BS-1139
TXR-7160

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

007160

MAY - 8 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Jeff Kempter, PM # 32
Registration Division H7505C

THRU: M. Ioannou, Ph.D., Acting Head
Rev. Sec. # I
HFASB/HED H7509C

THRU: Marcia Van Gemert, Ph.D.
Chief
HFASB/HED H7509C

FROM: D. Ritter, Toxicologist
Rev. Sec# I
HFASB/HED H7509C

Action Requested: Dowicil 75 [Cis/transl-(3-Chloroallyl)-3,5,7 -triaza -1-azonia-adamantane chloride]; review 13 week rabbit dermal toxicity study.

Registrant: Dow Chemical Co., Midland, MI.

Caswell #: 181.

TOX Project #: 8-0902.

Potomac #: P430.

Dow submitted a 13 week rabbit dermal toxicty study. It was reviewed by Dr. Claire Kruger-McDermott of Dynamac Corporation (Task # 1-45) and her DER is attached.

The study is identified as:

13 Week Dermal Toxicity Study in New Zealand White Rabbits , study # K-27342-61 and K-27342-061. Author R. A. Corley, et al. MIRD # 40650201, June 8, 1988.

Summary:

Male and female New Zealand White rabbits were exposed to daily doses of dermally applied test material at levels of 0, 50, 200 or 1000 mg/kg/day, five days a week for 13 weeks. No treatment-related mortalities or significant clinical or cageside observations were reported for any level tested, except for a dose-dependent increase in dermal irritation, characterized as being moderate to severe. The lesions were associated only with abrasions from clipping; otherwise the intact skin was unaffected. Gross and microscopic histopathology was unremarkable for effect at any level tested. The systemic NOEL was determined to be 1000 mg/kg, the highest level tested. The study is rated CORE Guideline.

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
13-Week Dermal - Rabbit; Dow Chemical Co, Midland, MI # K-27342-61; K-27342-061; 6/8/88	Cis/trans CTAC (90-95% ai)	406502-01	NOEL for Systemic toxicity >1000 mg/kg/day. Dose levels tested in New Zealand white rabbits: 0, 50, 200 and 1000 mg/kg/day		Guideline

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

007160

EPA No.: 68D80056
DYNAMAC No.: 145-A
TASK No.: 1-45A
April 28, 1989

DATA EVALUATION RECORD

DOWICIL 75

13-Week Dermal Toxicity Study in New Zealand White Rabbits

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Ronan J Pinta for

Date: April 27, 1989

007160

EPA No.: 68D80056
DYNAMAC No.: 145-A
TASK No.: 1-45A
April 28, 1989

DATA EVALUATION RECORD

DOWICIL 75

13-Week Dermal Toxicity Study in New Zealand White Rabbits

REVIEWED BY:

Claire Kruger-McDermott, Ph.D.
Principal Reviewer
Dynamac Corporation
Signature: Claire Kruger-McDermott
Date: April 27, 1989

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APPROVED BY:

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David Ritter
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(H-7509C)
Signature: _____
Date: _____

Mike Ioannou, Ph.D.
Acting EPA Section Head,
Section I
Toxicology Branch II (H-7509C)
Signature: M. Ioannou
Date: 5/3/89

007160

DATA EVALUATION RECORD

GUIDELINE §82-4

STUDY TYPE: Thirteen-week dermal toxicity study.

ACCESSION/MRID NUMBER: 406502-01.

TEST MATERIAL: cis/trans-CTAC.

SYNONYM(S): Dowicil 75; cis/trans-1-(3-chloroallyl)-3,5,7-triaza-1-azonia-adamantane chloride.

STUDY NUMBER(S): K-27342-61; K-27342-061.

SPONSOR: Dow Chemical Company, Midland, MI.

TESTING FACILITY: Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI.

TITLE OF REPORT: cis/trans-CTAC: 13-Week Dermal Toxicity Study in New Zealand White Rabbits.

AUTHOR(S): R.A. Corley, F.S. Cieszlak, and G.C. Jersey.

REPORT ISSUED: June 8, 1988.

CONCLUSIONS: Male and female New Zealand White rabbits were exposed to daily dermal applications of 0, 50, 200, or 1000 mg cis/trans-CTAC/kg/day 5 days/week for 13 weeks. There were no treatment-related mortalities or significant effects on clinical observations, body weights, clinical laboratory studies, organ weights, gross pathology, or histopathology. The only treatment-related effect was a dose-dependent increase in dermal irritation, characterized as moderate-to-severe chronic ulcerative dermatitis, which was limited to focal involvement of the epidermis and dermis at the application site. This lesion was correlated with the abrasions from clipping; areas unaffected by clipping were normal on gross and histopathological examinations. The NOEL for systemic toxicity is 1000 mg/kg/day.

Classification: CORE Guideline.

A. MATERIALS:

1. Test Compound: cis/trans-CTAC; description: light cream-colored powder; lot Nos.: GW-21-87-47 and GW-21-87-92; purity: 94.85% and 90.2%, respectively.

2. Test Animals: Species: rabbits; strain: New Zealand White; age: approximately 5 months; weight: males--3503 ± 171 g and females--3763 ± 189 g at study initiation; Source: Hazleton-Dutchland, Inc., Denver, PA.

B. STUDY DESIGN:

1. Animal Assignment: After 7 weeks of acclimation, animals were assigned to the following test groups using a computer-generated randomization procedure:

	Dosage Level (mg/kg/day)	Dose Volume (mL/kg/day)	Main Study (13 weeks) Males	Females
1 Control	0	1.7	10	10
2 Low (LDT)	50	1.7	10	10
3 Mid (MDT)	200	1.7	10	10
4 High (HDT)	1000	1.7	10	10

Lot No. GW-21-87-47 of the test material was used from study initiation to study week 7; lot No. GW-21-87-92 of the test material was used from study weeks 8 to 13.

Rationale for dose selection: The dose levels selected for this 13-week study were based on a probe study in which groups of two rabbits were treated via dermal application at dose levels of 0, 10, 25, 50, 100, or 150 mg/kg/day cis/trans-CTAC (lot No. GW-21-87-47) for 5 consecutive days. When no signs of toxicity were observed following 1 week of treatment, an additional animal treated with 300 mg/kg/day was assigned to the study during week 2. Dose levels during study weeks 3 and 4 were increased to 0, 20, 50, 100, 200, 300, and 600 mg/kg/day and 0, 35, 85, 170, 340, 1000 and 1000 mg/kg/day cis/trans-CTAC, respectively. Surface area of application of the test material was increased from 10% to 15-20% of the total body in order to elicit a response. One high-dose male (1000 mg/kg/day) exhibited moderate erythema, edema, and scabbing during the final 3 study days. No other treatment-related signs of toxicity were exhibited. The maximum dose level (1000 mg/kg/day) was selected as the high-dose level for the 13-week study.

2. Dose Preparations: Topical dosages of 0, 2.9, 11.8, or 60% cis/trans-CTAC at a rate of 1.7 mL/kg/day, which corresponds to 0, 50, 200, or 1000 mg/kg/day, were applied dermally to the test animals. Dose volumes were determined weekly based on body weights. The high-dose level (1000 mg/kg/day) represented the maximal dose level that could be retained on the application site. Aqueous concentrations of test material ranging from 2 to 60% were found to be homogeneous and stable up to 14 days; dosing solutions were reported to have been prepared at least every 2 weeks. Test solutions were analyzed three times during the 13-week study and found to be within 98 to 113% of the target concentration.

3. Preparation of Animal Skin: Prior to dosing and periodically thereafter, as needed, an area approximately 400 cm^2 on the back and sides of each rabbit was clipped free of hair. The test material (or distilled water for control animals) was uniformly spread over the clipped area. An occlusive bandage of absorbent gauze and nonabsorbent cotton held in place with an elastic jacket covered the dosing area. The bandage and jacket were removed 6 hours after application of each dose and the area was then wiped with a water-dampened towel to remove residual test material.

4. Food and Water Consumption: Animals received food, approximately 4 oz. feed/animal/day (Purina Certified Rabbit Chow No. 5322; Ralston Purina Company, St. Louis, MO) and water ad libitum.

5. Statistics: The following procedures were utilized in analyzing the numerical data. Means and standard deviations were reported for differential leukocyte counts and analyses of test solutions. Body weights, absolute and relative organ weights, clinical chemistry data, and appropriate hematology data were evaluated by Bartlett's test for equality of variances ($\alpha = 0.01$). This was followed by parametric or nonparametric analyses of variance ($\alpha = 0.01$) and followed respectively by Dunn t's test ($\alpha = 0.05$) or the Wilcoxon rank-sum test ($\alpha = 0.05$) with a Bonferroni correction for multiple comparisons. Statistical outliers were identified but not excluded from analyses.

6. Quality Assurance: A quality assurance statement was signed and dated June 8, 1988.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected daily for signs of toxicity and topical skin response.

Results: All except two male rabbits survived the dosing period with no overt signs of toxicity. The two rabbits that died (one control male, one mid-dose male) were sacrificed due to physical injuries sustained during restraining or escape. Local dermal irritation was observed at all dose levels in males (Table 1) and females (Table 2). This dermal irritation consisted of slight to severe erythema, edema and scaling, slight fissuring, scabbing, and scarring. Most of the irritation was limited to areas of abrasion resulting from clipping. The time of onset and degree of irritation were related to the dose. At 50 mg/kg/day, very little irritation was observed until after 25 applications; irritation was exhibited to a greater extent in females that were reported to have been clipped more frequently than males. At 200 mg/kg/day, 5 to 10 applications were required for irritation to become apparent. All rabbits dosed 200 mg/kg exhibited slight to severe erythema during the study. At least five applications of 1000 mg/kg/day were required for consistent dermal irritation. At study termination, most rabbits at this dose had moderate to severe erythema, edema and scaling, slight fissuring, scabs, and scarring.

TABLE 1. Summary of Dermal Observations in Male Rabbits Administered cis/trans-CTAC for 13 Weeks

Dosage Level (mg/kg/day)	Dermal Reactions on Test Day																			
	16 with Dermal Irriation Score					32 with Dermal Irriation Score					48 with Dermal Irriation Score					63 with Dermal Irriation Score				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Erythema[b]																				
0	10[a]	-	-	-	-	10	-	-	-	-	9[c]	-	-	-	-	9	-	-	-	-
50	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-	7	2	1	-	-
200	6	4	-	-	-	6	2	1	1	-	1	3	4	2	-	2[d]	6	1	-	-
1000	3	5	1	1	-	3	4	1	2	-	3	1	1	4	1	1	3	4	2	-
Edema[b]																				
0	10	-	-	-	-	10	-	-	-	-	9	-	-	-	-	9	-	-	-	-
50	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-	9	1	-	-	-
200	8	2	-	-	-	6	2	-	1	1	1	2	1	2	4	2	-	1	5	1
1000	3	2	2	2	1	3	3	1	1	2	3	1	-	1	5	3	-	-	2	5
Scaling/Fissuring[e]																				
0	10	-	-	-	-	10	-	-	-	-	9	-	-	-	-	9	-	-	-	-
50	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-
200	9	1	-	-	-	9	-	-	1	-	4	4	2	-	-	3	5	1	-	-
1000	6	2	1	1	-	6	2	-	-	2	4	1	5	-	-	3	2	3	2	-
Scabbing[f]																				
	(-)		(+)			(-)		(+)			(-)		(+)			(-)		(+)		
0	10		-			10		-			9		-			9		-		
50	10		-			10		-			9		1			8		2		
200	8		2			7		3			1		9			2		7		
1000	2		8			3		7			3		7			3		7		
Scarring[f]																				
	(-)		(+)			(-)		(+)			(-)		(+)			(-)		(+)		
0	10		-			10		-			9		-			9		-		
50	10		-			10		-			10		-			10		-		
200	9		1			8		2			6		4			2		7		
1000	6		4			7		3			6		4			3		7		

(continued)

[a]Number presented represents the number of rabbits in each group (based on a total of 10 rabbits/group) exhibiting a given observation.

Table 1. (continued)

[b]Dermal irritation scoring for erythema and edema based on modified Draize system: 0 = none; 1 = very slight; 2 = well defined; 3 = moderate to severe; 4 = severe.

[c]One control male sacrificed moribund on day 53.

[d]One mid-dose male sacrificed moribund on day 85.

[e]Dermal irritation scoring for scaling/fissuring based on modified Draize system: 0 = none; 1 = slight scalding; 2 = moderate severe scalding; 3 = slight fissuring; 4 = moderate to severe fissuring.

[f]Dermal irritation scoring for scabbing and scarring: absent (-) or present (+).

TABLE 2. Summary of Dermal Observations in Female Rabbits Administered cis/trans-CTAC for 13 Weeks

Dosage Level (mg/kg/day)	Dermal Reactions on Test Day																			
	16 with Dermal Irriation Score					32 with Dermal Irriation Score					48 with Dermal Irriation Score					63 with Dermal Irriation Score				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Erythema[b]																				
0	10[a]		-	-	-	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-
50	10	-	-	-	-	7	1	2	-	-	7	-	1	2	-	5	2	1	2	-
200	9	-	1	-		6	3	-	-	1	1	4	5	-	-	1	1	7	1	-
1000	7	3	-	-		1	1	6	2	-	1	[illegible]	3	6	-	-	1	-	8	1
Edema[b]																				
0	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-
50	10	-	-	-	-	10	-	-	-	-	7	1	1	-	1	7	-	2	1	-
200	9	1	-	-	-	9	-	-	1	-	2	2	4	1	1	1	1	3	3	2
1000	6	4	-	-	-	3	2	3	2	-	1	-	2	4	3	1	-	-	-	9
Scaling/Fissuring[c]																				
0	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-	10	-	-	-	-
50	10	-	-	-	-	8	1	1	-	-	7	1	2	-	-	7	1	2	-	-
200	7	3	-	-	-	9	-	1	-	-	4	6	-	-	-	2	4	3	1	-
1000	3	6	1	-	-	3	4	3	-	-	1	-	9	-	-	1	-	8	1	-
Scaling[d]																				
		(-)		(+)			(-)		(+)			(-)		(+)			(-)		(+)	
0		10		-			10		-			10		-			10		-	
50		10		-			10		-			9		1			7		3	
200		9		1			9		1			3		7			2		8	
1000		3		7			2		8			1		9			1		9	
Scarring																				
		(-)		(+)			(-)		(+)			(-)		(+)			(-)		(+)	
0		10		-			10		-			10		-			10		-	
50		10		-			10		-			10		-			8		2	
200		8		2			10		-			8		2			6		4	
1000		6		4			6		4			5		5			1		9	

(continued)

[a]Number presented represents the number of rabbits in each group (based on a total of 10 rabbits/group) exhibiting a given observation.

Table 2. Continued

[b] Dermal irritation scoring for erythema and edema based on modified Draize system: 0 = None; 1 = very slight; 2 = well defined; 3 = moderate to severe; 4 = severe.

[c] Dermal irritation scoring for scaling/fissuring: 0 = none; 1 = slight scalding; 2 = moderate to severe scalding; 3 = slight fissuring; 4 = moderate to severe fissuring.

[d] Dermal irritation scoring for scabbing and scarring: absent (-) or present (+).

2. Body Weight: Animals were weighed prior to the first treatment and weekly thereafter.

   Results: No effects on mean body weights were noted in either sex at any dose level (Table 3).

3. Food Consumption and Compound Intake: Food consumption was not determined.

4. Ophthalmology: Ophthalmological examinations were performed before the start of the study and just prior to sacrifice.

   Results: Results of ophthalmological examinations were not reported.

5. Hematology and Clinical Chemistry: Blood was collected from the ear vein from all animals prior to necropsy. The CHECKED (X) parameters were examined:

   a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation: thromboplastin time (PT)
	Reticulocyte count (RETIC)		
X	Red cell morphology		

   Results: There were no significant effects on hematological parameters in male rabbits. Leukocyte and platelet counts were significantly ($p < 0.05$) elevated in females in the 1000-mg/kg/day group; however, the counts were within the range of historical controls[1] and were not considered to be treatment related.

*Recommended by Subdivision F (October 1982) Guidelines.

[1]Historical and Published Control Data, CBI Table 19 of this study report.

TABLE 3. Representative Results of Mean Body Weights (± S.D.) of Rabbits[a] Treated Dermally with cis/trans-CTAC for 13 Weeks

Dosage Level (mg/kg/day)	Mean Body Weights (kg) on Day -1	42	91
	Males		
0	3.49 ± 0.21	3.67 ± 0.19	3.70 ± 0.20
50	3.52 ± 0.19	3.63 ± 0.17	3.70 ± 0.18
200	3.51 ± 0.16	3.71 ± 0.17	3.70 ± 0.20
1000	3.49 ± 0.14	3.62 ± 0.21	3.72 ± 0.26
	Females		
0	3.76 ± 0.16	4.06 ± 0.19	4.25 ± 0.19
50	3.76 ± 0.19	3.95 ± 0.26	4.11 ± 0.29
200	3.80 ± 0.21	4.11 ± 0.20	4.28 ± 0.15
1000	3.74 ± 0.19	4.01 ± 0.21	4.11 ± 0.19

[a]Ten animals/sex/group; one control male and one mid-dose male were sacrificed moribund on days 53 and 85, respectively.

b. Clinical Chemistry

	Electrolytes		Other
X	Calcium[+]	X	Albumin[+]
X	Chloride[+]		Albumin/globulin ratio
	Magnesium[+]	X	Blood creatinine[+]
X	Phosphorus[+]	X	Blood urea nitrogen[+]
X	Potassium[+]	X	Cholesterol[+]
X	Sodium[+]	X	Globulins
		X	Glucose[+]
	Enzymes	X	Total bilirubin[+]
X	Alkaline phosphatase (ALP)		Direct bilirubin
	Cholinesterase	X	Total protein[+]
	Creatinine phosphokinase[+]	X	Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)[+]		
X	Serum aspartate aminotransferase (SGOT)[+]		
	Gamma glutamyltransferase (GGT)		

Results: No treatment-related effects on clinical chemistry parameters were observed in males or females. Slightly but significantly ($p < 0.05$) decreased potassium and sodium levels were exhibited in mid- and high-dose males respectively; however, these values were similar to controls and were not considered to be of toxicological significance. Slight changes in blood urea nitrogen and cholesterol levels in high-dose females were within the range of values for laboratory controls[2] and were not considered to be of toxicological significance.

6. Urinalysis: Urinalyses were not performed.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

[+]Recommended by Subdivision F (October 1982) Guidelines.
[2]Historical and Published Control Data, CBI Table 19 of this study report.

Digestive System	Cardiovasc./Hemat.	Neurologic
Tongue	X Aorta[+]	XX Brain[+]
X Salivary glands[+]	XX Heart[+]	X Peripheral nerve (sciatic nerve)[+]
X Esophagus[+]	X Bone marrow[+]	X Spinal cord (3 levels)
X Stomach[+]	X Lymph nodes[+]	X Pituitary[+]
X Duodenum[+]	X Spleen[+]	X Eyes (optic nerve)[+]
X Jejunum[+]	X Thymus[+]	
X Ileum[+]		
X Cecum[+]		
X Colon[+]		
X Rectum	Urogenital	Glandular
XX Liver[+]	XX Kidneys[+]	XX Adrenals[+]
X Gallbladder[+]	X Urinary bladder[+]	Lacrimal gland
X Pancreas[+]	XX Testes[+]	X Mammary gland[+]
X Appendix	X Epididymides	X Thyroids[+]
	X Prostate	X Parathyroids[+]
Respiratory	X Seminal vesicle	Harderian glands
X Trachea[+]	X Ovaries	
X Lung[+]	X Uterus[+]	
Larynx	X Cervix	Other
Nasal tisues	X Oviducts	X Bone (sternum and femur)[+]
Oral tissues	X Vagina	X Skeletal muscle[+]
		X Skin
		X All gross lesions and masses
		X Nasal septum
		X Mediastinal tissues
		X Mesenteric tissues
		X Sacculus rotundus

Histopathology of low- and mid-dose animals was limited to skin from the application site, skin from an additional adjacent site, and gross lesions.

a. Organ Weights: No effects were observed in organ and organ/body weights in male rabbits. In female rabbits, a slight but significant ($p < 0.05$) increase in the relative, but not absolute, kidney weight at the high dose was not considered to be treatment related. The increase was not correlated with other indications of renal toxicity, including clinical chemistries and histopathology.

[+]Recommended by Subdivision F (October 1982) Guidelines.

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b. Gross Pathology: The gross pathologic alterations found at study termination were confined to the skin at the application site. The lesions consisted of scab-encrusted foci that ranged from less than 1 cm to several centimeters in size. The lesions appeared to be dose related; the lesions were more severe and more numerous as the dose level increased. In the 1000-mg/kg/day group, 8/10 males and 9/10 females were affected; in the 200-mg/kg/day group, 8/10 males and 7/10 females were affected; in the 50 mg/kg/day group, 1/10 males and 3/10 females were affected. No controls exhibited lesions.

c. Microscopic Pathology:

1) Nonneoplastic: The histopathologic examination revealed a localized inflammatory reaction at the compound application site in some males and females at all three dose levels. The reaction was limited to a focal involvement of the epidermis and dermis at the application site and was characterized as moderate or severe chronic ulcerative dermatitis. Study authors reported that minor epidermal abrasions from the electric clippers may have given rise to inflammatory foci, which produced the local intensive inflammatory lesions after repetitive compound application. In a number of animals, more frequently females than males, very slight or slight inflammatory degenerative lesions of the epidermis or superficial dermis were noted in skin sections adjacent to the treated skin. This was attributed to irritation from the wraps used to occlude the treatment area.

Histopathologic examination of the internal organs and tissues from high dose and control animals revealed no treatment-related systemic activity; all lesions noted were relatively common and spontaneously occurring in the laboratory rabbit.

D. STUDY AUTHORS' CONCLUSIONS:

Male and female New Zealand White rabbits were exposed to daily dermal applications of 0, 50, 200, or 1000 mg/kg cis/trans-CTAC for 13 weeks. No treatment-related mortalities were noted. There were no indications of systemic toxicity based upon clinical observation, body weights, clinical laboratory studies, organ weights, gross pathology, or histopathology. The only treatment-related effect observed was a dose-dependent dermal irritation consisting of slight-to-severe erythema, edema and scaling, slight fissuring, scabbing, and scarring. Histopathology revealed that the inflammatory reaction was limited to the epidermis and dermis at the application site and was characterized as moderate-to-severe chronic ulcerative dermatitis. These lesions were correlated with the abrasions

from the electric clippers. Areas unaffected by clipping were normal in appearance on gross and histopathological examination.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The conduct and reporting of the study were adequate. There were no indications of systemic toxicity at 50, 200, or 1000 mg/kg/day cis/trans-CTAC based upon clinical observations, body weights, clinical laboratory studies, organ weights, gross pathology, or histopathology. There were no treatment-related mortalities. The only treatment-related effect was a dose-dependent increase in dermal irritation, which was correlated with the abrasions associated with clipping. These lesions were characterized as moderate-to-severe chronic ulcerative dermititis limited to focal involvement of the epidermis and dermis at the site of application. Areas unaffected by clipping were normal in appearance.

We agree with the authors' conclusions that based upon the lack of systemic toxicity, the NOEL for systemic toxicity is 1000 mg/kg/day.