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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of 21-Day Dermal Toxicity Study of Thiabendazole in Rabbits

Project No. 0-0227 Tox. Chem. No. 849A
EPA No. 060101 Record No. 255161

TO: Franklin D. Rubis, PM Team # 50
Registration Division (H7505C)

FROM: Ann Clevenger, Ph.D. Ann Clevenger 9-19-90
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, ~~Acting~~ Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C) Roger L. Gardner 11/4/91 KB 11/5/91

Conclusions:

The study was designed to assess the dermal toxicity of thiabendazole in rabbits. Daily dermal application of thiabendazole for 21-22 days at dose levels or 0, 50, 200, or 1000 mg/kg/day did not produce any measurable dermal or systemic toxicity. Dermal exposure did not affect survival or produce clinical signs of toxicity. Body weight gain was highly variable both within and between groups, but the observed group differences did not show a pattern indicative of a treatment-related effect. Hematology, clinical chemistry, organ weights, and tissue morphology were unaffected by treatment.

This study is given a core classification of guideline and is considered to meet the requirements of testing guideline 82-2.

Attachment

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Reviewed by: Ann Clevenger, Ph.D. Ann Clevenger 9-19-90
Section 1, Toxicology Branch 1
Secondary Reviewer: Roger Gardner Roger L. Gardner 11/2/90
Section 1, Toxicology Branch 1

DATA EVALUATION RECORD

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

TOX. CHEM. NO.: 849A

MRID NUMBER: 412595-01

TEST MATERIAL: Thiabendazole. 98.9% purity. Lot no. L-585,216-0005159

SYNONYMS:

STUDY NUMBER(S): 284-161 TT#89-9011

SPONSOR: Merck and Co. Inc.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: Thiabendazole. Twenty-three Day Dermal Toxicity Study in Rabbits

AUTHOR(S): J. Cavagnaro

DATE REPORT ISSUED: 10-4-39

CONCLUSIONS: For 21-22 days groups of male and female rabbits were exposed dermally for six hours per day to 0, 50, 200, or 1000 mg/kg of thiabendazole. This treatment regimen did not produce any measurable dermal or systemic effect. All rabbits survived the duration of the study, and no signs of toxicity were noted. Body weight gain was highly variable both within and between groups, but the observed group differences did not show a pattern indicative of a treatment-related effect. Hematology, clinical chemistry, organ weights, and tissue morphology were unaffected by treatment.

Based on the results of this study, the NOEL for dermal exposure is defined as 1000 mg/kg/day (the highest dose tested) for male and female rabbits.

Core Classification: Guideline. No statistical comparisons of group means were performed on any of the data. However, statistical comparisons would not be expected to improve or alter interpretation of the results.

Testing Guideline Satisfied: 82-2

MATERIALS AND METHODS

Test Material: Thiabendazole was supplied by the sponsor as a white powder. The powder was stored at ambient temperature. The purity was reported as >98.9% by thin-layer chromatography. For dosage calculations, the purity was assumed to be 100%.

Test Species: Male and female Hra:(NZW)SPF rabbits, obtained from Hazleton Research Products, were used. Body weights one day before initiation of dosing were 2138-2606 g for males and 2079-2518 g for females. The rabbits were acclimated to collars for up to 6 hours/day for four days prior to dosing.

Experimental Procedure: Twenty-four hours prior to first dosing, the hair was shaved from the dorsal area so that 10% of the body surface area was shaved. Animals were re-shaved each Monday and Thursday and the day before sacrifice. Due to difficulty in removing the test material from the application site, collars were left in place continuously for all groups. Groups of 10 rabbits (5/sex) per dose level received dermal application of 0, 50, 200, or 1000 mg/kg/day. Animals were exposed 6 hours/day, 7 days/week, for three weeks. The test material was applied to a gauze pad (4 x 4 inch) moistened with 1 ml saline. The pad was held in place with a self-adhesive wrap and secured with surgical tape. The control group was treated with 1 ml saline. After 6 hours of exposure, the wrap was removed and the remaining material removed by wiping with dry gauze. Dosages were adjusted weekly according to individual body weight.

Observations: Animals were checked daily for morality and moribundity. Cageside observations were made at least daily. Physical examinations were conducted weekly. Body weights were measured weekly. A qualitative estimate of food consumption was made daily. Dermal irritation was scored twice daily according to the Draize method.

Pathology: The following clinical and histopathology data were collected:

Hematology

- Hematocrit
- Hemoglobin
- Erythrocyte count
- Mean cell hemoglobin
- Mean cell volume
- Mean cell hemoglobin concentration
- Reticulocyte
- Leukocyte count
- Differential leukocyte count and cell morph
- Platelet count
- Prothrombin time

Blood Chemistry

- Alanine amino-transferase
- Aspartate amino-transferase
- Albumin
- Urea nitrogen
- Total protein
- Globulin
- Albumin/Globulin ratio
- Creatinine
- Glucose
- Total bilirubin
- Na
- K
- Cl
- Ca
- Phosphorus

Organ Weights

- Liver with gallbladder
- Testes with epididymes
- Kidneys

Gross Necropsy Exam

External surfaces
All orifices
Cranial cavity
Carcass
External surfaces of the brain and spinal cord and cut surfaces of the spinal cord
Nasal cavity and paranasal sinuses
Thoracic, abdominal, and pelvic cavities and their viscera
Cervical tissues and organs

Tissues Preserved

Adrenals	Head	Brain
Cecum	Colon	Duodenum
Epididymides	Esophagus	Eyes/optic nerve
Vagina	Tongue	Ileum
Femoral bone/joint	Heart	Larynx
Jejunum	Kidneys	Mammary glands
Lungs	Lymph nodes	Pituitary
Ovaries	Pancreas	Salivary glands
Prostate	Rectum	Skeletal muscle
Sciatic nerve	Seminal vesicles	Spleen
Skin	Spinal cord	Testes
Sternum	Stomach	Thyroids (with parathyroids)
Thymus	Trachea	
Urinary bladder	Uterus	
Liver with gall bladder	Harderian glands	

Only liver, kidneys, treated and untreated skin, and gross lesions were examined histologically. Histopathology was performed by the sponsor.

Statistical Analysis: Group means and standard deviations were calculated. No other statistical analyses were performed.

REPORTED RESULTS

All animals survived the duration of the study. No clinical signs could be related to treatment. Three animals were noted to appear thin (one low-dose male; one mid-dose female; one high-dose male). These animals showed poor appetites and lost weight initially in the study. One low-dose male and one high-dose female had an inflammatory condition of the right eye. Slight dermal irritation was transiently observed in a few treated animals. One high-dose female showed slight erythema or edema throughout much of the treatment period.

Body weights and body weight gains were highly variable both within and between groups. These data are shown in Attachment A. Group mean body weight gains by treated groups were somewhat less than that by control groups but not in a dose-related manner. Each group had one or two animals that lost weight during the first or second week of the study. The weight loss by a few treated animals was primarily responsible for the lower treatment group weight gains. Because of the high variability within groups, the observed between group differences cannot be clearly associated with treatment. The author of the report suggested that the continuous use of a collar could have contributed to the decreased food intake and body weight gain by some animals.

Group mean values for hematology and clinical chemistry parameters did not differ between groups. Group mean organ weights also did not differ. Pale areas of the liver were noted at gross examination in 11 rabbits. The distribution in the 0, 50, 200, and 1000 mg/kg dose groups was 0, 2, 1, and 1, respectively, and 2, 1, 2, and 2, respectively, for females. Three rabbits had granular/pitted/ rough appearance of the kidneys (one control male; one low-dose male; one high-dose male). None of the gross lesions appeared to be related to treatment. Microscopic examination of tissue revealed slight changes in the liver and kidneys of several control and treated animals. However, niether the incidence nor the severity of the lesions suggested that these were related to treatment (See Attachment B).

The pathology report contained the following statements about the observed renal lesions:

> Very slight to slight renal lesions were observed grossly and/or microscopically in the control and most animals in the treatment groups...These small lesions did not interfere with the evaluation of the remaining normal kidney tissue for possible toxic changes...These very slight to slight renal lesions were comparable with the renal changes observed in rabbits infected with the common protozoan parasite Encephalitozoon cuniculi. Encephalitozoonosis is known to be an endemic, spontaneous infection in this rabbit colony.

The pathology report contained this following statements about the observed liver lesions:

> Also noted in control and all treatment groups were very slight to slight foci of hepatocellular degeneration and necrosis. These changes were usually confined to a small, discrete area of a single liver lobe and were not considered a treatment-related effect because of their occurrence in controls...Focal degeneration and necrosis have been observed in other control rabbits is this colony but its etiology is unknown. It is considered a spontaneous change with no clinical significance.

DISCUSSION

Daily dermal application of thiabendazole for 21-22 days at dose levels of 0, 50, 200, or 1000 mg/kg/day did not produce any measurable dermal or systemic effect in rabbits. Body weight gain was highly variable both within and between groups. The observed group differences did not show a pattern indicative of a treatment-related effect.

No histopathology changes were treatment-related. Minor histopathological changes in the liver and kidneys occurred in both controls and treated animals but did not increase in incidence or severity in a dose-related manner. The renal changes were considered by the pathologist to be consistent with a parasitic infection. The infection, if present, did not appear to compromise the study conduct or results.

ATTACHMENT A

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Table 3
Mean Body Weight Values (g) and Mean Body Weight Changes (g)
Thiabendazole: 23-Day Dermal Toxicity Study in Rabbits

Males

Mean Body Weight Values (g)

Group and Dose Level		Week 0	Week 1	Week 2	Week 3
1 Control (Saline)	Mean	2306.0	2338.2	2399.6	2502.4
	S.D.	157.31	162.63	185.01	162.88
	N[a]	5/5	5/5	5/5	5/5
2 50 mg/kg/day	Mean	2310.8	2192.6	2318.8	2407.0
	S.D.	54.72	274.34	145.90	163.02
	N[a]	5/5	5/5	5/5	5/5
3 200 mg/kg/day	Mean	2274.2	2253.0	2362.4	2411.8
	S.D.	83.47	119.50	88.16	95.67
	N[a]	5/5	5/5	5/5	5/5
4 1000 mg/kg/day	Mean	2394.4	2256.8	2358.0	2458.0
	S.D.	124.10	219.86	191.02	182.80
	N[a]	5/5	5/5	5/5	5/5

Mean Body Weight Changes (g)

Group and Dose Level		Week 0-1	Week 0-2	Week 0-3
1 Control (Saline)	Mean	32.2	93.6	196.4
	S.D.	45.6	62.1	51.0
	N[a]	5/5	5/5	5/5
2 50 mg/kg/day	Mean	-118.2	8.0	96.2
	S.D.	266.7	108.4	123.7
	N[a]	5/5	5/5	5/5
3 200 mg/kg/day	Mean	-21.2	88.2	137.6
	S.D.	80.3	73.0	112.0
	N[a]	5/5	5/5	5/5
4 1000 mg/kg/day	Mean	-137.6	-36.4	63.6
	S.D.	195.2	127.3	136.1
	N[a]	5/5	5/5	5/5

[a] The numerals indicate the number of animals examined at that particular interval over the number of animals at initiation of the study.

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Table 3 - Continued
Mean Body Weight Values (g) and Body Weight Changes (g)
Thiabendazole: 23-Day Dermal Toxicity Study in Rabbits

Females

Mean Body Weight Values (g)

Group and Dose Level		Week 0	1	2	3
1 Control (Saline)	Mean	2276.6	2265.4	2345.2	2427.8
	S.D.	42.88	83.06	109.24	107.61
	N[a]	5/5	5/5	5/5	5/5
2 50 mg/kg/day	Mean	2298.4	2294.0	2299.0	2416.4
	S.D.	204.21	265.15	258.62	315.01
	N[a]	5/5	5/5	5/5	5/5
3 200 mg/kg/day	Mean	2294.8	2282.6	2321.8	2389.8
	S.D.	100.34	184.01	241.55	246.12
	N[a]	5/5	5/5	5/5	5/5
4 1000 mg/kg/day	Mean	2275.0	2212.0	2221.8	2363.6
	S.D.	53.58	45.01	120.66	43.18
	N[a]	5/5	5/5	5/5	5/5

Mean Body Weight Changes (g)

Group and Dose Level		Week 0-1	0-2	0-3
1 Control (Saline)	Mean	-11.2	68.6	151.2
	S.D.	59.3	87.4	87.1
	N[a]	5/5	5/5	5/5
2 50 mg/kg/day	Mean	-4.4	0.6	118.0
	S.D.	81.2	60.0	121.1
	N[a]	5/5	5/5	5/5
3 200 mg/kg/day	Mean	-12.2	27.0	95.0
	S.D.	141.1	175.9	191.8
	N[a]	5/5	5/5	5/5
4 1000 mg/kg/day	Mean	-63.0	-53.2	88.6
	S.D.	68.1	121.2	81.8
	N[a]	5/5	5/5	5/5

[a] The numerals indicate the number of animals examined at that particular interval over the number of animals at initiation of the study.

ATTACHMENT B

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TABLE B-1. THIABENDAZOLE: 23-DAY DERMAL TOXICITY STUDY IN RABBITS. TT89-9011
SUMMARY OF HISTOMORPHOLOGY

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	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES
NUMBER NECROPSIED	5	5	5	5	5	5	5	5
LIVER								
NO. ANIMALS EXAMINED MICRO.	5	5	5	5	5	5	5	5
NUMBER NOT REMARKABLE	1	4	1	2	3	1	2	2
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION	-	1	2	2	-	3	-	2
VACUOLAR MULTIFOCAL DEGENERATION	4	-	2	1	2	2	3	1
GRANULOMATOUS FOCAL HEPATITIS	-	-	-	1	-	-	-	-
MULTIFOCAL NECROSIS	2	-	1	1	1	2	2	1
KIDNEY								
NO. ANIMALS EXAMINED MICRO.	5	5	5	5	5	5	5	5
NUMBER NOT REMARKABLE	5	4	5	3	5	1	4	3
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION	-	1	-	2	-	3	1	2
CORTICAL CYST	-	-	-	-	-	-	-	1
TUBULAR DILATATION	-	1	-	1	-	1	-	1
INTERSTITIAL FIBROSIS	-	1	-	1	-	1	-	1
MULTIFOCAL TUBULAR BASOPHILIA	-	1	-	2	-	3	-	2
SKIN								
NO. ANIMALS EXAMINED MICRO.	5	5	5	5	5	5	5	5
NUMBER NOT REMARKABLE	5	5	5	5	5	5	5	5
APPLICATION SITE								
NO. ANIMALS EXAMINED MICRO.	5	5	5	5	5	5	5	5
NUMBER NOT REMARKABLE	4	5	5	5	5	5	5	5
MULTIFOCAL MYOSITIS	1	-	-	-	-	-	-	-
LUNG								
NO. ANIMALS EXAMINED MICRO.	1	-	-	-	-	-	-	-
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-
FOCAL CELLULAR INFILTRATION	1	-	-	-	-	-	-	-
LYMPH NODE								
NO. ANIMALS EXAMINED MICRO.	-	-	-	1	-	-	-	-
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-
LYMPHOID HYPERPLASIA	-	-	-	1	-	-	-	-
EYE								
NO. ANIMALS EXAMINED MICRO.	-	-	-	1	-	-	-	-
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-
CHRONIC KERATO-IRITIS	-	-	-	1	-	-	-	-

KEY: GROUP 1 = CONTROL
GROUP 2 = 50 MG/KG/DAY
GROUP 3 = 200 MG/KG/DAY
GROUP 4 = 1000 MG/KG/DAY

TABLE B-2. THIABENDAZOLE: 23-DAY DERMAL TOXICITY STUDY IN RABBITS. TT#89-9011
HISTOMORPHOLOGY

CONTROL

ANIMAL NUMBER	048019	048020	048021	048022	048023	047999	048000	048001	048002	048003
SEX	F	F	F	F	F	M	M	M	M	M
NECROPSY NUMBER	170184	170185	170186	170187	170188	170164	170165	170166	170167	170168
NUMBER OF DOSES	21	21	22	22	22	21	21	21	22	22
LIVER			N			N	N		N	N
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION								1		
VACUOLAR MULTIFOCAL DEGENERATION	1	1		1	1					
GRANULOMATOUS FOCAL HEPATITIS										
MULTIFOCAL NECROSIS	1	1								
KIDNEY	N	N	N	N	N	N	N	N		N
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION									2	
CORTICAL CYST										
TUBULAR DILATATION									1	
INTERSTITIAL FIBROSIS									1	
MULTIFOCAL TUBULAR BASOPHILIA									1	
SKIN	N	N	N	N	N	N	N	N	N	N
APPLICATION SITE	N	N	N	N		N	N	N	N	N
MULTIFOCAL MYOSITIS					1					
LUNG										
FOCAL CELLULAR INFILTRATION				1						
LYMPH NODE										
LYMPHOID HYPERPLASIA										
EYE										
CHRONIC KERATO-IRITIS										

50 MG/KG/DAY

ANIMAL NUMBER	048024	048025	048026	048027	048028	048004	048005	048006	048007	048008
SEX	F	F	F	F	F	M	M	M	M	M
NECROPSY NUMBER	170189	170190	170191	170192	170193	170169	170170	170171	170172	170173
NUMBER OF DOSES	21	21	22	22	22	21	21	21	22	22
LIVER				N		N				N
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION			1		1		2		2	
VACUOLAR MULTIFOCAL DEGENERATION	2	2							2	
GRANULOMATOUS FOCAL HEPATITIS								2		
MULTIFOCAL NECROSIS	2								1	
KIDNEY	N	N	N	N	N	N		N		N
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION							2		2	
CORTICAL CYST										
TUBULAR DILATATION									1	
INTERSTITIAL FIBROSIS									1	
MULTIFOCAL TUBULAR BASOPHILIA							1		1	
SKIN	N	N	N	N	N	N	N	N	N	N
APPLICATION SITE	N	N	N	N	N	N	N	N	N	N
MULTIFOCAL MYOSITIS										
LUNG										
FOCAL CELLULAR INFILTRATION										
LYMPH NODE										
LYMPHOID HYPERPLASIA										1
EYE										
CHRONIC KERATO-IRITIS										1

200 MG/KG/DAY

ANIMAL NUMBER	048029	048030	048031	048032	048033	048009	048010	048011	048012	048013
SEX	F	F	F	F	F	M	M	M	M	M
NECROPSY NUMBER	170194	170195	170196	170197	170198	170174	170175	170176	170177	170178
NUMBER OF DOSES	21	21	22	22	22	21	21	21	22	22
LIVER		N	N	N		N				
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION							2		1	2
VACUOLAR MULTIFOCAL DEGENERATION	1				2			1		1
GRANULOMATOUS FOCAL HEPATITIS										
MULTIFOCAL NECROSIS					2			2		1
KIDNEY	N	N	N	N	N			N		
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION							1		3	1
CORTICAL CYST										
TUBULAR DILATATION									1	
INTERSTITIAL FIBROSIS									1	
MULTIFOCAL TUBULAR BASOPHILIA						1	1		1	
SKIN	N	N	N	N	N	N	N	N	N	N
APPLICATION SITE	N	N	N	N	N	N	N	N	N	N
MULTIFOCAL MYOSITIS										
LUNG										
FOCAL CELLULAR INFILTRATION										
LYMPH NODE										
LYMPHOID HYPERPLASIA										
EYE										
CHRONIC KERATO-IRITIS										

1000 MG/KG/DAY

ANIMAL NUMBER	048034	048035	048036	048037	048038	048014	048015	048016	048017	048018
SEX	F	F	F	F	F	M	M	M	M	M
NECROPSY NUMBER	170199	170200	170201	170202	170203	170179	170180	170181	170182	170183
NUMBER OF DOSES	21	21	22	22	22	21	21	21	22	22
LIVER			N		N	N			N	
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION							1			2
VACUOLAR MULTIFOCAL DEGENERATION	1	2		2				2		
GRANULOMATOUS FOCAL HEPATITIS										
MULTIFOCAL NECROSIS		2		2				2		
KIDNEY	N	N	N		N	N		N	N	
MULTIFOCAL MONONUCLEAR CELLULAR INFILTRATION				1			2			2
CORTICAL CYST							X			
TUBULAR DILATATION							1			
INTERSTITIAL FIBROSIS							2			
MULTIFOCAL TUBULAR BASOPHILIA							1			1
SKIN	N	N	N	N	N	N	N	N	N	N
APPLICATION SITE	N	N	N	N	N	N	N	N	N	N
MULTIFOCAL MYOSITIS										
LUNG										
FOCAL CELLULAR INFILTRATION										
LYMPH NODE										
LYMPHOID HYPERPLASIA										
EYE										
CHRONIC KERATO-IRITIS										

KEY: N = NOT REMARKABLE; A = AUTOLYSIS; B = TISSUE NOT PRESENT IN SECTION(S); 1 = VERY SLIGHT; 2 = SLIGHT OR SMALL; 3 = MODERATE; 4 = MARKED; 5 = SEVERE; 0 = NONE; X = PRESENT
NO ENTRY = GROSSLY NORMAL, NO MICROSCOPIC EXAMINATION
* AUTOLYSIS DOES NOT PRECLUDE EXAMINATION FOR NEOPLASTIC AND OBVIOUS NON-NEOPLASTIC CHANGES.

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