made 1, 2.5, and 4 hours after application of the test material. During the 14-day observation period, clinical observations and mortality checks (morning and afternoon) were made daily. The initial observation for dermal response was approximately 30 minutes after removal of the test material at days 3, 7, 10, and 14, according to the Draize technique.

Body weight interval

Body weights were measured day 0 (before application) and on observation days 7 and 14.

Gross pathology: Yes
Histopathology: No

C. RESULTS

Clinical observations

No overt signs of toxicity were observed. Table 1 shows the incidence of dermal irritation observations.

Body weights

All rabbits had gained weight by the end of the study. Minor weight loss (1-3%) was observed in 2 males and 2 females between days 7 and 14.

Mortality

All treated animals (5 males and 5 females) dosed with 2000 mg/kg body weight survived until study termination.

Table 1. Incidence of Dermal Irritation Scores (Draize Technique)

	Observation Period (days)				
	1	3	7	10	14
			Males (n=5)		
Erythema	0	1	1	0	0
Edema	0	2	0	0	0
Atonia	4	0	0	0	0
Desquamation	0	0	2	1	0
Coriaceousness	0	0	0	0	0
Fissuring	0	0	0	0	0
			Females (n=5)		
Erythema	0	0	0	0	0
Edema	2	2	0	0	0
Atonia	5	0	0	0	0
Desquamation	0	0	1	0	0
Coriaceousness	0	0	0	0	0
Fissuring	0	0	0	0	0

Gross necropsy

No compound-related gross changes were observed in any rabbit.

LD_{50} determination

The estimated acute dermal LD_{50} for male and female rabbits was greater than 2000 mg/kg body weight (limit dose), which corresponds to Toxicity Category III (Caution).

D. REVIEWERS' COMMENTS

The estimated acute dermal LD_{50} for male and female rabbits exposed to Rejex-it AP-50 under these study conditions was >2000 mg/kg body weight, which corresponds to Toxicity Category III (Caution). The dose level used in this study met the limit dose designated in the guideline. This study satisfies the guideline requirements (81-2) for an acute dermal toxicity study in rabbits.

010940

FINAL

DATA EVALUATION REPORT

Rejex-it AP-50

Study Type: Primary Eye Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date 1/23/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 156
Project Officer: Caroline Gordon

37

010960

Guideline Series 81-4: Primary Eye Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy Sjoblad
Date: 4/4/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-4; primary eye irritation study in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426087-04
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it AP-50
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305708
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Primary Eye Irritation Study of Rejex-it AP-50 in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	June 18, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed June 18, 1992, was submitted.
CONCLUSIONS:	Under the conditions of this study, Rejex-it AP-50 produced moderate to severe conjunctival irritation (Draize scores 2 and 3 at 24 hours) and corneal and iridal involvement (scattered or diffuse corneal opacity (Draize score 1 at 24 hours) and circumcorneal injection in iris) in rabbit eyes, which cleared within 14 days of treatment. Based

38

on these findings, the test material was classified Toxicity Category II.

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-4) for a primary eye irritation study in rabbits. However, there were insufficient data describing the test material (i.e., purity, stability, and lot number were not reported). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: II (Warning)

A. MATERIALS

Test Compound

Test material:	Rejex-it AP-50
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	White powder
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Bulk density:	0.39 g/mL
Dose volume:	0.1 mL (dose equivalent)
Dose level:	0.04 g

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo MI
Sex:	3 males and 3 females
Age:	Adult
Body weight:	2100-2262 g, males; 2130-2302 g, females
No. animals:	3/sex/dose
Temperature:	20-25°C
Relative humidity:	36-65%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Selection:	Animals free of ocular injury or irritation
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tag

B. TEST PERFORMANCE

Test Material Application

Eyes were examined the day before application using sodium fluorescein dye. The solid test material (0.04 g; 0.1 mL, dose equivalent) was placed in the everted lower lid of the right eye of each rabbit. The upper and lower lids were held together for 1 second and then released. The left eye of each animal served as the untreated control. The eyes of the rabbits were not flushed.

Observation Period

Observations for ocular irritation were made at 1, 24, 48, 72, and 96 hours, and days 7 and 14 after treatment.

Scoring System

Eyes were examined and scored for ocular lesions using the Draize scoring system. Sodium fluorescein was used to help assess corneal injury at all examinations except 1 hour after dosing.

C. RESULTS

Individual eye irritation scores and clinical observations are presented in Table 1. Blanching and purulent and/or clear discharge of the conjunctivae were seen at hours 1, 24, 48, and 72 and were clear at 96 hours. Corneal epithelial peeling were observed in most animals at 1 hour and was clear by day 7. Pannus was seen in 2/6 animals at day 7. By day 14, all clinical signs of eye irritation had cleared.

Table 1. Individual Eye Irritation Scores (Draize Technique)

Animal No.	Cornea		Iris	Conjunctivae		
	Opacity	Involvement	Irritation	Redness	Chemosis	Discharge
			1 hour			
1[t]	1[j]	2	1[i]	2[b]	3	2[d]
2[u]	1[j]	1	1[i]	2[b]	3	2[c]
3[u]	1	4	1[i]	2[b]	3	2[c]
4[u]	1[j]	1	1[i]	2[b,e**]	3	2[c]
5[u]	1[j]	4	1[i]	2[b]	2	2[d]
6[u]	1[j]	1	1[i]	2[b,e**]	3	2[d]
			24 hours			
1	1[j]	4	1[i]	2[b,e**]	2	1[d]
2	1[j]	2	1[i]	3[b]	2	2[d]
3	1[j]	4	1[i]	3[b]	2	2[d]
4	1[j]	1	1[i]	2[b, e,**]	2	1[c]
5	1[j]	3	1[i]	2[b]	2	2[d]
6	1[j]	2	1[i]	2[b]	2	1[c]

Table 1. Individual Eye Irritation Scores (continued)

Animal No.	Cornea		Iris	Conjunctivae		
	Opacity	Involvement	Irritation	Redness	Chemosis	Discharge
			48 hours			
1	1[j]	4	1[i]	2[b,e]	2	1[d]
2	1[j]	2	1[i]	2[b]	2	1[d]
3	1[j]	2	1[i]	2[b]	1	1[d]
4	1	1	0	2[e**]	0	0
5	1[j]	3	1[i]	2	0	0
6	1[j]	1	1[i]	2[e**]	1	0
			72 hours			
1	1[j]	1	0	2[e]	1	0
2	1	1	1[i]	2	1	1[c]
3	1[j]	1	0	2	1	2[c]
4	0	0	1[i]	2[a,e**]	1	1[c]
5	1[j]	1	1[i]	2	1	1
6	0	0	0	2[e**]	1	0
			96 hours			
1	1[j]	1	0	2	1	0
2	0	0	0	2	1	0
3	1[j]	1	0	2	1	0
4	0	0	0	2[a]	1	0
5	1[j]	1	0	2	0	0
6	0	0	0	2	1	0
			Day 7			
1	0	0	0	0	0	0
2	0[p]	0	0	0	0	0
3	0[p]	0	0	0	1	0
4	1	1	0	0	0	0
5	1	1	0	2	0	0
6	0	0	0	0	0	0

32

Table 1. Individual Eye Irritation Scores (continued)

Animal No.	Cornea		Iris	Conjunctivae		
	Opacity	Involvement	Irritation	Redness	Chemosis	Discharge
			Day 14			
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0

[a] Petite hemorrhaging
[b] Blanching
[c] Clear discharge
[d] Purulent discharge
[e] Hair loss around the eye
[**] Hair loss around the eye, possibly caused by restraint during dosing
[i] Injected
[j] Corneal epithelial peeling
[p] Pannus
[t] No pain response after test material instillation
[u] Excessive pawing at the treated eye after test material instillation

Positive ocular effects are summarized in Table 2. Table 3 presents the results of the sodium fluorescein examination. Six of six rabbits were positive for conjunctival redness, chemosis, corneal opacity and iridal involvement at 1 hour, but were resolved by day 14.

Table 2. Positive[a] Ocular Effects (sexes combined) at Observation Intervals (hours)

	1	24	48	72	96	Day 7	Day 14
Cornea							
Opacity	6/6	6/6	6/6	4/6	3/6	2/6	0/6
Iris							
Iritis	6/6	6/6	5/6	3/6	0/6	0/6	0/6
Conjunctivae							
Redness	6/6	6/6	6/6	6/6	3/6	0/6	0/6
Chemosis	6/6	4/6	2/6	0/6	0/6	0/6	0/6

[a] The following grades for each tissue are considered positive:
Opacity (density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (redness) - Grades 2 and 3
Conjunctivae (chemosis) - Grades 2, 3, and 4

Table 3. Results of the Sodium Fluorescein Examinination

	Observation Period (hours)						
Sex	0	24	48	72	96	Day 7	Day 14
M	Neg	Pos (85%)	Pos (75%)	Pos (25%)	Pos (<5%)	Neg	Neg
M	Neg	Pos (45%)	Pos (10%)	Neg	Neg	Neg	Neg
M	Neg	Pos (80%)	Pos (40%)	Pos (15%)	Pos (5%)	Neg	Neg
F	Neg	Pos (5%)	Neg	Neg	Neg	Neg	Neg
F	Neg	Pos (70%)	Pos (55%)	Pos (10%)	Pos (5%)	Neg	Neg
F	Neg	Pos (30%)	Pos (10%)	Neg	Neg	Neg	Neg

Neg Negative stain retention
Pos Positive stain retention (area of cornea involved)

D. REVIEWERS' COMMENTS

Under the conditions of this study, Rejex-it AP-50 produced moderate to severe conjunctival irritation and corneal and iridal involvment in rabbits. All positive signs had resolved by day 14 post-treatment; therefore, for primary eye irritation in rabbits, Rejex-it AP-50 is classified Toxicity Category II. This study satisfies the guideline requirements (81-4) for a primary eye irritation study in rabbits.

34

except for insufficient data on the test material, and may be upgraded pending submission of these data.

010940

35

010940

FINAL

DATA EVALUATION REPORT

Rejex-it AP-50

Study Type: Primary Dermal Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date 1/31/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/26/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 157
Project Officer: Caroline Gordon

36

010940

Guideline Series 81-5: Primary Dermal Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: [illegible]

[illegible]

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-5; primary dermal irritation study in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426087-05
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it AP-50
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305704
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Primary Dermal Irritation Study of Rejex-it AP-50 in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	June 5, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed June 5, 1992, was submitted.
CONCLUSIONS:	Dermal application of Rejex-it AP-50 under 4-hour semi-occluded conditions produced very slight edema in one rabbit. The average of the 4-, 24-, 48-, and 72-hour irritation scores was 0.1; therefore the test material is considered to be slightly irritating under these conditions.

37

010960

Guideline Series 81-5: Primary Dermal Irritation Study in Rabbits

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-5) for a primary dermal irritation study in rabbits. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it AP-50
Identification no.:	Lot number 56-612-69-02
Purity:	Determined by sponsor
Physical description:	White powder
Storage condition:	Room temperature
Stability:	Determined by sponsor
Dose level:	0.5 g moistened with an unspecified amount of 0.9% saline

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo, MI
Sex:	3 males and 3 females
Age:	Adult
Mean body weights:	2140-2292 g for males; 2168-2418 g for females
No. animals:	3/sex/dose
Temperature:	20-22°C
Relative humidity:	40-45%
Photoperiod:	12-hour dark/12-hour light
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals with unspecified weight limits were selected

B. TEST PERFORMANCE

Test Material Application

The back and flanks of each rabbit were clipped free of hair the day before application. The test material, 0.5 g moistened with an unspecified amount of 0.9% saline, was applied to the intact clipped skin of each animal. A semi-occluded dressing was provided by covering the treated area with a 2.5 cm X 2.5 cm gauze patch fastened with paper tape, loosely wrapping the area in Saran wrap, and securing the dressing

with Elastoplast tape. After 4 hours of exposure, the patch and wrappings were removed and the test sites were washed with tap water and dried with disposable paper towels.

Observation Period

The degree of erythema and edema at the test site were determined about 30 minutes after removal of the test material and recorded as the 4-hour score. Additional examinations were made at 24, 48, and 72 hours.

Scoring System

The Draize scoring system for primary dermal irritation was used.

C. RESULTS

Table 1 presents a summary of dermal irritation scores.

Table 1. Summary of Positive[a] Dermal Irritation Scores (sexes combined) (Draize Technique)

	Observation Intervals (hours)			
	4	24	48	72
Erythema	0/6	0/6	0/6	0/6
Edema	1/6	0/6	0/6	0/6

[a] The following dermal irritations scores were considered positive:
Erythema - Grades 1, 2, 3, and 4
Edema - Grades 1, 2, 3, and 4

Very slight edema was observed in only 1 rabbit. The average primary dermal irritation score was 0.2 at 4 hours and 0 at 24, 48, and 72 hours. The average of the 4-, 24- 48- and 72-hour scores was 0.1, which is considered slightly irritating. Based on these findings, Rejex-it AP-50 is classified as Toxicity Category IV (Caution).

D. REVIEWERS' COMMENTS

Rejex-it AP-50 was very slightly irritating when applied to the skin of rabbits under the 4-hour semi-occluded conditions of this study. Based on these findings, for primary dermal irritation Rejex-it AP-50 was classified Toxicity Category IV (Caution).

010940

FINAL

DATA EVALUATION REPORT

Rejex-it AP-50

Study Type: Dermal Sensitization Study in Guinea Pigs

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date [illegible]
Independent Reviewer	Carrie Rabe, Ph.D.	Date [illegible]
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3.36
Clement Number: 158
Project Officer: Caroline Gordon

4/0

010940

Guideline Series 81-6: Dermal Sensitization Study in Guinea Pigs

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 2/5/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 4/14/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-6; dermal sensitization study in guinea pigs
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426087-06
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it AP-50
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305712
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Dermal Sensitization Study of Rejex-it AP-50 in Guinea Pigs – Closed Patch Technique
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 27, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 27, 1992, was submitted.
CONCLUSIONS:	Delayed contact hypersensitivity was not observed in guinea pigs exposed to Rejex-it AP-50 under the conditions of this test. The test material was not considered to be a dermal sensitizer.
CORE CLASSIFICATION:	Core Supplementary. This study satisfies the guideline requirements (81-6) for a dermal sensitization study in guinea pigs. However, data

41

describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: Not applicable

A. MATERIALS

Test Compound

Test material:	Rejex-it AP-50
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	White powder
Storage condition:	Room temperature
Stability:	Determined by sponsor
Positive control material:	2,4-dinitrochlorobenzene (DNCB) (lot number 80H0121; 99.9% pure)
Naive control material:	Rejex-it AP-50 (animals treated at challenge only)
Irritation screening conc.:	Four animals each received two different concentrations of the test material, either as a 0.2 g dose (moistened with deionized water) or in 25%, 50%, or 75% w/v in 0.4 mL mineral oil.
Main study test material conc.:	Induction and challenge - 0.2 g Rejex-it AP-50 (moistened with deionized water)

Test Animals

Species:	Albino guinea pigs
Strain:	Haz:(DH)fBR
Source:	Hazleton Research Products, Inc., Denver, PA
Sex:	25 males and 3 females
No./group:	4 in irritation screening group (1 male; 3 females); 10 males in test group, 10 males in naive control group; 4 males in positive control group
Age:	Young adult
Body weights:	352-418 g, males; 368-458 g, females
Temperature:	14-25°C
Relative humidity:	30-66%
Photoperiod:	12-hour light/12-hour dark cycle
Feeding:	Purina Certified Guinea Pig Chow #5026, *ad libitum*
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals within unspecified body weight limits were selected

42

B. TEST PERFORMANCE

Skin Preparation

The hair on the back of each animal in the test and positive control groups was removed with electric clippers the day of test material application. Animals were depilated with Neet® 3 hours prior to the 24-hour examination.

Induction Phase

(a) Route of administration: The test material (0.2 g moistened with an unspecified amount of deionized water) was applied to a 25 mm diameter adhesive patch. The patch was placed on the test site (anterior left flank), covered with dental dam, and wrapped with Elastoplast tape. The patch was removed after 6 hours and the test site cleaned with a wet paper towel.

(b) Solutions used: Test group - 0.2 g (moistened with deionized water) test material; positive control group - 0.4 mL of 0.3% w/v DNCB in 80% v/v ethanol in deionized water; naive irritation control - untreated.

(c) Frequency of exposure: Test and positive control groups - 1 application per week for 3 weeks for a total of 3 applications.

(d) Duration of exposure: 6 hours

(e) Rest period: 2 weeks

(f) Observation period: 24 and 48 hours after each exposure

Challenge Phase

(a) Route of administration: Administration was the same as for the induction phase, except that the test material was placed on the right flank. The naive irritation control group of 10 was also given the challenge dose of 0.2 g test material moistened with deionized water.

(b) Solutions used: Test group and naive irritation control groups - 0.2 g test material; positive control group - 0.1% w/v DNCB in acetone.

(c) Duration of exposure: 6 hours

(d) Number of exposure: 1

(e) Observation period: 24 and 48 hours after each application

Scoring System

A modification of the Buehler method was used.

C. RESULTS

010940

Body weights

Body weight gain was normal in all animals.

Skin reactions

No dermal reactions were observed in the test group animals during induction or challenge with the test material. None of the animals from the naive control group reacted to the challenge application of the test material.

Mortality

No deaths occurred during the study period.

Clinical signs

No overt signs of toxicity were observed.

D. REVIEWERS' COMMENTS

A dermal sensitization reaction was not observed under the present study conditions in guinea pigs treated with Rejex-it AP-50. The test material was not considered to be a dermal sensitizer.

010940

FINAL

DATA EVALUATION REPORT

Rejex-it MA

Study Type: Acute Oral Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz Kate Rantz, M.P.H.	Date 1/3/94
Independent Reviewer	Carrie Rabe Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William L McLellan William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 159
Project Officer: Caroline Gordon

✓
45

D10940

Guideline Series 81-1: Acute Oral Toxicity in Rats

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 4/19/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 4/19/94

DATA EVALUATION REPORT

STUDY TYPE: Guideline series 81-1; acute oral toxicity in rats

CAS NUMBER:

TOX CHEM NUMBER:

MRID NUMBER: 426088-02

PC NUMBER: 128725

TEST MATERIAL: Rejex-it MA

SYNONYM(S): Methyl anthranilate (active ingredient)

SPONSOR: ERM Program Management Company
McLean, Virginia

STUDY NUMBER: HWI 20305693

TESTING FACILITY: Hazleton Wisconsin, Inc.
Madison, Wisconsin

TITLE OF REPORT: Acute Oral Toxicity Study of Rejex-it MA in Rats

AUTHOR: Steven M. Glaza

STUDY COMPLETED: July 22, 1992

QUALITY ASSURANCE: The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 22, 1992, was submitted.

CONCLUSIONS: Estimated acute oral LD_{50} for males: 3633 mg/kg body weight
Estimated acute oral LD_{50} for females: 3000 mg/kg body weight
Estimated acute oral LD_{50} for the sexes combined: 3288 mg/kg body weight

46

CORE CLASSIFICATION: Core Supplemental. This study satisfies the guideline requirements (81-1) for an acute oral toxicity study in rodents. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: III (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it MA
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Clear, pale-yellow liquid
Storage condition:	Room temperature
Bulk density:	1.15 g/mL
Stability:	Determined by sponsor
Vehicle:	None
Dose levels:	1000, 3000, and 4000 (females only) or 5000 (males only) mg/kg body weight

Controls

There were no controls.

Test Animals

Species:	Albino rat
Strain:	Crl:CD®BR
Source:	Charles River Laboratories, Inc., Portage, MI
Sex:	15 males and 15 females
Age:	Young adult
Initial body weights (fasted):	216-300 g for males; 202-244 g for females
No. animals:	5/sex/dose
Temperature:	17-28°C
Relative humidity:	24-64%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina Certified Rodent Chow #5001 *ad libitum*
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	5/cage, sexes separate
Identification:	Ear tags
Selection:	Healthy animals within unspecified body weight limits were selected

B. TEST PERFORMANCE

Method of administration:	Oral gavage
Animals fasted:	food was withheld 17-20 hours before dosing
Dosing:	Once __x__; Other _____ (describe)
Observation period:	14 days
Observation frequency:	Clinical observations and mortality checks were conducted 1, 2.5, and 4 hours after dosing. Clinical observations were conducted daily and mortality checks twice daily thereafter for 14 days.
Body weight interval:	Day 0 (before dosing), day 7, and day 14 (study termination)
Gross pathology:	Yes
Histopathology:	No

C. RESULTS

Mortality

Mortality results are summarized in Table 1. All treatment-related deaths occurred within 2 days of treatment.

Table 1. Mortality Ratios

Dosage (mg/kg)	Mortality Ratio
Males	
1000	0/5
3000	1/5
5000	5/5
Females	
1000	0/5
3000	3/5
4000	4/5

Clinical observations

Clinical signs of toxicity included the following: hypoactivity in males at all dose levels and in mid- and high-dose females; absence of

48

righting reflex in 5000 mg/kg males (1/5); absence of pain reflex in 4000 mg/kg females (2/5); staggered gait in 4000 mg/kg females (3/5) and 5000 mg/kg males (1/5); prostration in 4000 mg/kg females (1/5); red-stained urine in 4000 mg/kg females (1/5), and lacrimation in 3000 mg/kg females (1/5). All clinical signs resolved by day 2.

Body weights

All rats surviving to termination gained weight by the end of the 14-day observation period.

Gross necropsy

Necropsy revealed dark-brown areas of variable size in the glandular mucosa of the stomachs of 1 male and 2 female rats, which died following dosing with 3000 mg/kg of the test material. It is unclear whether these areas represented treatment-related effects or were due to post-mortem changes.

LD_{50} determination

LD_{50}s were calculated using a modified Behrens-Reed-Muench cumulant method. The estimated acute oral LD_{50} for males was >3633 mg/kg body weight, 95% confidence limits 2516-5248 mg/kg. The estimated acute oral LD_{50} for females was 3000 mg/kg body weight, 95% confidence limits 1907-4719 mg/kg. The estimated acute oral LD_{50} for the sexes combined was 3288 mg/kg body weight, 95% confidence limits 2489-4343 mg/kg. The acute oral LD_{50} for males, females, and the sexes combined corresponds to Toxicity Category III (Caution).

D. REVIEWERS' COMMENTS

The estimated acute oral LD_{50s} for rats fed Rejex-it MA under these study conditions were 3633, 3000, and 3288 mg/kg body weight for males, females, and the sexes combined, respectively. These LD_{50s} correspond to Toxicity Category III (Caution).

49

010940

FINAL

DATA EVALUATION REPORT

Rejex-it MA

Study Type: Acute Dermal Toxicity in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz Kate Rantz, M.P.H.	Date 1/24/94
Independent Reviewer	Carrie Rabe Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William L McLellan William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 160
Project Officer: Caroline Gordon

50 ✓

010940

Guideline Series 81-2: Acute Dermal Toxicity in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: 2/10/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-2: acute dermal toxicity in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426088-03
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it MA
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305697
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Acute Dermal Toxicity Study of Rejex-it MA in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 7, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 7, 1992, was submitted.
CONCLUSIONS:	Estimated acute dermal LD_{50} for males: >2000 mg/kg body weight Estimated acute dermal LD_{50} for females: >2000 mg/kg body weight Slight dermal irritation was observed.

51

010960

Guideline Series 81-2: Acute Dermal Toxicity in Rabbits

CORE CLASSIFICATION: Core Supplemental. This study satisfies the guideline requirements (81-2) for an acute dermal toxicity study in rabbits. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: III (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it MA
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Clear, pale yellow liquid
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Dose level:	2000 mg/kg body weight (as received); limit dose

Controls

There were no controls.

Test Animals

Species:	Albino rabbit
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo, MI
Sex:	5 males and 5 females
Age	Young adult
Initial body weights (fasted):	2146-2356 g for males; 2096-2394 g for females
No. animals:	5/sex/dose
Temperature:	20-25°C
Relative humidity:	36-65%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least ~ days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals within unspecified weight limits were selected

B. TEST PERFORMANCE

The hair on the back of each rabbit (approximately 10% of the total body surface area) was clipped on the day before dosing. The test material (2000 mg/kg body weight) was applied to the intact skin of the rabbit. The area of application was covered with a 10 cm X 10 cm gauze patch

52

secured with paper tape and overwrapped with Saran Wrap and Elastoplast tape. After 24 hours the wrappings were removed. Excess test material was washed from the test site with tap water and paper towels.

Observation period

Observations for clinical signs of toxicity and mortality were made 1, 2.5, and 4 hours after application of the test material. During the 14-day observation period, clinical observations and mortality checks (morning and afternoon) were made daily. The initial observation for dermal response (Draize technique) was approximately 30 minutes after removal of the test material; subsequent readings were made days 3, 7, 10, and 14.

Body weight interval

Body weights were measured on day 0 (before application) and on observation days 7 and 14.

Gross pathology: Yes
Histopathology: No

C. RESULTS

Mortality

All animals (5 males and 5 females) dosed with 2000 mg/kg body weight survived until study termination.

Clinical observations

No overt signs of toxicity were observed. Slight erythema (Draize score 1) was observed in all animals. Slight edema (Draize score 1) was observed in 2 males and 2 females. The erythema was resolved in all animals by day 14. The edema was observed only at the first observation (30 minutes after removal of the test material).

Body weights

All rabbits had gained weight by study termination. However, minor (1-6%) weight loss was observed in 4 males and 2 females between days 7 and 14.

Gross necropsy

No compound-related gross changes were observed in any rabbit.

LD_{50} determination

The estimated acute dermal LD_{50} was greater than 2000 mg/kg body weight for both male and for female rabbits. An acute dermal LD_{50} greater than 2000 mg/kg body weight corresponds to Toxicity Category III (Caution).

010940

D. REVIEWERS' COMMENTS

The estimated acute dermal LD_{50} for male and female rabbits exposed to Rejex-it MA under these study conditions was >2000 mg/kg body weight, which corresponds to Toxicity Category III (Caution). Only slight erythema and edema (Draize score 1) were observed at the test site. The dose level used in this study met the limit dose designated in the guideline.

010940

FINAL

DATA EVALUATION REPORT

Rejex-it MA

Study Type: Primary Eye Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer — Kate Rantz, M.P.H. — Date 1/24/94

Independent Reviewer — Carrie Rabe, Ph.D. — Date 1/24/94

QA Reviewer — William McLellan, Ph.D. — Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 161
Project Officer: Caroline Gordon

55

016940

Guideline Series 81-4: Primary Eye Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/3/93

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy S. Sjoblad
Date: 2/4/93

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-4: primary eye irritation study in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426088-04
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it MA
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305705
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Primary Eye Irritation Study of Rejex-it MA in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	June 16, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement signed June 16, 1992, was submitted.
CONCLUSIONS:	Under these study conditions, Rejex-it MA produced slight to moderate conjunctival irritation (Draize scores 0-2) to rabbit eyes, which cleared within 7 hours of treatment.
CORE CLASSIFICATION:	Core Supplemental. The data describing the test material were insufficient (i.e., lot number, purity, and stability were not reported). This

56

study may be upgraded pending submission of these data.

TOXICITY CATEGORY: III (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it MA
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Clear, pale-yellow liquid; pH not determined
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Dose level:	0.1 mL (as received)

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo MI
Sex:	3 males and 3 females
Age:	Adult
Mean body weights:	2146-2312 g for males; 2188-2292 g for females
No. animals:	3/sex/dose
Temperature:	20-22°C
Relative humidity:	40-60%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Animals without ocular injury or irritation were selected

B TEST PERFORMANCE

Test Material Application

Eyes were examined the day before application using sodium fluorescein dye. The undiluted test material (0.1 mL) was placed in the everted lower lid of the right eye of each rabbit. The upper and lower lids were held together for 1 second and then released. The left eye of each animal served as the untreated control. The eyes of the rabbits were not flushed.

Observation Period

Observations for ocular irritation were made 1, 24, 48, and 72 hours after treatment according to the Draize technique.

Scoring System

Eyes were examined and scored for ocular lesions using the Draize scoring system. At 72 hours after treatment, a sodium fluorescein examination was performed to help assess corneal injury.

C. RESULTS

Individual eye irritation scores are presented in Table 1 and positive ocular effects are presented in Table 2. Corneal epithelial peeling was observed at 1, 24, and 48 hours in 3/6 animals. Blanching and clear conjunctival discharge were observed in 5/6 and 6/6 animals, respectively, at 1 hour. All signs were clear at 72 hours.

The results of the sodium fluorescein examination were negative in all rabbits before dosing and at 72 hours post-treatment. Based on these findings, the primary eye irritation potential of Rejex-it MA was classified as Toxicity Category III (Caution).

58

010940

Guideline Series 81-4: Primary Eye Irritation Study in Rabbits

Table 1. Individual Eye Irritation Scores According to the Draize Technique

Animal No.	Cornea		Iris	Conjunctivae		
	Opacity	Involvement	Irritation	Redness	Chemosis	Discharge
			1 hour			
1[u]	1[j]	1	1[i]	2[b]	2	2[c]
2[u]	1[j]	1	1[i]	2[b]	2	2[c]
3[u]	0	0	1[i]	2[b]	2	2[c]
4[u]	0	0	1[i]	2[b]	2	2[c]
5[u]	1	1	0	1	1	1[c]
6[u]	0	0	0	2[b]	2	2[c]
			24 hours			
1	1[j]	2	0	2	1	0
2	1[j]	1	0	1	1	0
3	0	0	0	1	1	0
4	1[j]	2	0	2	2	1[c]
5	0	0	0	1	0	0
6	0	0	0	1	0	0
			48 hours			
1	1[j]	1	0	2	1	0
2	1[j]	1	0	1	0	0
3	0	0	0	1	0	0
4	1[j]	1	0	2	1	0
5	0	0	0	1	0	0
6	0	0	0	1	0	0
			72 hours			
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0

[b] Blanching
[c] Clear discharge
[i] Injected
[j] Corneal epithelial peeling
[u] Excessive pawing at the treated eye after test material instillation

59

Table 2. Summary of Positive[a] Ocular Effects (sexes combined)

	Observation Intervals (hours)			
	1	24	48	72
Cornea				
Opacity	3/6	3/6	3/6	0/6
Iris				
Iritis	4/6	0/6	0/6	0/6
Conjunctivae				
Redness	5/6	2/6	2/6	0/6
Chemosis	5/6	1/6	0/6	0/6

[a] The following grades for each tissue are considered positive:
Opacity (density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (redness) - Grades 2 and 3
Conjunctivae (chemosis) - Grades 2, 3, and 4

D. REVIEWERS' COMMENTS

Rejex-it MA produced slight to moderate cojunctival irritation (Draize scores 0-2) and corneal and iridal involvement (i.e., scattered or diffuse corneal opacity and circumcorneal injection in the iris) in the eyes of rabbit under conditions of this study. All positive signs were clear by 72 hours; therefore, the primary eye irritation potential of Rejex-it MA is Toxicity Category III (Caution). This study satisfies the guideline requirements (81-4) for a primary eye irritation study in rabbits; however, certain information on the lot number, purity, and stability of the test material was not provided.

60

C10940

FINAL

DATA EVALUATION REPORT

Rejex-it MA

Study Type: Primary Dermal Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date [illegible]
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 162
Project Officer: Caroline Gordon

61

010940

Guideline Series 81-5: Primary Dermal Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy Sjoblad
Date: 2/11/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-5; primary dermal irritation study in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426088-05
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it MA
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305701
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Primary Dermal Irritation Study of Rejex-it MA in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	June 5, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed June 5, 1992, was submitted.
CONCLUSIONS:	Dermal application of Rejex-it MA under 4-hour semi-occluded conditions produced no dermal irritation. Under the conditions of this test, Rejex-it MA is considered non-irritating.
CORE CLASSIFICATION:	Core Supplementary. This study satisfies the guideline requirements (81-5) for a primary dermal irritation study in rabbits. However, data

describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it MA
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Clear, pale-yellow liquid; pH not determined
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Dose level:	0.5 mL (as received)

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo MI
Sex:	3 males and 3 females
Age:	Adult
Initial body weights:	2206-2294 g for males; 2182-2278 g for females
No. animals:	3/sex/dose
Temperature:	20-22°C
Relative humidity:	40-45%
Photoperiod:	12-hour light/12-hour dark cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals within an unspecified body weight range were selected

B. TEST PERFORMANCE

Test Material Application

The back and flanks of each rabbit were clipped the day before application of the test material. The test material (0.5 mL) was applied to the intact clipped skin of each animal, and the treated area was covered with a 2.5 cm X 2.5 cm gauze patch, which was fastened with paper tape, loosly wrapped in Saran Wrap, and secured with Elastoplast tape to provide a semi-occlusive dressing. After 4 hours of exposure, the patch and wrappings were removed and the test sites were washed with tap water and dried with disposable paper towels.

Observation Period

The degree of erythema and edema at the test site were determined about 30 minutes after removal of the test material and was recorded as the 4-hour score. Additional examinations were made at 24, 48, and 72 hours. The Draize scoring system for primary dermal irritation was used.

C. RESULTS

A summary of dermal irritation scores is presented in Table 1.

Table 1. Summary of Positive[a] Dermal Irritation Scores (sexes combined) (Draize Technique)

	Observation Intervals (hours)			
	4	24	48	72
Erythema	0/6	0/6	0/6	0/6
Edema	0/6	0/6	0/6	0/6

[a] The following dermal irritations scores were considered positive:
Erythema - Grades 1, 2, 3, and 4
Edema - Grades 1, 2, 3, and 4

No erythema or edema was observed at any time. Based on these findings, Rejex-it MA was considered nonirritating and classified Toxicity Category IV (Caution).

D. REVIEWERS' COMMENTS

Rejex-it MA was found to be nonirritating when applied to the skin of rabbits under the 4-hour semi-occluded conditions of this study. As a primary dermal irritant, Rejex-it MA was classified Toxicity Category IV (Caution).

010940

FINAL

010940

DATA EVALUATION REPORT

Rejex-it MA

Study Type: Dermal Sensitization Study in Guinea Pigs

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz Kate Rantz, M.P.H.	Date 1/13/94
Independent Reviewer	Carrie Rabe Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William L. McLellan William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 163
Project Officer: Caroline Gordon

65

016940

Guideline Series 81-5: Dermal Sensitization Study in Guinea Pigs

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy Sjoblad
Date: 2/9/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-6; dermal sensitization study in guinea pigs
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426088-06
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it MA
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305709
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Dermal Sensitization Study of Rejex-it MA in Guinea Pigs – Closed Patch Technique
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 27, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 27, 1992, was submitted.
CONCLUSIONS:	Delayed contact hypersensitivity was not observed in guinea pigs exposed to Rejex-it MA under the conditions of this test.
CORE CLASSIFICATION:	Core Supplementary. This study satisfies the guideline requirements (81-6) for a dermal sensitization study in guinea pigs. However, data describing the test material were lacking (e.g.,

66

purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: Not applicable

A. MATERIALS

Test Compound

Test material:	Rejex-it MA
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Clear, pale-yellow liquid
Storage condition:	Room temperature
Stability:	Determined by sponsor
Positive control material:	2,4-dinitrochlorobenzene (DNCB)(lot number 80H0121; 99.9% pure)
Naive control material:	Rejex-it MA (animals treated at challenge only)
Irritation screening conc.:	Four animals each received two different concentrations of the test material, either undiluted or in 25%, 50%, or 75% w/v in mineral oil.
Main study test material conc.:	Induction and challenge - 0.4 mL Rejex-it MA

Test Animals

Species:	Albino guinea pigs
Strain:	Haz:(DH)fBR
Source:	Hazleton Research Products, Inc., Denver, PA
Sex:	19 males and 9 females
No./group:	4 in irritation screening group (1 male, 3 females); 10 in test group (8 males, 2 females); 10 in naive control group (8 males, 2 females); 4 in positive control group (2 males, 2 females)
Age:	Young adult
Mean body weights:	430-542 g, males; 398-542 g, females
Temperature:	14-25°C
Relative humidity:	30-66%
Photoperiod:	12-hour light/12-hour dark cycle
Feeding:	Purina Certified Guinea Pig Chow #5026, *ad libitum*
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags
Selection:	Healthy animals within unspecified body weight limits were selected

B. TEST PERFORMANCE

Skin Preparation

The hair on the back of each animal in the test and positive control groups was removed with electric clippers the day of test material application. Animals were depilatated with Neet® 3 hours prior to the 24-hour examination.

Induction Phase

(a) Route of administration: The test material (0.4 mL) was applied to a 25 mm diameter adhesive patch. The patch was placed on the test site (anterior left flank), covered with dental dam, and wrapped with Elastoplast tape. The patch was removed after 6 hours and the test site cleaned with a wet paper towel.

(b) Solutions used: Test group - 0.4 mL test material; positive control group - 0.4 mL 0.3% w/v DNCB in 80% v/v ethanol in deionized water; naive irritation control - untreated.

(c) Frequency of exposure: Test and positive control groups - 1 application per week for 3 weeks for a total of 3 applications.

(d) Duration of exposure: 6 hours

(e) Rest period: 2 weeks

(f) Observation period: 24 and 48 hours after each exposure

Challenge Phase

(a) Route of administration: Administration was the same as for the induction phase, except that the test material was placed on the right flank. The naive irritation control group of 10 was also given the challenge dose of 0.4 mL test material.

(b) Solutions used: Test group and naive irritation control groups - 0.4 mL test material; positive control group - 0.4 mL 0.3% w/v DNCB in acetone.

(c) Duration of exposure: 6 hours

(d) Number of exposure: 1

(e) Observation period: 24 and 48 hours after application

Scoring System

A modification of the Buehler method was used.

C. RESULTS

Clinical signs

No overt signs of toxicity were observed in treated rabbits.

Skin reactions

No dermal reactions were observed in the test group animals during induction or challenge with the test material. None of the surviving animals from the naive control group reacted to the challenge application of the test material.

Body weights

Body weight gain was normal in all animals, except in the single animal sacrificed moribund.

Mortality

One animal from the naive control group was sacrificed moribund on day 23. This animal appeared thin on days 15-23, had soft stool on day 16, few feces on days 17-23, lost 172 g body weight the first 21 days of the study, and was sacrificed on day 23.

D. REVIEWERS' COMMENTS

A dermal sensitization reaction was not observed under the present study conditions in guinea pigs treated with Rejex-it MA. The test material was not considered to be a dermal sensitizer in guinea pigs.

69

010940

FINAL

DATA EVALUATION REPORT

Rejex-it TP-40

Study Type: Acute Oral Toxicity in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date 1/24/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 164
Project Officer: Caroline Gordon

70

016940

Guideline Series 81-1: Acute Oral Toxicity in Rats

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy Sjoblad
Date: 4/14/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-1; acute oral toxicity in rodents
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426089-02
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it TP-40
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER	HWI 2030569
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Acute Oral Toxicity Study of Rejex-it TP-40 in Rats
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 7, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed July 7, 1992, was submitted.
CONCLUSIONS	Estimated acute oral LD_{50} for males: >5000 mg/kg body weight Estimated acute oral LD_{50} for females: >5000 mg/kg body weight
CORE CLASSIFICATION:	Core Supplementary. This study satisfies the guideline requirements (81-1) for an acute oral

toxicity study in rodents. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending sumbission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it TP-40
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Blue liquid
Bulk density:	0.95 g/mL
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Dose volume:	5.26 mL/kg body weight
Dose level:	5000 mg/kg body weight (limit dose)

Controls

There were no controls.

Test Animals

Species:	Albino rat
Strain:	Crl:CD®BR
Source:	Charles River Laboratories, Inc., Portage, MI
Sex:	5 males and 5 females
Age:	Young adult
Initial body weight (fasted):	212-244 g for males; 242-282 g for females
No. animals:	5/sex/dose
Temperature:	22-27°C
Relative humidity:	39-54%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina Certified Rodent Chow #5001, *ad libitum*
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	5/cage; sexes separate
Identification:	Ear tags
Selection:	Healthy animals within unspecified body weight limits were selected

B. TEST PERFORMANCE

Method of administration:	Oral gavage

72

Animals fasted:	Food was withheld 17-20 hours before dosing
Dosing:	Once __x__; Other _____ (describe)
Observation period:	14 days
Observation frequency:	Clinical observations and mortality checks were conducted 1, 2.5, and 4 hours after dosing. Clinical observations were conducted daily and mortality checks were conducted twice daily thereafter for 14 days.
Body weight interval:	Body weights were measured day 0 (before dosing), day 7, and day 14 (study termination).
Gross pathology:	Yes
Histopathology:	No

C. RESULTS

Mortality

There were no deaths during the study.

Clinical observations

Clinical signs of toxicity included soft stool in 1/5 males during the first hour after administration, and hypoactivity in 2/5 females on the day following treatment.

Body weights

All animals gained weight by the end of the observation period.

Gross necropsy

No compound-related changes were observed in any rats.

LD_{50} determination

The estimated acute oral LD_{50} was >5000 mg/kg body weight for both male and female rats. Toxicity Category IV (Caution).

D. REVIEWERS' COMMENTS

The estimated acute oral LD_{50} for both male and female rats administered Rejex-it TP-40 under these study conditions was greater than 5000 mg/kg body weight for both male and female rats. Toxicity Category IV (Caution). The study was done at the limit dose (5 g/kg) specified in guideline series 81-1.

C10940

FINAL

DATA EVALUATION REPORT

Rejex-it TP-40

Study Type: Acute Dermal Toxicity in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer	Kate Rantz, M.P.H.	Date 1/24/94
Independent Reviewer	Carrie Rabe, Ph.D.	Date 1/24/94
QA Reviewer	William McLellan, Ph.D.	Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 165
Project Officer: Caroline Gordon

74

010940

Guideline Series 81-2: Acute Dermal Toxicity in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: J. Thomas McClintock
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: Roy Sjoblad
Date: 2/9/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-2; acute dermal toxicity in rabbits
CAS NUMBER:	
TOX CHEM NUMBER:	
MRID NUMBER:	426089-03
PC NUMBER:	128725
TEST MATERIAL:	Rejex-it TP-40
SYNONYM(S):	Methyl anthranilate (active ingredient)
SPONSOR:	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 20305698
TESTING FACILITY:	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT:	Acute Dermal Toxicity Study of Rejex-it TP-40 in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	July 7, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement signed July 7, 1992, was submitted.
CONCLUSIONS:	Estimated acute dermal LD_{50} for males: >2000 mg/kg body weight Estimated acute dermal LD_{50} for females: >2000 mg/kg body weight Moderate to severe erythema (Draize scores 2-3 through day 7) and slight to severe edema (Draize scores 1-3) was observed in all animals. During

75

the second week the severity of these effects generally declined. However, on day 14, slight to moderate erythema (in 7/10 rabbits), slight edema (in 1/10 rabbits), slight atonia (in 2/10 rabbits), slight desquamation (in 5/10 rabbits), and slight coriaceousness (in 1/10 rabbits) persisted.

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-2) for an acute dermal toxicity study in rabbits. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: III (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it TP-40
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Blue liquid
Bulk density:	0.95 g/mL
Storage condition:	Room temperature
Stability:	Determined by sponsor
Dose level:	2000 mg/kg body weight (limit dose)

Controls

There were no controls.

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo, MI
Sex:	5 males and 5 females
Age:	Young adult
Initial body weights:	2140-2394 g for males; 2086-2368 g for females
No. animals:	5/sex/dose
Temperature:	20-25°C
Relative humidity:	36-65%
Photoperiod:	12-hour dark 12-hour light cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags

Selection: Healthy animals within unspecified body weight ranges were selected

B. TEST PERFORMANCE

Application

The hair on the back of each rabbit (approximately 10% of the total body surface area) was clipped on the day before dosing. The test material (2000 mg/kg body weight) was applied to the intact skin of the rabbit. The area of application was covered with a gauze patch secured with paper tape and overwrapped with Saran Wrap and Elastoplast tape. After 24 hours the wrappings were removed. Excess test material was washed from the test site with tap water and paper towels.

Observation period

Observations for clinical signs of toxicity were made 1, 2.5, and 4 hours after application of the test material. During the 14-day observation period, clinical observations and mortality checks (morning and afternoon) were made daily. The initial observation for dermal response (Draize technique) was approximately 30 minutes after removal of the test material; subsequent readings were made at days 3, 7, 10, and 14.

Body weight interval

Body weights were measured day 0 (before application) and on observation days 7 and 14.

Gross pathology: Yes
Histopathology: No

C. RESULTS

Mortality

All animals (5 males and 5 females) dosed with 2000 mg/kg body weight survived until study termination.

Clinical observations

No overt signs of toxicity were observed. Signs of dermal irritation included the following: moderate to severe erythema (Draize scores 2-3 through day 7) and slight to severe edema (Draize scores 1-3) in all animals; slight to moderate atonia in 9/10 animals (Draize scores 1-2); slight to moderate coriaceousness in all animals; slight to moderate fissuring in 9/10 animals; and slight desquamation (Draize score 1) in all animals. Blanching was observed in a single female on day 1. During the second week the severity of these effects generally declined. However, on day 14, slight to moderate erythema (in 7/10 rabbits), slight edema (in 1/10 rabbits), slight atonia (in 2/10 rabbits), slight desquamation (in 5/10 rabbits), and slight coriaceousness (in 1/10 rabbits) persisted.

77

Body weights

All rabbits gained weight by study termination. However, minimal (0.4-2.6%) body weight loss was observed in 2 males and 2 females between days 7 and 14.

Gross necropsy

No compound-related gross changes were observed in any rabbit.

LD_{50} determination

The estimated acute dermal LD_{50} was greater than 2000 mg/kg body weight for male and for female rabbits. An acute dermal LD_{50} greater than 2000 mg/kg body weight corresponds to Toxicity Category III (Caution).

D. REVIEWERS' COMMENTS

The estimated acute dermal LD_{50} for male and female rabbits exposed to dermal application of Rejex-it TP-40 under these study conditions was >2000 mg/kg body weight, Toxicity Category III (Caution). The dose level used in this study met the limit dose designated in the guideline.

The moderate to severe signs of dermal irritation reported in this study appear to be more severe than the dermal irritation observed in the primary dermal irritation study in rabbits (MRID 426089-05). In the primary dermal irritation study, very slight to severe erythema (Draize scores 0-3), very slight edema (Draize scores 0-1), and desquamation were observed after dermal application of Rejex-it TP-40 under 4-hour semi-occluded conditions. The primary irritation index of 1.9 indicated that the test material was slightly irritating under conditions of that test.

78

010940

FINAL

DATA EVALUATION REPORT

Rejex-it TP-40

Study Type: Primary Eye Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer: Kate Rantz, M.P.H. Date 1/24/94

Independent Reviewer: Carrie Rabe, Ph.D. Date 1/24/94

QA Reviewer: William McLellan, Ph.D. Date 1/25/94

Contract Number: 68D10075
Work Assignment Number: 3-36
Clement Number: 169
Project Officer: Caroline Gordon

39

010940

Guideline Series 81-4: Primary Eye Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date:

DATA EVALUATION REPORT

STUDY TYPE: Guideline series 81-4: primary eye irritation study in rabbits

CAS NUMBER:

TOX CHEM NUMBER:

MRID NUMBER: 426089-04

PC NUMBER: 128725

TEST MATERIAL: Rejex-it TP-40

SYNONYM(S): Methyl anthranilate (active ingredient)

SPONSOR: ERM Program Management Company
McLean, Virginia

STUDY NUMBER: HWI 20305706

TESTING FACILITY: Hazleton Wisconsin, Inc.
Madison, Wisconsin

TITLE OF REPORT: Primary Eye Irritation Study of Rejex-it TP-40 in Rabbits

AUTHOR: Steven M. Glaza

STUDY COMPLETED: June 16, 1992

QUALITY ASSURANCE: The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement, signed June 16, 1992, was submitted.

CONCLUSIONS: Under these study conditions, Rejex-it TP-40 produced slight conjunctival irritation in rabbit eyes, which cleared within 24 hours of treatment. The average primary irritation score was 3.3 at 1 hour.

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-4) for an eye irritation study in rabbits. However, data describing the

test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it TP-40
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Blue liquid; pH not determined
Storage condition:	Room temperature
Stability:	Determined by sponsor
Vehicle:	None
Dose volume:	0.1 mL (as received)

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo MI
Sex:	3 males and 3 females
Age:	Adult
Mean body weight:	2240-2328 g, males; 2186-2300 g, females
No. animals:	3/sex/dose
Temperature:	20-22°C
Relative humidity:	40-60%
Photoperiod:	12-hour dark/12-hour light cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Selection:	Animals without ocular injury or irritation were selected
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags

B. TEST PERFORMANCE

Test Material Application

Eyes were examined the day before application using sodium fluorescein dye procedures. The undiluted test material (0.1 mL) was placed in the everted lower lid of the right eye of each rabbit. The upper and lower lids were held together for 1 second and then released. The left eye of each animal served as the untreated control. The eyes of the rabbits were not flushed.

Observation Period

Observations for ocular irritation were made 1, 24, 48, and 72 hours after treatment. Eyes were examined and scored for ocular lesions using the Draize scoring system. At 72 hours after treatment, a sodium fluorescein examination was performed to help assess corneal injury.

C. RESULTS

A summary of positive ocular effects is presented in Table 1.

Table 1. Summary of Positive[a] Ocular Effects (sexes combined)

	Observation Intervals (hours)			
	1	24	48	72
Cornea				
Opacity	0/6	0/6	0/6	0/6
Iris				
Iritis	0/6	0/6	0/6	0/6
Conjunctivae				
Redness	0/6	0/6	0/6	0/6
Chemosis	0/6	0/6	0/6	0/6

[a] The following grades for each tissue are considered positive:
Opacity (density) - Grades 1, 2, 3, and 4
Iris - Grades 1 and 2
Conjunctivae (redness) - Grades 2 and 3
Conjunctivae (chemosis) - Grades 2, 3, and 4

No positive ocular effects were observed. Very slight conjunctival redness (Draize score 1) and chemosis (Draize score 1) were observed at 1 hour, but had cleared by 24 hours. The average primary irritation index at 1 hour was 3.3. Based on these findings Rejex-it TP-40 is classified Toxicity Category IV (Caution) for primary eye irritation.

D. REVIEWERS' COMMENTS

Rejex-it TP-40 was minimally irritating under the conditions of this study. Very slight redness and chemosis of the conjunctivae were clear by 24 hours; therefore the potential of Rejex-it TP-40 for primary eye irritation is Toxicity Category IV (Caution).

C10940

FINAL

DATA EVALUATION REPORT

Rejex-it TP-40

Study Type: Primary Dermal Irritation Study in Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Janaury 1994

Principal Reviewer	[illegible signature] Kate Rantz, M.P.H.	Date	[illegible]
Independent Reviewer	[illegible signature] Carrie Rabe, Ph.D.	Date	[illegible]
QA Reviewer	William L. McLellan William McLellan, Ph.D.	Date	1/25/94

Contract Number: 68D1[illegible]
Work Assignment Number: [illegible]
Clement Number: [illegible]
Project Officer: Caroline Gordon

83

010940

Guideline Series 81-5: Primary Dermal Irritation Study in Rabbits

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature: [signature]
Date: 4/4/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 81-5; primary dermal irritation study in rabbits
CAS NUMBER:	
C.W. CHEM. NUMBER:	
MRID NUMBER:	426089-05
EPA NUMBER:	128725
TEST MATERIAL:	Rejex-it TP-40
SYNONYMS:	Methyl anthranilate (active ingredient
SPONSOR	ERM Program Management Company McLean, Virginia
STUDY NUMBER:	HWI 2305702
TESTING FACILITY	Hazleton Wisconsin, Inc. Madison, Wisconsin
TITLE OF REPORT	Primary Dermal Irritation Study of Rejex-it TP-40 in Rabbits
AUTHOR:	Steven M. Glaza
STUDY COMPLETED:	June 5, 1992
QUALITY ASSURANCE:	The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement signed June 5, 1992, was submitted.
CONCLUSIONS:	Dermal application of Rejex-it TP-40 under occluded semi-occluded conditions produced very slight to severe erythema (Draize scores 0-3), very slight edema (Draize scores 0-1), and desquamation at day 7. The primary irritation index of 1.4 indicated that the test material is a slight irritant.

84

010940

Guideline Series 81-5: Primary Dermal Irritation Study in Rabbits

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-5) for a primary dermal irritation study in rabbits. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: IV (Caution)

A. MATERIALS

Test Compound

Test material:	Rejex-it TP-40
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Blue liquid; pH not determined
Storage condition:	Room temperature
Stability:	Determined by sponsor
Dose level:	0.5 mL (as received)

Test Animals

Species:	Albino rabbits
Strain:	Hra:(NZW)SPF
Source:	Hazleton Research Products, Inc., Kalamazoo MI
Sex:	3 males and 3 females
Age:	Adult
Mean body weight:	2190-2442 g, males; 2382-2380 g, females
No animals:	3/sex/dose
Temperature:	20-25°C
Relative humidity:	40-65%
Photoperiod:	12-hour light, 12-hour dark cycle
Feeding:	Purina High Fiber Rabbit Chow #5326, measured amount daily
Water:	*Ad libitum*
Acclimation period:	At least 7 days
Housing:	Individual
Identification:	Ear tags

B. TEST PERFORMANCE

Test Material Application

The back and flanks of each rabbit were clipped the day before application of the test material. The test material (0.5 mL) was applied to the intact clipped skin of each animal. The treated area was covered with a 2.5 cm x 2.5 cm gauze patch, which was fastened with paper tape, loosly wrapped in Saran Wrap, and secured with Elastoplast tape to provide a semi-occlusive dressing. After 4 hours of exposure, the patch and wrappings were removed and the test site was washed with tap water and dried with disposable paper towels.

85

Observation Period

The degree of erythema and edema at the test site was determined about 30 minutes after removal of the test material and was recorded as the 4-hour score. Additional examinations were made at 24, 48, 72, and 96 hours, and day 7. The Draize scoring system for primary dermal irritation was used.

C. RESULTS

A summary of dermal irritation scores is presented in Table 1.

Table 1. Summary of Positive[a] Dermal Irritation Scores (sexes combined) (Draize Technique)

	Observation Intervals (hours)					
	4	24	48	72	96	day 7
Erythema	4/6	6/6	5/6	5/6	5/6	0/6
mean score	1.0	1.2	1.7	1.7	1.7	0
Edema	3/6	4/6	3/6	3/6	3/6	0/6
mean score	1.0	1.0	1.0	1.0	1.0	0

[a] The following dermal irritations scores are considered positive:
Erythema - Grades 1, 2, 3, and 4
Edema - Grades 1, 2, 3, and 4

Erythema (Draize scores 0-3) was observed in all animals by 24 hours and increased in severity until 48 hours, when the severity plateaued through 96 hours. Slight edema (Draize scores 0-1) was observed in 3-4 rabbits through 96 hours. The erythema and edema resolved by day 7, but desquamation was observed in all animals at day 7. The average primary dermal irritation scores were 1.2 at 4 hours; 1.8 at 24 hours; 2.2 at 48, 72, and 96 hours, and 0 at day 7. The average of the 4-, 24-, 48- and 72-hour scores is 1.9, which is considered slightly irritating. Based on these findings, Rejex-it TP-40 is classified as Toxicity Category IV (Caution).

D. REVIEWERS' COMMENTS

Dermal application of Rejex-it TP-40 produced very slight to severe erythema, very slight edema, and desquamation under the 4-hour semi-occluded conditions of this study. Based on these findings, Rejex-it TP-40 is classified Toxicity Category IV (Caution).

86

C10940

FINAL

DATA EVALUATION REPORT

Rejex-it TP-40

Study Type: **Dermal Sensitization Study in Guinea Pigs**

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

January 1994

Principal Reviewer: Kate Rantz, M.P.H. Date: 1/24/94

Independent Reviewer: Carrie Rabe, Ph.D. Date: 1/24/94

QA Reviewer: William McLellan, Ph.D. Date: 1/25/94

Contract Number: 68D1 0[illegible]
Work Assignment Number: [illegible]
Clement Number: [illegible]
Project Officer: Caroline Gordon

87

010940

Guideline Series 81-6: Dermal Sensitization Study in Guinea Pigs

EPA Reviewer: J. Thomas McClintock
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 2/9/94

EPA Section Head: Roy Sjoblad
Biological Section, Science Analysis Branch
Health Effects Division

Signature:
Date: 2/10/94

DATA EVALUATION REPORT

STUDY TYPE: Guideline series 81-6: dermal sensitization study in guinea pigs

CAS NUMBER:

TOX CHEM NUMBER:

MRID NUMBER: 426089-06

PC NUMBER: 128725

TEST MATERIAL: Rejex-it TP-40

SYNONYM(S): Methyl anthranilate (active ingredient)

SPONSOR: ERM Program Management Company
McLean, Virginia

STUDY NUMBER: HWI 20305710

TESTING FACILITY: Hazleton Wisconsin, Inc.
Madison, Wisconsin

TITLE OF REPORT: Dermal Sensitization Study of Rejex-it TP-40 in Guinea Pigs — Closed Patch Technique

AUTHOR: Steven M. Glaza

STUDY COMPLETED: July 27, 1992

QUALITY ASSURANCE: The test was performed under Good Laboratory Practice Standards. A Quality Assurance Statement signed July 27, 1992, was submitted

CONCLUSIONS: Delayed contact hypersensitivity was not observed in guinea pigs exposed to Rejex-it TP-40 under the conditions of this test. Very faint erythema was seen in 2 of 9 surviving guinea pigs at the challenge site. No erythema was observed in any of the 10 naive control animals at challenge.

38

010940

Guideline Series 81-6: Dermal Sensitization Study in Guinea Pigs

CORE CLASSIFICATION: Core Supplementary. This study satisfies the guideline requirements (81-6) for a dermal sensitization study in guinea pigs. However, data describing the test material were lacking (e.g., purity, stability, and lot number/identification number). This study may be upgraded pending submission of these data.

TOXICITY CATEGORY: Not applicable

A. MATERIALS

Test Compound

Test material:	Rejex-it TP-40
Identification no.:	Not reported
Purity:	Determined by sponsor
Physical description:	Blue liquid
Storage condition	Room temperature
Stability:	Determined by sponsor
Positive control material:	2,4-dinitrochlorobenzene (DNCB) lot number 30H0121; 99.9% pure)
Naive control material	Rejex-it TP-40 (animals treated at challenge only
Irritation screening conc	Four animals each received two different concentrations of the test material, either undiluted or in 25%, 50%, or 75% w/v in mineral oil.
Main study test material conc.	Induction/challenge - [illegible] mL Rejex-it TP-40 undiluted)

Test Animals

Species:	Albino guinea pigs
Strain:	Hsd: DH)fBR
Source:	Hazleton Research Products, Inc Denver PA
Sex:	[illegible] males and [illegible] females
[illegible] group:	[illegible] in irritation screening group 1 male, 3 females), 10 in test group 8 males, 2 females 1) in naive control group 3 males, 2 females) [illegible] in positive control group 2 males 2 females
Age	Young adult
Initial body weights	[illegible]36-540 g, males; [illegible] g females
Temperature	14-25°C
Relative humidity	30-70%
Photoperiod	12-hour light 12-hour dark cycle
Feeding:	Purina Certified Guinea Pig Chow #5026, ad libitum
Water	Ad libitum
Acclimation period	At least [illegible] days

89

Housing: Individual
Identification: Ear tags
Selection: Healthy animals within unspecified body weight limits were selected

B. TEST PERFORMANCE

Skin Preparation

The back of the animal was used as the test site. The hair on the back of each animal in the test and positive control groups was removed the day of test material application. Animals were depilatated with Neet 3 hours prior to the 24-hour examination.

Induction Phase

(a) Route of administration: The test material (0.4 mL) was applied to a 25 mm diameter adhesive patch. The patch was placed on the test site (anterior left flank), covered with dental dam, and wrapped with Elastoplast tape. The patch was removed after 6 hours and the test site cleaned with a wet paper towel.

(b) Solutions used: Test group - 0.4 mL test material; positive control group - 0.4 mL 0.3% w/v DNCB in 80% v/v ethanol in deionized water; naive irritation control - untreated.

(c) Frequency of exposure: Test and positive control groups - 1 application per week for 3 weeks for a total of 3 applications

(d) Duration of exposure: 6 hours

(e) Rest period: 2 weeks

(f) Observation period: 24 and 48 hours after each exposure

Challenge Phase

(a) Route of administration: Administration was the same as for the induction phase, except that the test material was placed on the right flank. The naive irritation control group of 10 was also given the challenge dose of 0.4 mL test material

(b) Solutions used: Test group and naive irritation control groups - 0.4 mL test material; positive control group - 0.1% w/v DNCB in acetone

(c) Duration of exposure: 6 hours

(d) Number of exposures: 1

(e) Observation period: 24 and 48 hours after application

Scoring System

A modification of the Buehler method was used.

C. RESULTS

C10940

Mortality

One animal in the test group was found dead on day 4. Gross necropsy revealed red mucoid semifluid in the abdominal cavity.

Body weights

Body weight gain was normal in all animals, except for a weight loss of 86 grams during the last 4 days of the study in 1 animal from the naive control group.

Skin reactions

By the third induction dose, all of the surviving test group animals showed very faint to faint erythema (average Buehler scores, 0.1-0.5; high scores, 0.5-1.0). Following challenge, 2 of the surviving test group animals had very faint erythema reactions (nonsensitizations) to the test material (Buehler score, 0.5). None of the naive control group animals showed skin reactions after challenge application of the test material.

Clinical signs

One animal in the naive control group had soft stool on days 8-14.

D. REVIEWERS' COMMENTS

A dermal sensitization reaction was not observed under the present study conditions in guinea pigs treated with Rejex-it TP40. Based on these data, the test material was not considered to be a dermal sensitizer in guinea pigs.

91