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008866

DATA EVALUATION REPORT

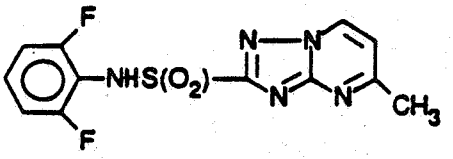
STUDY TYPE: 21-Day Dermal Study in Rabbits (Guideline 82-2)

EPA IDENTIFICATION NOS.:
MRID NO.: 419938-10
HED PROJECT NO.: 1-2384
CASWELL NO.: 889

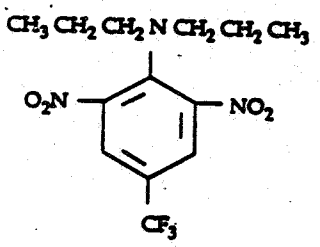
TEST MATERIAL: XRM-5313

SYNONYMS: Formulation containing: 2.6% XRD-498 [N-(2,6-difluorophenyl)-5-methyl(1,2,4)triazolo(1,5a) pyrimidine-2-sulfonamide] and 35.8% Trifluralin (Treflan; α,α,α-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine)

XRD-498:



Trifluralin:



STUDY NUMBER: M-005313-003

SPONSOR: DowElanco
9002 Purdue Road
Indianapolis, Indiana 44268-1189

TESTING FACILITY: The Toxicology Research Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, Michigan 48674

TITLE OF REPORT: XRM-5313, A Formulation Containing Trifluralin and XRD-498: 21 Day Dermal Study in New Zealand White Rabbits

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DATE REPORT ISSUED: May 17, 1991

SUMMARY/CONCLUSION: The test material, XRM-5313, was applied undiluted to the skin of New Zealand White rabbits (five/sex/group) at dose levels of 100, 500, and 1000 mg/kg/day. The animals were exposed for six-hour periods on a total of 15 days during the 21-day duration of the study. A sham-treated control group (treated with dermal application of water) was run simultaneously. Dose- and

treatment-related dermal irritation was noted at all dose levels. However, the results of this study, including analysis of clinical observation, body weight, hematology, clinical chemistry, gross necropsy, organ weight, and histopathology data, indicated that repeated dermal application of XRM-5313 over a period of 21 days produced no evidence of systemic toxicity at the dose levels tested.

Due to the absence of any indication of systemic toxicity, it is unclear whether absorption of the test substance occurred following dermal application.

NOEL (Dermal Effects) = Not determined
LOEL (Dermal Effects) = 100 mg/kg/day

NOEL (Systemic Toxicity) = At least 1000 mg/kg/day
LOEL (Systemic Toxicity) = Not determined

Core Classification: Guideline

MATERIALS:

1. Test compound: Description: Orange-red liquid suspension
Sample reference: AGR 291670
Source: DowElanco, Midland, Michigan
Active ingredients: 2.6% XRD-498 and
35.8% Trifluralin

2. Control material: Substance: Water
Source: Not provided

2. Test animals: Species: Rabbit
Strain: New Zealand White
Source: Hazleton Research Products, Inc.
Denver, Pennsylvania
Age: Approximately 5 months
Weight: Males 3.4-3.8 kg; Females 3.6-4.2 kg

METHODS:

A copy of the "Materials and Methods" section from report No. M-005313-003, pages 11-19 and 28, is appended as Attachment 1.

Dermal probe study: An initial probe study was conducted with four New Zealand White rabbits, two/sex, to evaluate the potential for irritation following repeated dermal exposure to the test substance, XRM-5313. Each rabbit received a topical application of 1000 mg/kg of the test material for four days, with exposure durations of six hours, and dose volumes based upon body weight. The animals were observed for signs of systemic toxicity, and dermal reactions were scored. At the end of the dosing regimen, the animals were sacrificed. The only observations reported were very slight to well-defined erythema in one male and one female rabbit during the four-day period. Based upon these results, 1000 mg/kg/day was selected as an acceptable high-dose level for the 21-day dermal study. Per EPA FIFRA Pesticide Assessment Guideline 82-2, 1000 mg/kg/day is deemed an acceptable limit dose value, unless expected human exposure data would indicate the need for testing at a higher dose level.

Group assignment and dosage levels: New Zealand White rabbits were acclimated to laboratory conditions for 14 days and assigned randomly to the following test groups:

Dose Group	Dose Level (mg/kg)	No. of Rabbits	
		Male	Female
Control	0	5	5
Low-Dose	100	5	5
Mid-Dose	500	5	5
High-Dose	1000	5	5

The study rabbits were maintained under acceptable environmental conditions.

Test substance application: A dorsal area of the trunk, approximately 10 x 15 cm and representing at least 10% of the surface area of the animal, was clipped free of fur on each rabbit prior to the start of dosing and as needed thereafter. Fifteen repeated doses of the undiluted test material, XRM-5313, were administered to each animal over a 21-day period. Doses were adjusted weekly based on the most recent body weight. A dressing consisting of absorbent gauze and non-absorbent cotton was used to hold the test material in dermal contact. A water-moistened patch served as the control dosage. An elastic jacket, to which the animals were acclimated prior to the first application, was used to hold the test dressing in dermal contact. The jacket and dressing were removed approximately six hours after application and the test site was wiped with a water-dampened disposable towel and a mild soap solution to remove any residual test substance.

Clinical observations: Clinical examinations were conducted prior to the start of the study and at approximately weekly intervals thereafter. Cageside observations were made daily during the workweek. Observations for mortality, moribundity, and the availability of feed and water were made daily on workweek days and twice daily on weekends and holidays.

Dermal observations: The dermal test site was evaluated each day that wraps were removed and scored weekly on the last day of a dosing week and on the after noon prior to necropsy. The following dermal scoring system was used:

Erythema and Eschar	
Within normal limits	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema to slight eschar formation	4
Edema	
Within normal limits	0
Very slight (barely perceptible)	1
Well-defined (edges raised)	2
Moderate (raised approximately 1 mm)	3
Severe (raised more than 1 mm)	4
Scaling and Fissuring	
Within normal limits	0
Slight scaling	1
Moderate to severe scaling	2
Slight fissuring	3
Moderate to severe fissuring	4

In addition to the above, necrosis, scabs, and/or scars were noted if present, but no gradings were assigned to these observations.

Body weights: Animals were weighed prior to dosing, and on weekly intervals thereafter (Days -2, 5, 13, and 20 of test). The rabbits were provided an allotted ration of 4 ounces of feed per day, and food consumption was not measured.

Hematology and Clinical Chemistry: Blood was collected from the auricular artery of all animals at study termination for hematology and clinical chemistry analyses. The following parameters were examined:

a. Hematology:

Hematocrit (HCT)*
Hemoglobin (HGB)*
Erythrocyte count (RBC)*
Total leukocyte count (WBC)*
Platelet count (PLAT)*
Leukocyte differential count*

b. Clinical Chemistry:

Electrolytes

Calcium (CALC)*
Phosphorus (PHOS)*
Chloride (CL)*
Sodium (NA)*
Potassium (K)*

Enzymes

Serum alanine aminotransferase (ALT)*
Serum aspartate aminotransferase (AST)*
Alkaline phosphatase (AP)
Gamma glutamyltransferase (GGT)

Other

Albumin (ALB)*
Blood creatinine (CREAT)*
Urea nitrogen (UN)*
Glucose (GLUC)*
Total bilirubin (TBILI)*
Total protein (TP)*
Globulin (GLOB)

* Recommended by Subdivision F Pesticide Assessment Guideline 82-2.

c. Urinalysis: Urinalysis was not performed.

Sacrifice and postmortem evaluations: All animals were sacrificed and subjected to gross pathological examination approximately 24 hours after the last dermal application. Tissues presented in the following list were collected and preserved.

The liver, kidneys, and testes were weighed and the organ-to-terminal-body weight ratio was calculated for all rabbits. Sections of skin from the dermal application site, skin from a site immediately adjacent to the dermal test site, liver, and kidneys were examined microscopically from all animals on study.

Digestive System	Cardiovasc./Hemat./Lymph	Skin
Tongue	Aorta	Dermal test site*
Salivary glands	Heart	Immediately adjacent to dermal test site*
Esophagus	Bone marrow	Inguinal
Stomach	Lymph node, mediastinum	
Rectum	Lymph node, mesenteric	
Colon	Spleen	Neurologic
Cecum	Thymus	Brain
Sacculus rotundus		Peripheral nerve
Ileum	Urogenital	Spinal cord
Jejunum	Kidney*	Pituitary
Duodenum	Urinary bladder	Eyes
Liver*	Testes	
Gallbladder	Epididymides	Glandular
Pancreas	Prostate	Adrenal glands
Oral tissues	Ovaries	Mammary gland
	Oviducts	Thyroid gland
Respiratory	Uterus	Parathyroid glands
Trachea	Cervix	
Lung	Vagina	Other
Nasal tissues		Bone with joint
Larynx		Gross lesions
		Mediastinal tissues
		Mesenteric tissues
		Skeletal muscle

* Recommended by Subdivision F Pesticide Assessment Guideline 82-2.

Note: Report No. M-0005313-003 also listed the appendix as a collected tissue (see Table 1, page 28). This tissue is not listed in the above table since the appendix is the human/primate equivalent of the lagomorph cecum and the listing was most likely erroneous.

Statistics: Body weight values, hematology (excluding differential WBC counts) and serum chemistry values, and absolute and relative organ weights were examined statistically for equality of variance, using Bartlett's test. If the results were significant, the parameter was subjected to appropriate parametric analysis using a three-way repeated measures analysis of variance (RM-ANOVA) for in-life body weights; a two-way analysis of variance (ANOVA) for terminal body weight, absolute and relative organ weights (excluding testes), hematology (excluding differentials), and clinical chemistry values; and a one-way ANOVA for absolute and relative testes weights. Further description of the statistical methods, including the nominal alpha levels used at each step of the analysis, are included in report No. M-005313-003, page 17-19, presented as Attachment 1 of this Data Evaluation Report.

RESULTS:

Mortality, Clinical Observations, and Dermal Findings:

All rabbits survived until study termination, and no clinical signs of systemic toxicity were noted throughout the duration of the study. Dermal observations are presented in Tables 1A and 1B for male and female rabbits, respectively. Treatment-related observations of erythema, edema, and scaling and fissuring were reported for all test groups treated with the test substance, generally increasing in incidence and severity as the dosage increased. Lesions were not pronounced in severity; most observations were graded as very slight to slight. Dermal observations noted in the low-dose (100 mg/kg) rabbits were reversed by study termination, with all skin observations graded as normal at that time. No incidence of scabs, necrosis or scarring was reported in either male or female rabbits.

Body Weight Data:

Body weight data are summarized in Table 2. There were no significant differences between control and treated groups, and the animals generally gained or maintained body weight during the study.

Clinical Pathology

Hematology - Hematology data are summarized in Table 3A (mean hematology values) and 3B (mean differential values). A significant decrease in mean erythrocyte (RBC) count was noted for male rabbits at 1000 mg/kg, but this was not considered to be a treatment-related effect since a dose-response was not identified, a similar response was not noted in the females, and the high-dose male RBC value was within the range of historical control values tabulated by the performing laboratory. All other parameters appeared to be similar between control and treated groups.

Clinical chemistry - A summary of clinical chemistry values is presented in Table 3C. No treatment-related effects were observed.

Gross Pathology:

Selected gross pathology findings are presented in Table 4. There was a treatment-related increase in the incidence of multifocal scales and erythema in the mid- and high-dose animals; the incidence of erythema in these groups was also apparently related to dose. Additional observations (not presented in Table 4) included remarks on yellow discoloration of the skin, a dose-related effect attributable to application of the colored test substance, and a unilateral focal depression of the renal cortex of one mid-dose male. These observations were not considered to be indications of toxic response.

Table 1A. Summary of dermal observations - males

Dermal Observations[a]	Application 3 (3 Days on Test)				Application 8 (10 Days on Test)				Application 13 (17 Days on Test)				Application 15 (21 Days on Test)			
	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
Erythema																
Within normal limits	5	5	4	5	5	5	2	4	5	5	1	0	5	5	5	3
Very slight	0	0	1	0	0	0	3	1	0	0	3	4	0	0	0	2
Well-defined	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Severe (to slight eschar)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Edema																
Within normal limits	5	5	5	5	5	5	3	3	5	5	1	0	5	5	5	4
Very slight	0	0	0	0	0	0	2	1	0	0	4	4	0	0	0	1
Well-defined; edges raised	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Moderate; raised ~1mm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Severe; raised >1mm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scaling and fissuring																
Within normal limits	5	5	5	5	5	3	0	1	5	3	0	0	5	5	0	0
Slight scaling	0	0	0	0	0	2	2	0	0	2	2	3	0	0	5	4
Moderate-severe scaling	0	0	0	0	0	0	3	4	0	0	3	1	0	0	0	1
Slight fissuring	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Moderate-severe fissuring	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scab (crust)																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scar																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a Five rabbits were examined at each interval.
Note: Data were extracted from report No. M-005313-003, pages 29-32.

Table 1B. Summary of dermal observations - females

Dermal Observationa	Application 3 (3 Days on Test)				Application 8 (10 Days on Test)				Application 13 (17 Days on Test)				Application 15 (21 Days on Test)			
	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
Erythema																
Within normal limits	5	5	4	5	5	5	2	2	5	4	0	2	5	5	3	3
Very slight	0	0	1	0	0	0	3	3	0	1	5	3	0	0	2	2
Well-defined	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Severe (to slight eschar)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Edema																
Within normal limits	5	5	5	5	5	5	1	0	5	2	0	1	5	5	5	5
Very slight	0	0	0	0	0	0	4	5	0	3	4	4	0	0	0	0
Well-defined; edges raised	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Moderate; raised ~1mm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Severe; raised >1mm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scaling and fissuring																
Within normal limits	5	5	5	5	5	3	0	0	5	1	0	0	5	5	0	1
Slight scaling	0	0	0	0	0	2	2	0	0	4	2	5	0	0	4	4
Moderate-severe scaling	0	0	0	0	0	0	3	5	0	0	3	0	0	0	1	0
Slight fissuring	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Moderate-severe fissuring	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scab (crust)																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scar																
Within normal limits	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Condition present	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

a Five rabbits were examined at each interval.
Note: Data were extracted from report No. M-005313-003, pages 33-36.

Table 2. Mean body weight data (g)

Dose (mg/kg/day)		Males				Females			
		Day -2	Day 5	Day 13	Day 20	Day -2	Day 5	Day 13	Day 20
0	Mean	3586	3631	3602	3640	3933	3993	3957	4025
	S.D.	166	113	152	142	182	186	157	153
	N	5	5	5	5	5	5	5	5
100	Mean	3621	3662	3589	3643	3909	3950	3916	3938
	S.D.	137	159	154	149	234	226	173	239
	N	5	5	5	5	5	5	5	5
500	Mean	3609	3678	3646	3674	3910	3924	3882	3922
	S.D.	136	132	135	121	233	247	262	248
	N	5	5	5	5	5	5	5	5
1000	Mean	3639	3666	3659	3681	3938	3978	3904	3941
	S.D.	118	106	108	80	161	189	225	255
	N	5	5	5	5	5	5	5	5

Note: Data were extracted from report No. M-005313-003, Pages 37-38.

Table 3A. Mean hematology values

Parameter		Males				Females			
		0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
RBC X10E6/ CU MM	Mean	6.82	6.40	6.55	6.11*	6.13	6.14	6.13	6.39
	S.D.	0.26	0.32	0.46	0.38	0.17	0.32	0.40	0.50
	N	5	5	5	5	5	5	5	5
HGB G/DL	Mean	13.3	13.2	13.0	12.8	12.8	12.5	12.6	13.2
	S.D.	0.3	0.5	0.5	0.4	0.7	0.4	0.5	0.5
	N	5	5	5	5	5	5	5	5
HCT %	Mean	45.2	44.3	43.8	42.7	43.0	42.2	42.9	44.0
	S.D.	1.0	1.5	2.1	2.1	1.6	1.6	2.7	1.9
	N	5	5	5	5	5	5	5	5
PLAT X10E3/ CU MM	Mean	363	360	367	440	368	393	415	412
	S.D.	118	32	37	35	45	66	74	33
	N	5	5	5	5	5	5	5	5
WBC X10E3/ CU MM	Mean	6.6	6.8	7.0	6.6	5.7	5.4	6.1	6.4
	S.D.	1.9	0.7	1.2	1.1	0.8	1.1	1.6	0.9
	N	5	5	5	5	5	5	5	5

* Significantly different from control value, $p \leq 0.05$.
Note: Data were extracted from Report No. M-005313-003, pages 39 and 41.

Table 3B. Mean differential white blood cell count values

Parameter		Males				Females			
		0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
SEG	Mean	24	27	34	29	34	21	36	29
%	S.D.	8	7	7	7	9	3	7	5
	N	5	5	5	5	5	5	5	5
BAND	Mean	0	0	0	0	0	0	0	0
%	S.D.	0	0	0	0	0	0	0	0
	N	5	5	5	5	5	5	5	5
LYM	Mean	72	70	63	68	63	75	60	68
%	S.D.	8	6	7	7	9	2	7	4
	N	5	5	5	5	5	5	5	5
MONO	Mean	3	3	3	4	3	4	3	3
%	S.D.	1	1	1	1	1	1	1	1
	N	5	5	5	5	5	5	5	5
EOS	Mean	0	0	0	0	0	0	0	0
%	S.D.	0	0	0	0	0	0	0	0
	N	5	5	5	5	5	5	5	5
NRBC	Mean	0	0	0	0	0	0	0	0
/100	S.D.	0	1	0	0	0	0	0	0
WBC	N	5	5	5	5	5	5	5	5

Statistical analysis of differential WBC data not performed.
Note: Data were extracted from Report No. M-005313-003, pages 40 and 42.

Table 3C. Mean clinical chemistry and electrolyte values

Parameter		Males				Females			
		0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
UN	Mean	14	13	14	15	16	16	14	17
MG/DL	S.D.	3	1	1	2	3	2	1	3
	N	5	5	5	5	5	5	5	5
ALT	Mean	40	27	24	25	32	29	24	27
MU/ML	S.D.	20	14	7	10	7	14	6	7
	N	5	5	5	5	5	5	5	5
AP	Mean	111	103	110	99	74	75	63	59
MU/ML	S.D.	24	19	7	19	16	20	21	11
	N	5	5	5	5	5	5	5	5
AST	Mean	26	21	20	18	18	19	17	18
MU/ML	S.D.	8	8	7	5	4	2	6	2
	N	5	5	5	5	5	5	5	5
GLUC	Mean	133	134	133	134	126	132	124	125
MG/DL	S.D.	14	6	6	12	5	10	10	5
	N	5	5	5	5	5	5	5	5
TP	Mean	6.5	6.2	6.1	6.0	6.1	6.1	6.2	6.1
G/DL	S.D.	0.2	0.3	0.2	0.4	0.2	0.4	0.1	0.1
	N	5	5	5	5	5	5	5	5

Table 3C. Mean clinical chemistry and electrolyte values - continued

Parameter		Males				Females			
		0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
ALB G/DL	Mean	4.1	4.0	3.9	3.8	3.9	3.9	3.8	3.9
	S.D.	0.2	0.1	0.1	0.3	0.2	0.2	0.1	0.1
	N	5	5	5	5	5	5	5	5
GLOB G/DL	Mean	2.4	2.2	2.2	2.2	2.2	2.3	2.4	2.2
	S.D.	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.1
	N	5	5	5	5	5	5	5	5
TBILI MG/DL	Mean	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
	N	5	5	5	5	5	5	5	5
CREAT MG/DL	Mean	1.5	1.3	1.3	1.3	1.6	1.6	1.4	1.6
	S.D.	0.2	0.2	0.1	0.2	0.1	0.1	0.2	0.2
	N	5	5	5	5	5	5	5	5
CALC MG/DL	Mean	14.2	14.2	14.0	14.0	14.1	13.9	13.5	13.7
	S.D.	0.4	0.6	0.2	0.5	0.2	0.1	0.4	0.3
	N	5	5	5	5	5	5	5	5
PHOS MG/DL	Mean	5.3	5.1	5.3	5.3	4.8	4.7	4.8	4.8
	S.D.	0.6	0.5	0.4	0.5	0.4	0.5	0.5	0.4
	N	5	5	5	5	5	5	5	5
NA MMOL/L	Mean	147	147	146	147	147	146	147	146
	S.D.	3	3	3	3	1	2	2	2
	N	5	5	5	5	5	5	5	5
K MMOL/L	Mean	4.4	4.3	4.2	4.0	4.1	4.0	4.0	3.9
	S.D.	0.4	0.3	0.3	0.1	0.2	0.3	0.1	0.3
	N	5	5	5	5	5	5	5	5
CL MMOL/L	Mean	111	111	112	110	113	111	113	112
	S.D.	2	3	3	3	1	2	2	2
	N	5	5	5	5	5	5	5	5

Note: Data were extracted from report No. M-005313-003, pages 43-46.

Table 4. Selected gross pathology observations

Finding	Males				Females			
	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
Number examined	5	5	5	5	5	5	5	5
Skin								
Scales, multifocal - very slight	0	0	5	5	0	0	5	4
Erythema, multifocal - very slight	0	0	0	3	0	0	2	5

Note: Data were extracted from report No. M-005313-003, page 54.

Organ Weight Data:

Absolute and relative organ weight data are summarized in Tables 5A (males) and 5B (females). Mean values were similar between control and treated groups.

Table 5A. Mean absolute and relative organ weight values - males

Dose (mg/kg/day)		Final body wt (g)	Kidneys (g)	Kidneys (g/100)	Liver (g)	Liver (g/100)	Testes (g)	Testes (g/100)
0	Mean	3566	17.534	0.492	98.647	2.763	5.319	0.149
	S.D.	199	0.995	0.020	12.096	0.261	0.705	0.015
	N	5	5	5	5	5	5	5
100	Mean	3644	19.065	0.521	95.110	2.605	5.399	0.149
	S.D.	126	3.173	0.069	16.198	0.381	1.304	0.038
	N	5	5	5	5	5	5	5
500	Mean	3652	18.958	0.520	104.496	2.851	6.669	0.182
	S.D.	114	1.319	0.040	21.117	0.493	0.835	0.021
	N	5	5	5	5	5	5	5
1000	Mean	3660	19.068	0.521	95.048	2.599	6.416	0.175
	S.D.	85	1.094	0.032	6.641	0.209	0.892	0.025
	N	5	5	5	5	5	5	5

Note: Data were extracted from report No. M-005313-003, page 47.

Table 5B. Mean absolute and relative organ weight values - females

Dose (mg/kg/day)		Final body wt (g)	Kidneys (g)	Kidneys (g/100)	Liver (g)	Liver (g/100)
0	Mean	3960	17.212	0.435	81.543	2.059
	S.D.	180	0.579	0.018	6.559	0.139
	N	5	5	5	5	5
100	Mean	3890	16.666	0.428	88.754	2.290
	S.D.	189	0.946	0.012	6.543	0.251
	N	5	5	5	5	5
500	Mean	3885	17.578	0.453	84.583	2.187
	S.D.	267	1.096	0.026	6.963	0.255
	N	5	5	5	5	5
1000	Mean	3890	17.452	0.448	84.961	2.188
	S.D.	244	1.834	0.025	2.846	0.082
	N	5	5	5	5	5

Note: Data were extracted from report No. M-005313-003, page 48.

Histopathology:

Skin lesions noted at histopathological evaluation are summarized in Table 6. Treatment-related increases in incidence and severity of various lesions were noted in the treated and untreated (adjacent to dermal test site) skin. These included epidermal encrustation at the test site, and hyperkeratosis, thickening, and inflammation of the epidermis and inflammation of the dermis at both the test site and adjacent untreated areas. Other histopathological findings, renal cortical inflammation in one mid-dose male and focal hepatic reticuloendothelial cell aggregates in one control and low-dose male and one female of each test group (not included in Table 6), were not considered to be related to treatment.

Table 6. Incidence summary of selected histopathology observationsa

Finding	Males				Females			
	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg	0 mg/kg	100 mg/kg	500 mg/kg	1000 mg/kg
Number examined	5	5	5	5	5	5	5	5
Skin - dermal test site								
Within normal limits	5	0	0	0	5	0	0	0
Epidermal encrustations, epidermis								
Slight	0	0	0	1	0	0	3	3
Hyperkeratosis, epidermis								
Very slight	0	0	4	2	0	1	3	1
Slight	0	0	0	3	0	0	2	4
Thickened, epidermis								
Very slight	0	3	2	1	0	3	2	2
Slight	0	0	3	4	0	0	3	3
Inflammation - subacute to chronic, dermis								
Very slight	0	5	0	0	0	5	3	2
Slight	0	0	5	5	0	0	2	3
Inflammation - subacute to chronic, epidermis								
Very slight	0	0	0	1	0	0	3	3
Skin - untreatedb								
Within normal limits	5	5	2	2	4	4	4	2
Hyperkeratosis, epidermis								
Very slight	0	0	0	3	0	0	1	1
Slight	0	0	1	0	0	0	0	1
Thickened, epidermis								
Very slight	0	0	3	3	0	0	1	2
Slight	0	0	0	0	0	0	0	1
Inflammation - subacute to chronic, dermis								
Very slight	0	0	2	3	1	1	0	1
Slight	0	0	0	0	0	0	1	1
Inflammation - subacute to chronic, epidermis								
Very slight	0	0	1	0	0	0	1	1

a Data are the number of animals with the specified observation.
b Adjacent to dermal test site.
Note: Data were extracted from report No. M-005313-003, pages 55-56.

STUDY DEFICIENCIES: The following study deficiencies were noted; none compromise the quality of the study data or the interpretation of the results.

1. The rabbits used on this study exceeded the 2.0-3.0 kg body weight values suggested by Guideline 82-2 (G)(1)(ii)(B).
2. The source and/or other defining characteristics of the control material

(water) was not provided, as required by EPA FIFRA GLP.
3. Weekly food consumption data was not collected, as recommended by Guideline 82-2 (g)(9)(v).
4. The percentage of animals displaying each type of lesion and an evaluation of body weight changes were not reported as suggested by Guideline 82-2 (h)(1)(i)(D) and (h)(2)(i)(E).

COMPLIANCE:

The following signed and dated statements were included:
Statement of No Data Confidentiality
GLP Compliance Statement
Flagging Statement (negative)
Quality Assurance Statement

CONCLUSIONS:

Although dose- and treatment-related dermal irritation was noted at all dose levels, the results of this study indicated that repeated dermal application of XRM-5313 over a period of 21 days produced no evidence of systemic toxicity at the dose levels tested (100, 500, and 1000 mg/kg/day). Due to the absence of systemic toxicity, it is unclear whether absorption of the test substance, XRM-5313, occurred following dermal application.

NOEL (Dermal Effects) = Not determined
LOEL (Dermal Effects) = 100 mg/kg/day

NOEL (Systemic Toxicity) = At least 1000 mg/kg/day
LOEL (Systemic Toxicity) = Not determined

Core Classification: Guideline

Page_____ is not included in this copy.

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