

12-3-96

TOX 012107

MEMORANDUM

SUBJECT: CHLOROTHALONIL: A 21-Day Dermal Toxicity Study
in Rats

FROM: Alan C. Levy, Ph.D., Toxicologist
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Health Effects Division (7509C)

TO: Walter I. Waldrop, Jr./Andrew W. Ertman, PM 71
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and

Tom Myers, Reregistration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Jess Rowland, M.S., Acting Section Head
Review Section I, Toxicology Branch II
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and

Yiannakis M. Ioannou, Ph.D., Acting Branch Chief
Toxicology Branch II
Health Effects Division (7509C)

EPA IDENTIFICATION: DP Barcode: D230222
MRID No.: 44119101
PC Code: 081901
Submission Code: S512162

Registrant: ISK Biosciences Corporation, Mentor, OH

REQUEST: Review a 21-day dermal toxicity study in rats with
CHLOROTHALONIL.

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EXECUTIVE SUMMARY:

In a dermal toxicity study (MRID No. 44119101), male Fischer 344 rats (10/group) received 15 repeated dermal applications of CHLOROTHALONIL (98.1%) at 60, 100, 250 or 600 mg/kg/day, 6 hours/day for 5 days/week during a period of 21 days. The vehicle control group received 0.2% aqueous methyl-cellulose (2.4 mg/kg) on the same schedule. Parameters evaluated were survival, clinical observations, dermal evaluations, clinical chemistry, organ weights, gross pathology and histopathology of the kidneys, forestomach, treated and untreated skin and gross lesions.

There was no mortality. Clinical signs at doses $\leq$ 100 mg/kg/day were limited to rough hair coat and colored material around the nose and/or eyes. Dermal irritation, characterized as erythema and desquamation, was observed at all dose levels. No systemic toxicity was observed. Treatment-related dermal lesions were hyperkeratosis and hyperplasia of the squamous epithelium of all rats at all dose levels.

The objective of this study was to establish a NOEL for kidney effects after dermal administration as the kidney was the target organ following oral administration to rats and dogs. Results of this study indicate a NOEL of $>$ 600 mg/kg/day (highest dose tested) for kidney effects after repeated dermal applications to male rats.

The systemic toxicity NOEL = 600 mg/kg/day

The systemic toxicity LOEL = $>$ 600 mg/kg/day

The dermal toxicity NOEL = $<$ 60 mg/kg/day (Lowest Dose Tested)

The dermal toxicity LOEL = 60 mg/kg/day based on erythema, desquamation, hyperkeratosis and squamous epithelial hyperplasia of the skin

This dermal study is **Acceptable/Guideline** and satisfies the data requirement for OPPTS 870.3100 (§82-2) for a 21-day dermal toxicity study in rats.

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EPA Reviewer: Alan C. Levy, Ph.D. _____, Date _____
Review Section I, Toxicology Branch II (7509C)

EPA Secondary Reviewer: Jess C. Rowland, M.S. _____, Date _____
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 21-Day Dermal Study in Rats (\$82-2)

EPA IDENTIFICATION: PC Code: 081901 MRID No.: 44119101
DP Barcodes: D230222 Submission Code: S512162

TEST MATERIAL: Chlorothalonil (technical; 98.1%)

SYNONYMS: none

CITATION: Mizens, M., September 5, 1996, A 21-Day Repeated Dose Dermal Toxicity Study in Rats with Technical Chlorothalonil, Ricerca, Inc., Painesville, OH, 6859-96-0113-TX-002, MRID No. 44119101.

SPONSOR: ISK Biosciences Corporation, Mentor, OH

EXECUTIVE SUMMARY:

In a dermal toxicity study (MRID No. 44119101), male Fischer 344 rats (10/group) received 15 repeated dermal applications of CHLOROTHALONIL (98.1%) at 60, 100, 250 or 600 mg/kg/day, 6 hours/day for 5 days/week during a period of 21 days. The vehicle control group received 0.2% aqueous methyl-cellulose (2.4 ml/kg) on the same schedule.

There was no mortality. Clinical signs at doses $\leq$ 100 mg/kg/day were limited to rough hair coat and colored material around the nose and/or eyes. Dermal irritation, characterized as erythema and desquamation, was observed at all dose levels. No systemic toxicity was observed. Treatment-related dermal lesions were hyperkeratosis and hyperplasia of the squamous epithelium of all rats at all dose levels.

The objective of this study was to establish a NOEL for kidney effects after dermal administration as the kidney was the target organ following oral administration to rats and dogs. Results of this study indicate a NOEL of $>$ 600 mg/kg/day (highest dose tested) for kidney effects after repeated dermal applications to male rats.

The systemic toxicity NOEL = 600 mg/kg/day

The systemic toxicity LOEL = > 600 mg/kg/day

The dermal toxicity NOEL = < 60 mg/kg/day (Lowest Dose Tested)

The dermal toxicity LOEL = 60 mg/kg/day based on erythema, desquamation, hyperkeratosis and squamous epithelial hyperplasia of the skin

This dermal study is **Acceptable/Guideline** and satisfies the data requirement for OPPTS 870.3100 (§82-2) for a 21-day dermal toxicity study in rats.

Compliance

A signed and dated Good Laboratory Practice Compliance statement, a Quality Assurance statement and a list of Quality Assurance inspections were included in the Report.

A signed and dated statement of no confidentiality claim was provided.

I. OBJECTIVE

The objective of this study was to establish NOEL for kidney effects following repeated dermal application to rats as the kidney was the target organ following oral administration to rats and dogs. Although a 21-day dermal toxicity study in rabbits is available, a dermal toxicity study in rats was conducted at the Agency's request. In addition, only male rats were used in this study as this sex was shown to be more sensitive to CHLOROTHALONIL-induced toxicity than females. [Memos: R. Zendzian, Tox. to M. Clock, RCAB dated 3/28/96 and R. Zendzian, HED to A. Ertman, RD dated 5/8/96]

II. MATERIALS and METHODS**A. Materials****1. TEST MATERIAL: Chlorothalonil; tetrachloroisophthalonitrile**

Description: technical; gray powder

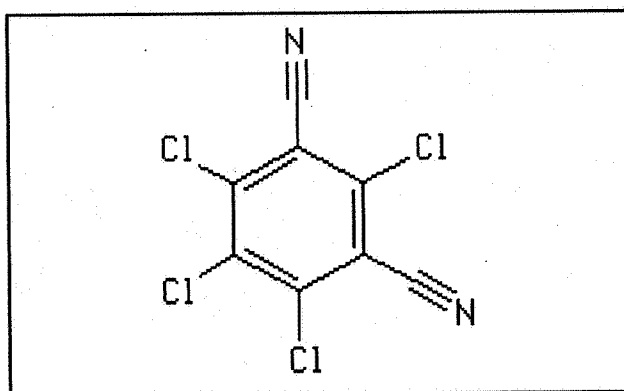
Lot/Batch No.: 313012

Code name: SDS-2787-2401-0301

Purity: 98.1%

CAS No.: 1897-45-6

Formula:

**2. VEHICLE: 0.2% aqueous methyl-cellulose; a 1:4 ratio (mg test material:μL vehicle)****3. TEST ANIMALS:**

Species: rat;

Sex: males

Strain: Fischer-344

Age and Weight at Study Initiation: 70 days old;
202.7-205.9 g (group mean body weights at
week 0)Source: Charles River Breeding Laboratory Inc.,
Raleigh, NC

Housing: 1/cage

Diet: PMI Feeds, Inc.TM Lab DietTM Certified
Rodent Diet (No. 5002 Checkers) ad libitumWater: Automatic system ad libitum

Environmental conditions: Temperature: 65 - 79°F

Humidity: 40 - 70%

Air Changes: ≥ 10

Photoperiod: 12-hour light/dark

Acclimation period: a total of 12 days; **NOTE:**

Elizabethan collars: prior to test material administration (week 0), collars were placed on the rats for 5 days (1 hour the first day, 2 hours the second day, 3 hours the third day, 4 hours the fourth day and 5 hours the fifth day)

B. Study Design

1. IN LIFE DATES: June 11, 1996 - July 2, 1996

2. ANIMAL ASSIGNMENT

Randomization design; group mean body weights were similar.

Table 1

ANIMAL ASSIGNMENT IN A 21-DAY DERMAL RAT STUDY
WITH CHLOROTHALONIL

mg/kg/day	No. males/group
0	10
60	10
100	10
250	10
600	10

NOTE: rats were dosed 6 hours/day, 5 days/week over a 21-day study period.

3. PREPARATION OF ANIMALS FOR DERMAL APPLICATION

Electric clippers were used to remove the hair from the backs prior to application of the test article. The rats were reclipped twice/week (Sunday and Wednesday). If clipping was on a dosing day, it was done about one hour after the removal of the occlusive material.

4. DOSING PROCEDURE

The test article was mixed with the vehicle (0.2% aqueous methyl-cellulose) in a constant ratio of 1:4 (test article:vehicle). Therefore, the volume of the application varied with the dose (60, 100, 250 and 600 mg/kg/day). The controls received 2.4 mL/kg (the volume given to the 600 mg/kg/day rats) of the vehicle only. **NOTE:** In this study, the test article (98.1% active ingredient) was mixed with the vehicle using the assumption that it had a purity of 100%.

The test material was mixed with the vehicle in a weigh boat and, using a spatula, the mixture was applied to the back of the animals (about 10% of the total body surface area) as uniformly as possible. At lower doses, an effort was made to cover as much of the treatment area as possible with the test material.

The treated area was covered with porous gauze which was held in place with Dermiform tape. Rats were fitted with Elizabethan collars in order to prevent the animal from destroying the gauze/tape cover and possibly ingesting the test article/vehicle. After at least 6 hours, the gauze/tape was removed and any remaining test article/vehicle was wiped with water-moistened gauze.

Report page 20 indicated that all rats received the correct amount of test article with the exception of one on day 15 (600 mg/kg/day) which apparently was given one tenth of the amount scheduled to be applied. The volume of test article/vehicle and the amount recorded did not appear to be consistent. If the incorrect dose was given, the Study Author did not believe that this had a detrimental effect on the study. This Reviewer agrees.

5. ANALYSES OF DOSING PREPARATIONS

A. Test Article Purity

The purity of Chlorothalonil was $98.1 \pm 0.92\%$ at the 95% confidence level. Particle size was 3.7 microns.

B. Residue of Applied Material

Assays were performed to determine the efficiency of the transfer of the dosing material

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from the weighing boat and spatula to the animal. The procedure for this analysis was described.

Table 2

ASSAYS FOR THE RECOVERY OF CHLOROTHALONIL FROM THE WEIGH BOATS
AND SPATULAS

gm applied	µg found	corrected µg found†	% recovered (mean±SD)
0.012-0.013	351-420	325-389	2.8±0.17
0.020-0.021	435-738	403-683	2.6±0.70
0.048-0.054	438-480	406-444	0.8±0.06
0.123-0.126	816-978†	756-906	0.7±0.06

gm applied = range for 3 rats; mean ± SD for 3 rats

+ = corrected for concurrent recoveries

† = for each rat, 2nd wipe of same weigh boat with 2nd gauze pad

Data extracted from Report Appendix D, Table 1, page 163.

As shown in Table 2, results of the assay for recovery of CHLOROTHALONIL indicate that, based on the mean percent recovered, the test article/vehicle mixture was effectively (i.e., quantitatively) transferred from the weigh boat to the treatment area (skin) of the test animals.

6. STATISTICS

For body weight, food consumption, organ weights and clinical chemistry parameters, normality of the data and variance homogeneity were first submitted to Bartlett's test. Non parametric procedures were used if Bartlett's test was significant. To compare the treatment groups to the control group, Dunn's summed-rank test was employed. To test for a (monotonic) trend, Jonckheere's test was used. If Bartlett's test was not significant, parametric procedures were employed. Bonferroni t-test compared the treatment group means to the mean of the control group. To test for a linear trend over the doses, regression analysis was used.

In both nonparametric and parametric instances, significance was expressed at the two-sided experiment-wise error rates of 1 and 5%. Significance was reported as two-sided 1% level in the test for trend. Regarding

parametric situations, the linear trend test was performed only if the test (for lack-of-fit) was not significant at the 1% level. In the nonparametric case, a test for lack-of-fit was not applicable.

C. Methods

1. OBSERVATIONS

All rats were observed each morning and afternoon for mortality and morbidity. When the test article was administered, once-daily cageside inspections were made and clinical signs, time of onset, duration of signs and time of recovery were recorded. The Draize Scoring System was used to evaluate gross skin observations.

2. BODY WEIGHT

Individual body weights were recorded weekly (starting one week before test article administration) and at study termination.

3. FOOD CONSUMPTION

This parameter was measured weekly (starting one week before test article administration). Data were collected for 5 days each week and excessive spillage was recorded.

4. CLINICAL CHEMISTRY

At the time of scheduled necropsy (after 16-25 hour fast) blood was taken from the abdominal aorta. The following parameters were examined:

ELECTROLYTES

xCalcium*
xChloride*
xPhosphorus*
xPotassium*
xSodium*

ENZYMES

xCreatine phosphokinase
xAlanine aminotransferase*
xAspartate aminotransferase*
xGamma glutamyl transferase

OTHER

xAlbumin*
xBlood creatinine*
xBlood urea nitrogen*
xTotal cholesterol
xGlobulins
xGlucose*
xTotal bilirubin
xTotal serum protein*
xAlbumin/globulin ratio

* = EPA Guideline requirement

x = parameter examined

5. SACRIFICE AND PATHOLOGY

Rats were fasted 16-25 hours prior to terminal sacrifice. They were anesthetized with ether, blood was removed from the abdominal aorta for clinical chemistry determinations and they were exsanguinated. The brain and kidneys were weighed and the weights expressed as absolute and relative (to body and to brain weights).

NOTE: Agency Guideline states that the testes are to be weighed. The following tissues were collected from all rats and preserved in 10% neutral buffered formalin:

DIGESTIVE SYSTEM

xSalivary glands*
xEsophagus*
xStomach*
xDuodenum*
xJejunum*
xIleum*
xCecum*
xColon*
xRectum*
xLiver*
xPancreas*

CARDIOVASC/HEMAT

xAorta*
xHeart*
xBone marrow*
xLymph nodes*
xSpleen*
xThymus*

NEUROLOGIC

xxBrain*
xPeripheral nerve*
xSpinal cord (3 levels)
xPituitary*
xEyes (optic n.)

UROGENITAL

xxKidneys*
xUrinary bladder*
xTestes*
xEpididymides
xProstate
xSeminal vesicle

GLANDULAR

xAdrenals
xLacrimal gland
xMammary gland
xParathyroids*
xThyroids*

RESPIRATORY

xTrachea*
xLung*

OTHER

xBone
xSkeletal muscle
xSkin (treated and untreated)
xGross lesions/masses

* = EPA Guideline Requirement x=tissue preserved
xx=organ weighed

The kidneys, forestomach, treated skin, untreated skin and gross lesions from all animals were examined microscopically.

III. RESULTS

A. Observations

1. MORTALITY

All animals survived until scheduled terminal sacrifice.

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2. CLINICAL SIGNS

Rats at 250 and 600 mg/kg/day had a higher incidence of rough coat beginning with study day 10 and continuing until study termination. Colored material around the nose was reported in a higher incidence in the 600 mg/kg/day group, primarily from day 15 until study termination. Colored material around eyes was noted in 1-2 rats/day at doses of or above 100 mg/kg/day. No other findings appeared to be test article related.

Table 3

CLINICAL SIGNS IN RATS TREATED WITH CHLOROTHALONIL
(animal-days with observation)

Observation	mg/kg/day				
	0	60	100	250	600
Rough coat	0	0	9	44	73
Colored material around nose	1	1	1	7	27

10 males/group; 22 study days

Data extracted from Report Table 1, pages 33-37.

3. DERMAL TOXICITY

Table 4

GROUP MEAN DERMAL ERYTHEMA VALUES FOR RATS TREATED
WITH CHLOROTHALONIL

Days	mg/kg/day				
	0	60	100	250	600
8	0	1.0a(1=10)b	1.0(1=10)	0.9(0=1,1=9)	1.0(1=10)
9	0	1.0(1=10)	1.1(1=9,2=1)	0.9(0=1,1=9)	1.0(1=10)
10	0	1.8(1=2,2=8)	1.8(1=2,2=8)	1.2(1=8,2=2)	1.5(1=5,2=5)
11	0	2.0(2=10)	2.0(2=10)	1.9(1=1,2=9)	2.0(2=10)
12	0	2.0(2=10)	2.1(2=9,3=1)	2.0(2=10)	2.0(2=10)
15	0	1.9(1=1,2=9)	2.0(2=10)	2.0(2=10)	2.0(2=10)
16	0	1.9(1=1,2=9)	2.0(2=10)	2.0(2=10)	2.0(2=10)
17	0	1.8(1=2,2=8)	2.0(2=10)	2.0(2=10)	2.0(2=10)
18	0	1.6(1=4,2=6)	2.0(2=10)	2.0(2=10)	2.0(2=10)
19	0	1.4(1=6,2=4)	1.9(1=1,2=9)	2.0(2=10)	2.0(2=10)
20	0	1.3(0=1,1=5, 2=4)	1.9(1=1,2=9)	2.0(2=10)	2.0(2=10)

FOOTNOTES ON NEXT PAGE

NOTE: Days 1-5, 0 erythema; days 6/7 and 13/14, no dermal evaluation

a = Mean Draize Score

b = Number of rats with Draize Score

Draize Scoring: 0 = no erythema; 1 = very slight erythema; 2 = well defined erythema; 3 = moderate to severe erythema

Data extracted from Report Table 2, pages 38-52.

As shown in Table 4, dermal irritation, characterized as erythema, was observed at all dose levels. Erythema was well defined (2.0 according to Draize) from days 11 through 20 at doses of 100, 250 and 600 mg/kg/day. At 60 mg/kg/day, the mean score for erythema declined from day 15 with the mean score being 1.8, 1.6, 1.4 and 1.3 on days 17, 18, 19 and 20, respectively.

The incidence of skin desquamation is shown in Table 5.

Table 5

THE INCIDENCE OF SKIN DESQUAMATION IN RATS TREATED WITH
CHLOROTHALONIL (1)

Day	mg/kg/day				
	0	60	100	250	600
10	0	0	0	0	2
11	0	0	0	0	4
12	0	7	7	4	7
13	-	-	-	-	-
14	-	-	-	-	-
15	0	9	9	9	10
16	0	10	10	9	10
17	0	10	10	10	10
18	0	8	9	9	10
19	0	5	7	8	10
20	0	5	7	7	9

(1) = No. of rats with lesion out of 10/group.

- = not examined

Data extracted from Report table on page 26.

Desquamation was reported in 9 or 10/10 rats in all treated groups for at least 3 observation days. On days 19 and 20, there was a dose-related increase in the incidence of desquamation; the incidences were 5/10, 7/10, 7 or 8/10 and 9 or 10/10 rats at 60, 100, 250 and 600 mg/kg/day, respectively.

2. BODY WEIGHTS

Table 6

GROUP MEAN BODY WEIGHTS IN RATS TREATED WITH CHLOROTHALONIL

Week	mg/kg/day				
	0	60	100	250	600
0	203±4.5	203±8.1	204±6.2	206±8.5	206±4.7
1	203±6.4	197±12.1	198±7.4	197±10.7	195±6.0
2	215±9.9	207±15.9	205±7.6	207±13.4	201±6.6*
3	220±10.3	216±18.1	214±8.6	213±14.0	210±6.3

No. of rats/group = 10

Values are means ± S.D.

Statistical Significance: * = $p < 0.05$

Data extracted from Report Table 4, page 58.

As shown in Table 6, at week 1, the mean body weights were equal to or lower than that of week 0 for all groups including the control. At week 2, only the rats at the high dose exhibited a significant decrease in the mean body weight. At week 3, mean body weights of treated rats were comparable to that of the controls. There was a dose-related decrease in body weight gain, but the decrease reached statistical significance only at the high dose; body weight gains were 17, 13, 10, 7 and 4 g at 0, 60, 100, 250 and 600 mg/kg/day, respectively.

3. FOOD CONSUMPTION

Mean food consumption (g/day) was lower in both the control and treated groups during week 1. Food consumption values, however, were similar for all groups during week 2 and higher during week 3. The Author attributed the lower food consumption seen during week 1 to the handling of the rats as well as the collars worn by them. This lower food consumption was reflected in the lower mean body weight observed during the same period (week 1).

4. CLINICAL CHEMISTRY

The only parameter for which there was a significant difference between the treated and control values was alanine aminotransferase where there were group mean lower values ($p < 0.01$) for the 250 and 600 mg/kg/day group. The Author indicated that lower values for this enzyme have also been reported following dermal applications to rabbits and oral administration to rats and dogs for 90 days.

5. NECROPSY

A. Macroscopic Pathology

Other than dermal changes, there were no apparent test article related findings at necropsy. There were 9 or 10/10 rats with yellow skin in all treated groups. Desquamation was reported in 0, 4, 7, 4 and 6 rats at 0, 60, 100, 250 and 600 mg/kg/day.

B. Organ Weights

Statistically significant increases in group mean absolute kidney weights were seen in rats at 250 and 600 mg/kg/day when compared with controls.

Table 7

GROUP MEAN ($\pm$ S.D.) ABSOLUTE AND RELATIVE KIDNEY WEIGHTS IN RATS
TREATED WITH CHLOROTHALONIL

	mg/kg/day				
	0	60	100	250	600
BODY WT-g	200 $\pm$ 9.9	194 $\pm$ 16.4	191 $\pm$ 7.1	192 $\pm$ 12.3	186 $\pm$ 5.1*
Absol Wt-g	1.46 $\pm$ 0.11	1.54 $\pm$ 0.15	1.54 $\pm$ 0.09	1.59 $\pm$ 0.11*	1.61 $\pm$ 0.07*
Rel BW-g/100g	0.73 $\pm$ 0.03	0.79 $\pm$ 0.02**	0.81 $\pm$ 0.03**	0.83 $\pm$ 0.03	0.86 $\pm$ 0.03**
Rel Br-g/g	0.83 $\pm$ 0.05	0.89 $\pm$ 0.07*	0.88 $\pm$ 0.04	0.90 $\pm$ 0.05	0.91 $\pm$ 0.05**

Rel BW-g/100g = relative kidney weight (g)/100 g of body weight

Rel Br-g/g = relative kidney weight (g)/g of brain weight

10 rats/group

Statistical Significance: * = $p < 0.05$; ** = $p < 0.01$

Data extracted from Report Table 11, page 69.

The kidney weights (absolute/relative) in this study were compared to the kidney weights of a control group in another study at the testing facility which utilized the same sex/strain of rats (Table 8). This comparison indicated that the kidney weights of the concurrent control were lower (1.46 g) than the kidney weights of the control group in the "other study" (1.56 g) which was similar to the kidney weights seen in treated rats (1.54 to 1.61 g) in this study. Thus, the lower kidney weights in the concurrent controls may have caused a "statistical significance" but not a "biological significance." This is further substantiated by the lack of histopathological lesions in the kidneys at any dose level.

Table 8

COMPARISON OF CONTROL GROUP MEAN KIDNEY WEIGHTS ($\pm$ S.D.) IN THIS
21-DAY DERMAL STUDY WITH HISTORICAL CONTROL VALUES

Study	Age (days)	Body Weight (g)	Kidney Wt (g)	Rel to BW (g/100 g)	Rel to Br (g/g)
This Study	93	200 $\pm$ 9.9	1.46 $\pm$ 0.11	0.73 $\pm$ 0.03	0.83 $\pm$ 0.05
Other Study	92	230 $\pm$ 8.0	1.56 $\pm$ 0.07	0.67	0.88 $\pm$ 0.04

Relative kidney-to-body weight for historical study calculated by this Reviewer.

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Data extracted from a table on Report page 29.

C. Microscopic Pathology

No test article related effects were seen on the kidney or forestomach. Treatment affected only the skin where there were hyperkeratosis and squamous epithelial hyperplasia in 10/10 animals in all treated groups; none were seen in the controls. Though severity of the lesions varied from minimal to moderate for individual rats, there did not appear to be a dose-related increase in the degree of severity. This was consistent with observations of the skin during the 21 days.

III. DISCUSSION

Male fischer 344 rats received 15-repeated dermal applications of CHLOROTHALONIL at 0, 60, 100, 250 or 600 mg/kg/day over a period of 21 days. There was no mortality. Clinical signs at doses $\leq$ 100 mg/kg/day were limited to rough hair coat and colored material around nose and/or eyes. Dermal irritation, characterized as erythema and desquamation, was observed at all dose levels. Although the mean body weights of treated rats were comparable to that of the controls, there was a slight numerical dose-related decrease in mean body weight gains with the decrease reaching statistical significance at 600 mg/kg/day. This decrease in body weight gains was not considered to be of toxicological significance.

Clinical chemistry analysis indicated a decrease in alanine aminotransferase levels at 250 and 600 mg/kg/day; the toxicological significance of this is not known due to a lack of corroborative histopathological lesions. It is, however, interesting to note that a decrease in this enzyme level was also seen in other studies after dermal application to rabbits as well as oral administration to rats and dogs. The slight increases seen in kidney weights were not considered to be treatment related due to a lack of histopathological lesions in the kidneys and also because the increase may have been caused by lower weights in the concurrent control group. No treatment-related histopathological lesions were seen in the kidneys or forestomach. Treatment-related dermal lesions were hyperkeratosis and hyperplasia of the squamous epithelium of all rats at all dose levels.

The objective of this study was to establish a NOEL for kidney effects after dermal administration as the kidney was the target organ following oral administration to rats and dogs. Results of this study indicate a NOEL $>$ 600 mg/kg/day (highest dose tested)

for kidney effects after repeated dermal applications to male rats.

The dermal toxicity of CHLOROTHALONIL was also investigated in the rabbit; the results of that study are as follows:

In a 21-day dermal toxicity study (MRID No. 00158254), CHLOROTHALONIL was administered to six/sex New Zealand white rabbits at dose levels of 0 (vehicle of aqueous methylcellulose), 0.1, 2.5 and 50 mg/kg/day. Parameters examined were survival, physical condition, skin condition, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and microscopic pathology. .

Dermal irritation was observed grossly at 2.5 and 50 mg/kg/day. Microscopic skin changes were characterized as generally minimal to slight acanthosis and hyperkeratosis. No significant dermal effects were noted in the 0.1 mg/kg/day group. All other parameters were negative with the exception of a decrease in alanine aminotransferase levels at 2.5 and 50 mg/kg/day. For dermal toxicity the NOEL was 0.1 mg/kg/day. For systemic toxicity, the NOEL was > 50 mg/kg/day (highest dose tested); a LOEL was not established.

CHLOROTHALONIL

21-Day Dermal, Rat (\$82-2)

Sign-off date: 12/03/96
DP Barcode: D230222
HED DOC Number: 012107
Toxicology Branch: TB2