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DATA EVALUATION REPORT

ETOFENPROX

STUDY TYPE: REPEATED DOSE DERMAL – RABBIT]OPPTS 870.3200 (§82-2)]
MRID 45186501

Prepared for

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

Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Repeated Dose Dermal – Rabbit [OPPTS 870.3200 (§82-2)]

DP BARCODE: D269184
P.C. CODE: 128965

SUBMISSION CODE: S583957
TOX. CHEM. NO: none

TEST MATERIAL (PURITY): Etofenprox (99.18%)

SYNONYM: Technical MTI-500, Technical Etofenprox

CITATION: Killeen, J.C., Jr. (2000) A 28-Day Repeated Dose Dermal Toxicity Study in Rabbits with Technical MTI-500. Toxicology & Metabolism Ricerca, LLC, 7528 Auburn Road, Painesville, OH 44077-1000. Study Number 011077-1, June 28, 2000. MRID 45186501. Unpublished.

SPONSOR: Mitsui Chemicals, Inc., 3-2-5 Kasumigaseki, Chiyoda-ku, Tokyo 100-6070, Japan.

EXECUTIVE SUMMARY: In a 28-day repeated dose dermal toxicity study (MRID 45186501), groups of 10 male and 10 female New Zealand White rabbits were treated with Etofenprox (99.18%, Lot No. 21049). An additional 10 rabbits/sex were included in the control and high-dose groups as recovery animals: they were kept an additional 14 days during which time they were not dosed. Treatment was by dermal occlusion for 6 hours/day for 28 days at doses of 0, 400, 650, or 1000 mg/kg/day.

None of the rabbits died on study or had evidence of systemic toxicity: clinical signs, body weights, hematology, clinical chemistry, organ weights, and the incidence of gross lesions were comparable to controls. Both males and females had treatment-related dermal irritation and microscopic lesions. The incidence of erythema, scabbing, crusting, desquamation, and exfoliation was increased in both sexes at all test doses (not statistically analyzed). Mid- and high-dose rabbits additionally had minimal edema and females had dermal fissuring and thickening. Observation incidences peaked during weeks 2 or 3 and were generally greater in females than males. Although the incidence of these observations was elevated compared to controls, the response was not linearly proportional to dose among the treated groups. Microscopic lesions with an increased incidence ($p<0.05$ or 0.01) included diffuse epidermal hyperplasia in both sexes (all treated male groups and high-dose females) as well as chronic diffuse dermal inflammation and diffuse heterophil dermal infiltration in high-dose males. A dose-response was seen in males, but the dose-relationship was less clear in females. Use of variable volumes of undiluted test material, the dosing procedure (i.e., bandaging, etc.), and the close spacing of the test dose levels may have contributed to the lack of a linear dose-response in

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female microscopic changes and in skin observations in both sexes. The incidence and severity of the microscopic skin lesions after the 2-week recovery period was substantially lower in both sexes, indicating that the lesions were resolving.

The systemic NOAEL is the limit dose of 1000 mg/kg/day; a systemic LOAEL was not identified. The dermal LOAEL is 400 mg/kg/day, the lowest dose tested, based on an increased incidence of dermal observations (scabbing, crusting, desquamation, exfoliation) and histopathological changes (diffuse epidermal hyperplasia) in both sexes of rabbits. A dermal NOAEL was not identified.

This chronic study in rabbits is **acceptable-guideline** and does satisfy the guideline requirements for a repeated-dose dermal study [OPPTS 870.3200 (§82-2)] in rabbits. However, a dermal NOAEL was not established and the test material was not applied in a constant volume.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

MATERIALS AND METHODS

A. MATERIALS

1. Test material: Etofenprox (99.18%)

   Synonym: Technical MTI-500
   Description: Clear to straw-colored liquid (may be crystal or liquid at room temperature; was warmed to 101°F to be liquid for dosing).
   Lot #: 21049
   Purity/Stability: 99.18%; stability not addressed
   Structure: not provided

2. Vehicle and/or positive control

   Vehicle: none; applied undiluted
   Positive control: none

3. Test animals

   Species: rabbit
   Strain: New Zealand White (NZW)
   Age and weight at study initiation: 12-13 weeks; males: 2460-3007 g, females: 2440-3076 g
   Source: Myrtle's Rabbitry, Thompson Station, TN
   Housing: 1/cage; cages not described but met accepted standards ("Guide for the Care and Use of Laboratory Animals", NRC, 1996)
   Diet: PMI Feeds, Inc. Certified High Fiber Rabbit Diet #5325, *ad libitum*
   Water: tap water, *ad libitum*

Environmental conditions:
Temperature: 63-72°F (17.2-22.2°C); two excursions of <1°F
Humidity: 30-70% (several excursions >70%, within 5%)
Air changes: at least 10/hour
Photoperiod: 12 hour light/12 hour dark cycle
Acclimation period: 6 days (animals were acclimated to collars during this period)

B. STUDY DESIGN

1. In life dates

Start: November 9, 1999 End: December 22, 1999 (The initiation of dosing of males and females was staggered by one day to facilitate necropsy.)

2. Animal assignment

Rabbits were completely randomly distributed, based on body weight, to the experimental groups shown in Table 1.

Table 1. Experimental design

Group	Dose Level (mg/kg/day)	No. of Animals	
		Male	Female
1 (Control)	0	20[1]	20[1]
2 (Low-dose)	400	10	10
3 (Mid-dose)	650	10	10
4 (High-dose)	1000	20[1]	20[1]

Data taken from MRID 45186501, p. 14.
[1]Ten of the 20 animals were used for the recovery experiment (i.e. held an additional 14 days without treatment).

3. Dose selection rationale

A rationale for the selection of doses was not provided. Judging by the nature and severity of the observed responses, the limit dose of 1000 mg/kg/day was appropriate as the upper dose. The failure to identify a dermal NOAEL suggests that the low dose was not low enough (or, a different application method should have been used; see discussion section).

4. Test substance preparation and analysis

The test substance was applied undiluted using 3 or 5 mL syringes in a volume calculated using a specific gravity of 1.07 and each animal's most recent body weight.

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Results –

Homogeneity analysis – Homogeneity analysis was not required since Etofenprox was applied in its neat form.

Stability analysis – The report states that a sample of Etofenprox was tested just prior to the in life phase of the study (October 20, 1999). Results from this analysis were not provided.

Concentration analysis – Concentration analysis was not required since Etofenprox was applied in its neat form.

Homogeneity and concentration analyses were not required. Stability of the test material was not addressed in the study report.

5. Dose application

Rabbits were acclimated to flexible plastic collars during the 6-day acclimation period prior to the first dose application. The back of each rabbit (~10% of total body surface area) was clipped free of hair the day prior to the first treatment day and as necessary thereafter. The test material was incubated overnight in a 101°F water bath to keep it in a liquid state because it tended to solidify at room temperature (101°F was below the normal rabbit body temperature but was above the melting point of Etofenprox of 97.3-100.4°F). The liquid material was applied directly to the skin using 3 or 5 mL syringes over ~10% of the total body surface area for high-dose animals, and over "as much of the treatment area as possible" at the lower doses. The test substance was held in place with an 8-ply porous gauze. The gauze patch was secured with nonirritating tape (Johnson and Johnson Dermiform) and covered with a layer of Vetwrap™ (not defined) that was also secured with nonirritating tape. The animals were fitted with Elizabethan collars (not described) during the exposure period. After 6 hours, the collars and dressings were removed and the treated sites wiped with a paper towel moistened with dishwashing liquid followed by a paper towel moistened with clean tap water. Animals were treated daily for 28 days. Control animals were treated the same way, except water was substituted for the test material in a volume equal to that of the highest dose group.

6. Statistics

Statistical analysis to compare the treated and control groups was performed on body weight, food consumption, hematology, clinical chemistry, and organ weight data; evidence for a dose-related trend was evaluated for the body weight and food consumption. The normality of the data and its variance homogeneity (1% level of significance) were tested by Bartlett's test. Nonparametric procedures (Dunn's summed-rank test; unpaired t-test with Welch's correction for recovery group animals) were used when Bartlett's test was significant. When Bartlett's test was not significant, parametric procedures were used (Dunnett's test). For both the parametric and nonparametric analyses, "significance was reported at the two-sided experiment-

wise error rates of 1% and 5%." The statistical significance of differences from controls for the incidences of histopathological changes were calculated by the reviewer using the Fischer exact test at the 5% and 1% levels of probability.

C. METHODS

1. Observations

Animals were examined for mortality and signs of toxicity twice daily. Comprehensive clinical examinations were performed prior to treatment and weekly during the treatment period, after bandage removal. The skin was examined for signs of irritation just prior to each daily application, at pretest, and the morning following the last application.

2. Body weight

Animals were weighed on the day prior to the initial dosing and on days 7, 14, 21, and 28 of the study. The recovery group animals were additionally weighed on days 35 and 42. The fasted weight was obtained at termination for all rabbits.

3. Food consumption

Individual food consumption was recorded for 6 days each week during the study and during the post-treatment recovery period. Exceptions were the baseline period, which was 4 days, and during treatment week 3 only a 3-day food consumption was conducted for males (inadvertent omission).

4. Food efficiency

Food efficiency was not calculated by the study authors.

5. Ophthalmoscopic examination

Ophthalmoscopic examination was performed prior to the first treatment, just prior to the completion of the 28-day treatment period, and the recovery group animals were additionally examined just prior to day 42. The examination was performed using an indirect ophthalmoscope following topical mydriasis.

6. Blood samples were obtained from the dorsal aorta or the inferior vena cava following fasting for approximately 16-24 hours. Blood was collected at terminal necropsy from all animals (day 29 for main group and day 43 for recovery group). The blood of one control and one high-dose male clotted, precluding their hematology determinations. The CHECKED (X) parameters were examined.

a. Hematology

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X		X	
x	Hematocrit (HCT)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		
	(Kaolin-cephalin time)		
	Erythrocyte morphology		

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium	x	Albumin
x	Chloride	x	Blood creatinine
	Magnesium	x	Blood urea nitrogen
x	Phosphorus	x	Total Cholesterol
x	Potassium	x	Globulins (calculated)
x	Sodium	x	Albumin/globulin ratio (calculated)
		x	Glucose
	ENZYMES	x	Total bilirubin
	Alkaline phosphatase (ALK)	x	Total serum protein (TP)
	Cholinesterase(ChE)		Triglycerides
x	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		
x	Serum alanine amino-transferase (also SGPT)		
x	Serum aspartate amino-transferase(also SGOT)		
x	Gamma glutamyl transferase(GGT)		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase		

7. Urinalysis

Urinalysis was not required and was not performed.

8. Sacrifice and pathology

On day 29 (main study) or on day 43 (recovery group), rabbits that had been fasted 16-24 hours were sacrificed with an intravenous injection of Sleepaway® followed by exsanguination. The CHECKED (X) tissues were preserved in formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined in all control and high-dose animals. All gross lesions and the treated skin were evaluated in all groups of animals. Additionally examined for the control and high-dose groups were nontreated skin (shaved adjacent area not treated with the test material) and "other" skin (unshaven skin sampled along with the mammary gland). The (*) organs, in addition, were weighed.

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X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	x	Aorta	x*	Brain
x	Salivary glands	x*	Heart	x	Periph. nerve
x	Esophagus	x	Bone marrow	x	Spinal cord
x	Stomach	x	Lymph nodes	x*	Pituitary
x	Duodenum	x*	Spleen	x	Eyes (optic n.)
x	Jejunum	x*	Thymus		
x	Ileum				GLANDULAR
x	Cecum		UROGENITAL	x*	Adrenal gland
x	Colon	x*	Kidneys		Lacrimal gland
x	Rectum	x	Urinary bladder	x	Mammary gland
x*	Liver	x*	Testes	x	Parathyroids
x	Gall bladder	x*	Epididymides	x*	Thyroids
x	Pancreas	x	Prostate		
		x	Seminal vesicle		OTHER
	RESPIRATORY	x*	Ovaries	x	Bone
x	Trachea	x*	Uterus	x	Skeletal muscle
x	Lung	x	Vagina	x	Skin (treated and untreated)
x	Nose	x	Cervix	x	All gross lesions and masses
x	Pharynx				
x	Larynx				

II. RESULTS

A. OBSERVATIONS

No animals died on study. A low incidence (≤2/10 for each sign per treatment group) of clinical signs occurred, including sores on ears, neck, head, nose, and abdomen. These were not compound-induced and were likely caused by the treatment method. Treatment-related dermal effects were seen in males and females, and were generally greater in females, as shown in Table 2. The incidences of the observations were not statistically analyzed. Both sexes had very slight erythema, with a low incidence found in the controls and a higher incidence found in the treated animals. A few Etofenprox-treated rabbits (more females than males) had moderate or severe erythema during weeks 1 or 2. The incidence of scabbing, crusting, desquamation, and exfoliation was increased in both sexes at all test doses. Mid- and high-dose rabbits additionally had minimal edema and females had dermal fissuring and thickening. The peak incidences of the dermal observations occurred during week 2 or 3 in both sexes, and were generally greater in females than males. Although the incidence of the dermal observations was greater in the treated than in control groups, there was not a clear linear dose-response among the treated groups (with the exception of slight erythema during week 1 in both sexes). Use of undiluted liquid test material, the dosing procedure (i.e., bandaging, etc.), and the close spacing of the test doses may have contributed to the lack of a linear dose-response.

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TABLE 2. Incidence of daily dermal observations in rabbits treated with Etofenprox for 28 days.

Study Week (no. rabbits)	Dose (mg/kg/day)							
	0		400		650		1000	
	Erythema scores:[1] 0/1/2/3	Other observ.[2]	Erythema scores: 0/1/2/3	Other observ.	Erythema scores: 0/1/2/3	Other observ.	Erythema scores: 0/1/2/3	Other observ.
Males								
1 (20) 1 (10)	137/3/0/0 –	0 –	– 55/14/1/0	– 0	– 51/19/0/0	– 0	82/55/3/0 –	1C –
2 (10)	138/2/0/0	0	56/14/0/0	9A	57/11/2/0	2A, 6B	128/12/0/0	2A, 3B
3 (10)	140/0/0/0	0	60/10/0/0	26A, 14B	56/14/0/0	4A, 22B	133/7/0/0	11A, 45B
4 (20) 4 (10)	140/0/0/0 –	0 –	– 63/7/0/0	– 16A,10B	– 63/7/0/0	– 3B	128/12/0/0 –	15B –
Females								
1 (20) 1 (10)	126/9/3/2 –	0 –	– 30/34/4/2	– 0	– 26/36/8/0	– 2B, 4C, 2D	45/87/8/0 –	10B, 3C –
2 (10)	140/0/0/0	0	47/23/0/0	16A, 25B	56/13/1/0	3A, 9B, 3C, 7D	109/30/1/0	32A, 38B, 2C, 3D
3 (10)	140/0/0/0	0	55/15/0/0	16A, 17B	65/5/0/0	11A, 22B	131/9/0/0	50A, 61B
4 (20) 4 (10)	139/1/0/0 –	7A, 12B –	– 63/7/0/0	– 2A, 2B	– 61/9/0/0	– 4B	118/22/0/0 –	15A, 13B, 3E –

Data from pp. 30 and 31, MRID 45186501.
[1]Incidence per total observations over 1 week (140 for control and high-dose; 70 for low- and mid-dose), using the key: 0= no erythema; 1= very slight erythema; 2=well-defined erythema; 3=moderate to severe erythema
[2]Number of observations per week x observation type, using the key:
A = Scabbing or crusting D = Fissuring either with or without bleeding
B = Desquamation/exfoliation E = Thickening C = Edema (grade 1)

B. BODY WEIGHT

Body weights of the control and treated groups were comparable throughout the study, including during the 2-week recovery period.

C. FOOD CONSUMPTION AND EFFICIENCY

1. Food consumption

Low-dose males had 11% lower food consumption ($p<0.05$) than controls during week 2. This decrease is considered incidental to treatment in light of its transitory nature and the lack of dose-response. No other effects were noted.

2. Food efficiency

Food efficiency was not calculated but no difference from controls is expected, based on the lack of effect on animal body weight gain and food consumption.

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D. OPHTHALMOSCOPIC EXAMINATION

Ophthalmoscopic examination yielded no toxic findings at study termination or after the recovery period.

E. BLOOD WORK

No treatment-related hematology or clinical chemistry effects were found. The statistically significant differences from controls ($p < 0.05$) found for several parameters in high-dose males were not dose-related and were of too small a magnitude to be biologically significant. These alterations included a 4-5% decrease in prothrombin time (seen for low dose males also); a 16% decrease in the lymphocyte count; a decrease from 0.7 to 0.0% in the eosinophil count; and decreases of 2% and 8%, respectively, for serum calcium and inorganic phosphate.

F. URINALYSIS

Urinalysis was not required and was not performed.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

No treatment-related effects were noted on organ weights: both the absolute and relative (to body weight) organ weights were comparable to the controls.

2. Gross pathology

No treatment-related gross lesions were found. The incidences of all lesions were not statistically significantly different from the controls.

3. Microscopic pathology

Treatment-related histopathological changes were found in the skin of both sexes, as shown in Table 3. Lesion severities are shown in the table in parentheses for the terminal (i.e. day 29) sacrifice; the lesions after the 2-week recovery period were all of minimal severity (i.e., 1.0) but the group severity scores were not calculated. At terminal sacrifice, Etofenprox-treated males had dose-related increases in the incidences of chronic diffuse dermal inflammation and diffuse heterophil dermal infiltration ($p<0.01$ at 1000 mg/kg/day), as well as diffuse epidermal hyperplasia ($p<0.01$ for all doses). The lesion severity was minimal or slight/mild. The incidence of these lesions after the 2-week recovery period was substantially lower. The incidence of dermal inflammation and epidermal hyperplasia were, however, also increased ($p<0.05$ or 0.01 at 1000 mg/kg/day) in nontreated skin of the high-dose males (i.e. shaved region adjacent to the test site), although at incidences lower than for the treated skin. The latter finding may be due to extension of the test material from the treated to the untreated skin or to the dosing procedure (i.e. bandaging).

Etofenprox-treated females had an increased incidence of diffuse epidermal hyperplasia (10/10; $p<0.05$) at 1000 mg/kg/day, the incidence decreased greatly after the 2-week recovery period (1/10). Although the incidence of this lesion did not differ greatly among the treated groups, its severity appeared to increase with dose: the severity in one high-dose female was moderate but was either minimal or slight/mild for all other animals. Epidermal hyperplasia also occurred at lower incidences in nontreated skin of control and high-dose females, again, possibly due to extension of the test material and/or to the dosing procedure. Etofenprox-treated females also had a non-significant elevation in the incidence of chronic focal dermal inflammation, which did not resolve with time. It is unclear whether this lesion is compound-induced since its severity was the same for all dose groups (minimal) and a comparable incidence was seen in nontreated skin of control and high-dose females.

TABLE 3. Incidence and severity of histopathologic lesions in rabbits treated with Etofenprox for 28 days and sacrificed immediately [or after a 14-day recovery period].[1]

Organ: Lesion	Dose (mg/kg/day)			
	0	400	650	1000
Males				
Skin, nontreated, 28-day [42-day] sacrifice:[2]				
Dermis, diffuse heterophil infiltrate	0/10 [NR]	n/a	n/a	1/10 (0.1) [NR]
Dermis, chronic diffuse inflammation	0/10 [NR]	n/a	n/a	4/10* (0.5)[NR]
Epidermis, diffuse hyperplasia	0/10 [0/10]	n/a	n/a	6/10** (0.9) [1/10]
Skin, treated, 28-day [42-day] sacrifice:				
Dermis, diffuse heterophil infiltrate	0/10 [0/10]	0/10 [n/a]	2/9 (0.2) [n/a]	7/10** (0.9) [0/10]
Dermis, chronic diffuse inflammation	0/10 [0/10]	0/10 [n/a]	2/9 (0.3) [n/a]	8/10** (1.2) [0/10]
Epidermis, diffuse hyperplasia	0/10 [1/10]	6/10** (0.6) [n/a]	9/9**(1.4) [n/a]	9/10** (1.4) [1/10]
Females				
Skin, nontreated, 28-day [42-day] sacrifice:[2]				
Dermis, chronic focal inflammation	6/10 (0.6) [5/10]	n/a	n/a	4/10 (0.4) [9/10]
Epidermis, diffuse hyperplasia	3/10 (0.6) [0/10]	n/a	n/a	3/10 (0.4) [0/10]
Skin, treated, 28-day [42-day] sacrifice:				
Dermis, chronic focal inflammation	3/10 (0.3) [4/10]	7/10 (0.7) [n/a]	5/10 (0.5) [n/a]	6/10 (0.6) [8/10]
Epidermis, diffuse hyperplasia	5/10 (0.7) [5/10]	9/10 (1.3) [n/a]	8/10 (1.0) [n/a]	10/10* (1.5) [1/10]

Data from pp. 254-276 and 279-310, MRID 45186501.
NR = This specific lesion was not reported.
n/a = not analyzed
[1]The numbers in brackets are the results for the recovery animals. Numbers in parentheses are the severity ratings, calculated from responses including 1=minimal, 2=slight/mild, 3=moderate. The severity of all lesions following the 2-week recovery period was minimal, but the group severity scores were not calculated.
[2]Nontreated skin was shaved skin adjacent to the test site. Lesions found in nontreated skin may be due to extension of the test material from the test site or to the bandaging procedure.

III. DISCUSSION

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A. None of the rabbits died on study or had evidence of systemic toxicity: clinical signs, body

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weights, hematology, clinical chemistry, organ weights, and the incidence of gross lesions were comparable to controls. Both male and female rabbits, however, had treatment-related dermal irritation (not statistically analyzed) and histopathological skin changes. Dermal observations and lesions were also seen in a few control animals at the "test" site, as well as in a few control and treated animals in "untreated" skin, i.e. shaved skin adjacent to the test site. The findings in control and untreated skin are most likely due to spillover of the test material from the test site and/or to the dosing procedure (i.e bandaging, etc.).

The incidences of erythema, scabbing, crusting, desquamation, and exfoliation were increased in both sexes at all test doses. The erythema was generally minimal or slight but was moderate or severe in some animals during weeks 1 or 2. Mid- and high-dose rabbits additionally had minimal edema and females had dermal fissuring and thickening. Observation incidences were generally greater in females than males and peaked during weeks 2 or 3. Although the incidences of these observations were elevated compared to controls, and more severe effects (edema, fissuring, thickening) were seen at higher doses, the responses were not generally proportional to dose among the treated groups.

Treatment-related histopathological lesions included diffuse epidermal hyperplasia in both sexes ($p<0.01$ for all treated male groups and $p<0.05$ for high-dose females) and chronic diffuse dermal inflammation and diffuse heterophil dermal infiltration in males ($p<0.01$ at 1000 mg/kg/day). A dose-response was seen in males, but the dose-relationship was less clear in females. The incidence and severity of these lesions after the 2-week recovery period was substantially lower in both sexes, indicating that the skin lesions were resolving.

The lack of a clear linear correlation between test dose and resulting dermal effects (skin observations in both sexes; microscopic changes in females) made interpretation of the study results, including defining the study NOAEL, difficult. For example, the incidence of diffuse epidermal hyperplasia in high-dose females was significantly greater than in controls (5/10 vs. 10/10, $p<0.05$), yet the incidence in the low-dose group was 9/10 (NS). The study methodology likely contributed to the inconsistencies: use of variable volumes of undiluted liquid test material, the dosing procedure (i.e., bandaging, etc.), and the close spacing of the test dose levels.

The systemic NOAEL is the limit dose of 1000 mg/kg/day; a systemic LOAEL was not identified. The dermal LOAEL is 400 mg/kg/day, the lowest dose tested, based on an increased incidence of dermal observations (scabbing, crusting, desquamation, exfoliation) and histopathological changes (diffuse epidermal hyperplasia) in both sexes of rabbits. A dermal NOAEL was not identified.

This study does satisfy the guideline requirements for a repeated-dose dermal study [OPPTS 870.3200 (§82-2)] in rabbits.

B. STUDY DEFICIENCIES

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A dermal NOAEL was not established and the test material was not applied in a constant

volume. The latter may have contributed to the lack of a linear response for dermal effects among the treated groups. A minor deficiency is failure to report the stability of the test substance.