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2-20-92

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

009294

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

FEB 20 1992

MEMORANDUM

SUBJECT: DEET: Review of a 90-day dermal toxicity study in micropigs[R]

Caswell No. 346 **HED Project No.** 1-2462
MRID No. 419874-01 **EPA ID No.** 080301

TO: Jane Mitchell, PM Team (70)
Special Review and Re-registration Division (H7508C)

FROM: Whang Phang, Ph.D. 2/6/92
Pharmacologist
HFAS/Tox. Branch II/ HED (H7509C)

THROUGH: James Rowe, Ph.D. James Rowe 2/7/92
Section Head, Section III
and
Marcia van Gemert, Ph.D. 2/7/92
Branch Chief
HFAS/Tox. Branch II/ HED (H7509C)

Toxicology Branch II has been requested to review a 90-day dermal toxicity study in micropigs[R] with DEET. The review of this study is completed, and the conclusions is the following:

The purpose of this study was to determine if a renal lesion related to an increase in hyaline droplet formations and presence of $\alpha_{2\mu}$-globulin in the kidney tubules observed in male rats of previously conducted 90-day oral and dermal toxicity studies (MRID No's. 402417-02 & 402417-03, respectively) in rats would occur in micropigs[R].

Groups of micropigs[R] were dermally applied DEET at dose levels of 0 (water), 100, 300, and 1000 mg/kg b.w. for 13 weeks. The results indicated that DEET did not produce any mortality and changes in body weights, hematological and biochemical parameters, gross pathology, and organ weights. In the skin application sites, gross pathology showed that the DEET treated animals had an increase in the incidence of desquamation and/or dry skin; histopathology showed an increase in the incidence of

acanthosis and/or hyperkeratosis in the skin application sites of DEET treated animals. The report concluded that if the test article exposure was removed, these findings would be totally reversible with no lasting dermal effects. It is quite possible that the dermal effects produced by DEET treatment are reversible.

Under the conditions of this study, DEET did not produce any renal lesions in micropigs[R]. It also did not cause any renal lesions in hamsters which received DEET in dietary concentrations up to 15,000 ppm (MRID No. 413441-01). These findings indicate that the renal lesion produced by DEET was unique to male rats.

This study meets the data requirement for a non-rodent 90-day toxicity study (82-1), and it is classified as **minimum.**

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Reviewer: Whang Phang, Ph.D. 2/6/92
HFAS/Tox. Branch II (H7509C)

Secondary Reviewer: James Rowe, Ph.D., Section Head 2/6/92
HFAS/Tox. Branch II (H7509C)

DATA EVALUATION REPORT

Study Type: 90-day dermal toxicity study in micropigs

Chemical: DEET (N, N-diethyl-m-toluamide)

Caswell No. 346	**HED Proj. No.** 1-2462
MRID No. 419874-01	**EPA Case No.** 819244
EPA ID No. 080301	**Submission No.** S402919

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association

Testing Facility: International Research and Development Corp. Mattawan, Michigan

Citation: Goldenthal, E. I. (1991) Evaluation of DEET in a 90-day subchronic dermal toxicity study in micropigs. Study conducted by International Research and Development, Corp.; Study No. 555-018. Submitted to EPA by DEET Joint Venture/Chemical Specialties Manufacturers Association. MRID No. 419874-01.

Conclusion: The purpose of this study was to determine if a renal lesion related to an increase in hyaline droplet formations and presence of $\alpha_{2\mu}$-globulin in the kidney tubules observed in male rats of previously conducted 90-day oral and dermal toxicity studies (MRID No's. 402417-02 & 402417-03, respectively) in rats would occur in micropigs^R.

Groups of micropigs^R were dermally applied DEET at dose levels of 0 (water), 100, 300, and 1000 mg/kg b.w. for 13 weeks. The results indicated that DEET did not produce any mortality and changes in body weights, hematological and biochemical parameters, gross pathology, and organ weights. In the skin application sites, gross pathology showed that the DEET treated animals had an increase in the incidence of desquamation and/or dry skin; histopathology showed an increase in the incidence of acanthosis and/or hyperkeratosis in the skin application sites of DEET treated animals. The report concluded that if the test article exposure was removed, these findings would be totally reversible with no lasting dermal effects. It is quite possible that the dermal effects produced by DEET treatment are reversible.

Under the conditions of this study, DEET did not produce any renal lesions in micropigs^R. It also did not cause any renal lesions in hamsters which received DEET in dietary concentrations up to 15,000 ppm (MRID No. 413441-01). These findings indicate that the renal

lesion produced by DEET was unique to male rats.

This study meets the data requirement for a non-rodent 90-day toxicity study (82-1), and it is classified as **minimum.**

Methods and Materials

Test Article: DEET (N,N-diethyltoluamide); 98.3% purity. The test article was a mixture of equal parts of 4 representative production runs supplied by McLaughlin Gormley King Co. (Lot No. 0.10111), Miles Laboratories (Lot No. 90003), Virginia Chemical Co. (Lot No. 85227), and Morflex Chemical Co. (Lot No. N61214-S9401). The test chemical was described as a pale yellow liquid.

Test Animals: Micropigs® (20/sex) were obtained from Charles River Laboratories, Windham, Maine. These animals were approximately 3 months old. These pigs were acclimated to the laboratory environment for 32 days, and they were given a detailed physical examination to determine their general health.

Study Design

From the 20 male and 20 female animals, 16 males (weighing 18.8-24.7 kg) and 16 females (weighing 14.3-24.1 kg) were selected for the study. They were randomly assigned to the following test groups:

Dose group mg/kg	Number of micropig®/dose group Males	Females
0	4	4
100	4	4
300	4	4
1000*	4	4

*: 1000 mg/kg was maximum dose which could be applied without significant runoff.

The animals were offered approximately 500 gm of diet (Agway PROLAB® Mini-pig diet, Troy. Illinois) twice daily, and water was available ad lib.

Approximately 24 hrs prior to dosing, the dorsal area of each animal was shaven. This procedure was repeated on the last day of each study week or as needed to prevent matting of the hair. The test article was applied uniformly over the shaven area with a glass rod daily on the first 5 days of each week. The control animals were handled in a similar manner as the treated animals except tap water was applies at a volume of 1 ml/kg. As the animals gained weight beginning on study day 57. The application

was expanded from the dorsal surface to the dorsal and lateral surface for the controls and the 1000 mg/kg animals. The skin application was not covered.

The animals were observed twice daily for toxicity and mortality. The skin application site was observed for any signs of irritation and scored according to the Draize method (Appendix A).

The individual animal weights were measured at pretest period and weekly during the study. The individual food consumptions were also measured daily.

Prior to the initiation of the study, a serum sample was collected from each animal by the jugular vein while the animal was anesthetized. A blood sample was also collected from each animal at sacrifice. The hematological and biochemical analyses were conducted on the blood samples of each animal. The parameters examined are listed as follows:

Hematological parameters	
leukocyte counts	erythrocyte counts
hemoglobin	hematocrit
mean corp. volume (MCV)	mean corpus. hemo. (MCH)
mean corp. hemo. con. (MCHC)	platelet counts
differential leukocyte count	reticulocytes

Biochemical parameters	
sodium	potassium
chloride	calcium
inorganic phosphorus	total bilirubin
aspartate aminotransferase (AST)	alanine aminotransferase (ALT)
urine nitrogen	creatinine
total protein	albumin
globulin	glucose

All test animals received a gross examination. At terminal sacrifice, the weights of the following organs were measured:

adrenals	liver
brain	ovaries
kidneys	testis

Histopathology was conducted on the representative samples of the following organ and tissues:

adrenals	pancreas
aorta	parathyroid
bone (femur)	pituitary
bone marrow (sternum)	prostate and seminal vesicle
brain	rectum

cecum	salivary gland
colon	sciatic nerve
duodenum	skeletal muscle
esophagus	skin
eyes	spinal cord
heart	spleen
ileum	stomach
jejunum	testis with epididymis
kidneys	thymic region
liver	thyroid
lung	trachea
lymph nodes	urinary bladder
mammary	uterus
ovary	gross lesions

The following statistical methods were applied:

- analysis of variance (one-way classification)
- Bartlett's test
- appropriate t-test as described by Steel and Torrie and Ostle
- Dunnett's multiple comparison tables were used to determine the significant differences
- Conover and Iman method was used for total bilirubin values

Results

Clinical observation: Compound-related clinical signs were not found in treated animals.

Mortality: All test animals survived to the scheduled sacrifice.

Dermal toxicity: The data on possible dermal irritation have been excerpted from the report and are presented in Table 1. The incidence of desquamation at the application sites in the treated animals was increased relative to that of the controls. In the control group, only one animal showed signs of slight desquamation beginning on week 12 of the study; in contrast, one or more animals showed slight desquamation on week 4 and persisted until the termination of the study. In addition, beginning at week 8, the severity of desquamation was increased in 300 and 1000 mg/kg groups. The erythema was seen in one male of the 100 mg/kg group at week 5, but it was cleared by week 6. One of the males of 300 mg/kg group also showed erythema from weeks 5 to 7.

Body weights: The body weights of treated and control animals were comparable at various measuring intervals (Table 2).

Clinical biochemistry: The biochemical parameters measured showed no compound-related or significant changes between the

treated and control animals.

Hematology: The hematological findings were comparable between the control and treated animals.

Gross pathology: The macroscopic findings were essentially comparable between the treated and the control animals. However, the report indicated that there was a treatment-related finding of dry skin (mild) on the apllication sites. According to the individual animal data, all compound-treated males and females showed signs of dry skin (mild); all females and 1 male of the control group also had dry skin. This could not be considered as an compound-related effect, but it was a result of the process of treatment. It is odd that the daily observation did not identify any incidence of dry skin in any of the test-article-treated animals.

Organ weights: No significant changes in organ were seen in treated animals relative to those of the controls (Table 3a & 3b).

Histopathology: Histopathological findings were comparable between the treated animals and the controls except for the skin application sites. In the skin application sites of the treated animals, the incidence of acanthosis and hyperkeratosis was increased in certain groups of the treated animals relative to the controls (Table 4). The increase in the incidence of acanthosis was found in males and females of 300 and 1000 mg/kg groups, and hyperkeratosis was found in essentially all the compound-treated animals.

Discussion

Groups of micropigs[2] were dermally exposured to DEET at dose levels of 0 (water), 100, 300, and 1000 mg/kg b.w. for 13 weeks. The results indicated that DEET did not produce any mortality or changes in body weights, hematological and biochemical parameters, gross pathology, and organ weights. In the skin application sites, gross pathology showed that the DEET treated animals had an increase in the incidence of desquamation and/or dry skin; histopathology showed an increase in the incidence of acanthosis and/or hyperkeratosis in the skin application sites of DEET treated animals. The report concluded that if the test article exposure was removed, these findings would be totally reversible with no lasting dermal effects. It is quite possible that the dermal effects produced by DEET treatment are reversible.

Under the conditions of this study, DEET did no produce any renal lesions in micropigs[2].

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TABLE 1†

0 mg/kg (Control)

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Edema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Desquamation														
None	8	8	8	8	8	8	8	8	8	8	8	7	7	7
Slight												1	1	1
Dry Skin														
No (None)	8	8	8	8	8	8	8	8	8	7	7	3	3	3
Yes (Present)										1	1	5	5	5
Abrasion														
No (None)	8	8	8	8	8	8	8	7	7	8	8	7	7	7
Yes (Present)								1	1			1	1	1
Laceration														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Scabbed Area														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Number of Animals	8	8	8	8	8	8	8	8	8	8	8	8	8	8

†: TABLE EXCERPTED FROM THE REPORT (MRID No. 419874-01)

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Table 1. (Cont.)
100 mg/kg

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	8	8	8	8	6	8	8	8	8	8	8	8	8	8
Slight					2									
Edema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Desquamation														
None	8	8	8	7	7	7	5	3	3	2	1			
Slight				1	1	1	3	5	5	5	3	4*	2	2
Moderate										1	4	5*	6	6
Dry Skin														
No (None)	8	4	4											
Yes (Present)		4	4	8	8	8	3	8	8	8	8	8	8	8
Abrasion														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Laceration														
No (None)	8	8	8	8	8	7	7	7	8	8	8	8	8	8
Yes (Present)						1	1	1						
Scabbed Area														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Number of Animals	8	8	8	8	8	8	8	8	8	8	8	8	8	8

*One animal observed with grades of slight and moderate in the same week

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Table 1. (Cont.)
300 mg/kg

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	8	8	8	8	7	7	8*	8	8	8	8	8	8	8
Slight					1	1	1*							
Edema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Desquamation														
None	8	8	8	1	1									
Slight				7	7	8	8	7	7	4	2	1	1	1
Moderate								1	1	4	6	7	7	7
Dry Skin														
No (None)	8													
Yes (Present)		8	8	8	8	8	8	8	8	8	8	8	8	8
Abrasion														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Laceration														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Scabbed Area														
No (None)	8	8	8	8	8	8	8	8	7	8	8	8	8	8
Yes (Present)									1					
Number of Animals	8	8	8	8	8	8	8	8	8	8	8	8	8	8

*One animal observed with grades of none and slight in the same week

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TABLE 1 (Cont.)
1,000 mg/kg

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Edema														
None	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Desquamation														
None	8	3	8	6*	5	5	4	1	1					
Slight				4*	3	3	4	6	6	7	6	6	6	5
Moderate								1	1	1	2	2	2	3
Dry Skin														
No (None)	8	2	2											
Yes (Present)		6	6	8	8	8	8	8	8	8	8	8	8	8
Abrasion														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Laceration														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Scabbed Area														
No (None)	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Number of Animals	8	8	8	8	8	8	8	8	8	8	8	8	8	8

*Two animals observed with grades of slight and normal in the same week

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TABLE 2†

Males: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1,000 MG/KG MEAN	S.D.	N
ody Weight	Pretest	21.3	2.54	4	21.6	1.69	4	21.4	1.76	4	21.7	1.35	4
ilograms	1	22.0	2.39	4	22.2	1.95	4	22.0	1.64	4	22.8	1.44	4
	2	24.2	2.08	4	24.4	2.07	4	24.5	1.49	4	24.6	1.41	4
	3	25.1	2.22	4	25.6	1.98	4	26.1	1.51	4	26.2	1.61	4
	4	26.3	2.37	4	27.0	2.01	4	27.7	1.22	4	27.4	1.93	4
	5	27.5	2.78	4	27.8	1.99	4	28.8	0.94	4	28.7	1.86	4
	6	28.9	2.92	4	29.2	1.86	4	30.2	0.93	4	30.0	1.98	4
	7	29.4	2.26	4	29.7	1.91	4	31.0	0.70	4	30.6	1.57	4
	8	31.9	2.15	4	31.9	1.93	4	33.5	0.49	4	32.5	1.10	4
	9	32.2	2.29	4	32.4	2.21	4	33.5	0.78	4	33.8	1.51	4
	10	33.9	1.96	4	34.5	1.87	4	35.1	0.78	4	35.1	1.78	4
	11	34.9	1.83	4	34.4	2.29	4	35.9	0.59	4	36.2	1.84	4
	12	36.0	1.57	4	35.7	2.30	4	37.1	0.67	4	36.9	1.62	4

55-018

Females: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1,000 MG/KG MEAN	S.D.	N
ody Weight	Pretest	18.4	1.98	4	19.2	3.34	4	17.2	1.30	4	17.8	2.84	4
ilograms	1	19.5	1.74	4	19.7	2.78	4	18.7	1.42	4	18.8	2.68	4
	2	21.4	1.88	4	21.5	2.88	4	20.3	1.47	4	20.7	2.57	4
	3	22.2	2.11	4	22.5	2.82	4	21.7	1.15	4	22.2	2.78	4
	4	23.7	1.41	4	23.8	2.96	4	22.7	1.14	4	23.4	2.75	4
	5	24.7	1.59	4	25.0	3.15	4	23.9	1.36	4	24.5	2.40	4
	6	26.1	1.45	4	26.1	3.16	4	24.9	1.31	4	26.0	2.33	4
	7	27.0	1.42	4	27.0	3.05	4	26.0	1.08	4	26.8	2.32	4
	8	29.0	1.58	4	29.1	3.27	4	27.2	0.96	4	28.9	2.28	4
	9	29.5	1.40	4	29.5	3.46	4	28.3	1.09	4	29.8	2.26	4
	10	31.0	1.35	4	31.3	3.50	4	30.0	1.00	4	31.3	1.89	4
	11	31.2	1.17	4	31.8	3.24	4	30.8	1.28	4	31.9	2.39	4
	12	32.3	1.00	4	32.5	3.65	4	31.2	1.16	4	32.4	1.89	4

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S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

†: TABLE EXCERPTED FROM THE REPORT (MRID No. 419874-01)

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TABLE 3a+

Males: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	0 mg/kg (Control) MEAN	S.D.	N	100 mg/kg MEAN	S.D.	N	300 mg/kg MEAN	S.D.	N	1,000 mg/kg MEAN	S.D.	N
Body Weight kg	36.03	1.513	4	35.63	2.257	4	37.05	0.854	4	37.20	1.349	4
Brain g	81.74	2.716	4	82.13	3.732	4	87.13	4.391	4	87.39	6.772	4
Brain/Body Weight %	0.23	0.015	4	0.23	0.024	4	0.24	0.007	4	0.24	0.019	4
Adrenal g	2.71	0.154	4	2.92	0.638	4	2.79	0.416	4	3.28	0.647	3
Adrenal/Body Weight %x10	0.08	0.007	4	0.08	0.021	4	0.08	0.010	4	0.09	0.012	3
Adrenal/Brain Weight %x10	33.16	1.679	4	35.54	7.955	4	31.88	3.381	4	37.90	8.683	3
Kidney g	111.03	13.070	4	120.16	35.373	4	118.05	15.142	4	147.30	11.215	4
Kidney/Body Weight %	0.31	0.027	4	0.33	0.079	4	0.32	0.045	4	0.40	0.021	4
Kidney/Brain Weight %	136.02	17.734	4	146.95	46.598	4	136.10	21.642	4	169.34	18.281	4
Liver g	657.08	42.284	4	671.32	108.783	4	703.00	51.619	4	777.53	108.057	4
Liver/Body Weight %	1.82	0.071	4	1.88	0.208	4	1.90	0.165	4	2.09	0.238	4
Liver/Brain Weight %	805.78	78.666	4	820.15	152.133	4	809.82	90.490	4	889.89	110.130	4
Testis g	114.87	27.229	4	141.29	29.063	4	151.30	25.023	4	154.70	22.501	4
Testis/Body Weight %	0.32	0.061	4	0.40	0.066	4	0.41	0.075	4	0.42	0.066	4
Testis/Brain Weight %	141.22	37.563	4	172.64	38.987	4	174.72	35.675	4	177.11	23.763	4

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S.D. - Standard Deviation
N - Number of Animals
*No statistical significance observed

+: DATA EXCERPTED FROM THE REPORT (MRID No. 419874-01)

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TABLE 36†

TABLE 7. Cont. Females: Summary of Organ Weight Values - Terminal Sacrifice*

Parameters Measured	0 mg/kg (Control) MEAN	S.D.	N	100 mg/kg MEAN	S.D.	N	300 mg/kg MEAN	S.D.	N	1,000 mg/kg MEAN	S.D.	N
Body Weight kg	32.20	1.236	4	32.45	3.675	4	31.45	0.881	4	33.15	2.381	4
Brain g	80.52	4.897	4	79.55	6.954	4	77.42	1.689	4	79.58	5.798	4
Brain/Body Weight %	0.25	0.007	4	0.25	0.022	4	0.25	0.011	4	0.24	0.030	4
Adrenal g	2.91	0.376	4	3.25	0.637	4	3.03	0.267	4	2.93	0.425	4
Adrenal/Body Weight %x10	0.09	0.007	4	0.10	0.024	4	0.10	0.010	4	0.09	0.016	4
Adrenal/Brain Weight %x10	36.08	2.805	4	40.79	6.376	4	39.13	3.260	4	36.65	3.203	4
Kidney g	93.67	7.094	4	98.58	27.924	4	84.24	10.714	4	91.06	5.101	4
Kidney/Body Weight %	0.29	0.030	4	0.30	0.082	4	0.27	0.035	4	0.28	0.019	4
Kidney/Brain Weight %	116.95	14.901	4	122.96	27.888	4	108.83	13.760	4	114.97	12.042	4
Liver g	593.04	35.892	4	580.09	68.016	4	567.98	11.530	4	580.08	21.566	4
Liver/Body Weight %	1.84	0.084	4	1.79	0.138	4	1.81	0.051	4	1.76	0.125	4
Liver/Brain Weight %	736.85	24.569	4	733.73	105.920	4	734.11	28.331	4	731.22	49.372	4
Ovary g	6.83	0.715	4	5.97	2.728	4	5.15	2.623	4	7.15	3.730	4
Ovary/Body Weight %x10	0.21	0.027	4	0.18	0.068	4	0.16	0.084	4	0.22	0.031	4
Ovary/Brain Weight %x10	85.27	13.280	4	73.79	30.972	4	66.39	33.368	4	90.20	11.383	4

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S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

†: DATA EXCERPTED FROM THE REPORT (MRID No. 419874-01)

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TABLE 4+. Microscopic Findings in Skin Application Sites

APPLICATION SITE A								
Group	0 mg/kg		100 mg/kg		300 mg/kg		1,000 mg/kg	
	M	F	M	F	M	F	M	F
Number Examined	4	4	4	4	4	4	4	4
Microscopic Finding:								
Acanthosis,	0	0	0	0	0	0	2	0
- trace	0	0	0	0	0	0	1	0
- mild	0	0	0	0	0	0	1	0
Hyperkeratosis,	0	0	3	0	4	1	4	3
- trace	0	0	3	0	4	1	1	2
- mild	0	0	0	0	0	0	3	1

APPLICATION SITE B/C								
Group	0 mg/kg		100 mg/kg		300 mg/kg		1,000 mg/kg	
	M	F	M	F	M	F	M	F
Number Examined	0	0	3	3	4	4	4	4
Microscopic Finding:								
Acanthosis,	0	0	0	0	3	1	4	3
- trace	0	0	0	0	2	0	2	1
- mild	0	0	0	0	1	1	2	2
Hyperkeratosis,	0	0	3	3	4	4	4	4
- trace	0	0	1	3	0	2	0	0
- mild	0	0	2	0	4	2	4	4

+: DATA EXCERPTED FROM THE REPORT (MRID No. 41987CL-01)

Appendix A+

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SCALE FOR SCORING PRIMARY SKIN IRRITATION*

Erythema and Eschar Formation:	Score
No erythema (none)	0
Very slight erythema (barely perceptible)	1
Well defined erythema (slight)	2
Moderate to severe erythema (mocerate)	3
Marked erythema (beet redness to slight eschar formation [injuries in depth])	4

Edema Formation:	
No edema (none)	0
Very slight edema (barely perceptible)	1
Slight edema (edges or area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Marked edema (raised more than 1 mm and extending beyond area of exposure)	4

*Based on Skin Reaction Code, Draize, J. H., The Appraisal of Chemicals in Foods, Drugs and Cosmetics, Association of Food and Drug Officials of the United States, 1959, page 48.

+: INFORMATION EXCERPTED FROM THE REPORT (MRID No. 419374-01).

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