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

AUG - 6 1993

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID 018301; Chlorpropham; CIC DER on a 21-Day Dermal Toxicity Study (MRID# 418999-01).

Tox.Chem. No.: 510A.
HED Project No: 1-1504.
Case: 818637.
Action Code: 627.
DP Barcode: D165226.
Submission No.: S397523.
Contract No.: 68D10075.
Work Assignment No.: 1-43.1.
Clement No.: 91-143.
DOC930007.

From: David G Anderson, PhD David G Anderson 10/9/92
Section 3
Toxicology Branch-1
Health Effects Division (H7509C)

To: Walter Waldrop/Venus Eagle PM-71
Reregistration Branch
Special Review and
Registration Division (H7508C)

Thru: Karen Hamernik, PhD. K. Hamernik 7/30/93 KB 8/2/93
Acting Section Head
Section 3, Toxicology Branch-1
Health Effects Division (H7509C)

A. CONCLUSIONS:

Chlorpropham was applied dermally to the clipped backs of 7 New Zealand White rabbits per sex per group at 0, 100, 500 or 1000 mg/kg/day for 21-days.

Dermal Effects :
NOEL: < 100 mg/kg/day.
LEL: < 100 mg/kg/day for dermal irritation at all dose levels and minimal acanthosis, hyperkeratosis and focal inflammatory cells (8/14). At higher dose levels minimal to slight acanthosis, hyperkeratosis and focal inflammatory cells occurred.

Systemic toxicity:
NOEL: 500 mg/kg/day.
LEL: 1000 mg/kg/day for increased reticulocytes (possibly related spleen weight relative to brain weight ↑ increased in males and females were observed).

Core classification: Minimum. On 3 occasions some animals were dosed for 24 hours rather than 6 hours. The animals subjected to this excessive dosing period were not identified. The effects noted may not have been noted if the study had been conducted according to the guidelines. Although the study was initially classified as supplementary, by the contractor repeating the study would not supply the Agency with meaningful additional data.

B. ACTION REQUESTED:

Review the reported toxicology in the rabbit 21-day dermal toxicity study on the effects of chlorpropham (MRID# 418999-01).

C. Bases for the Conclusions:

The following study was reviewed by Clement International Corp.

Krohmer, RW 21-Day Dermal Toxicity Evaluation of Chlorpropham in Rabbits, Project No.: 393F-304-231-89, conducted by T.P.S., Inc. for the Chlorpropham Task Force, John Wise Associates, July 5, 1990. MRID# 418999-01.

The study was initially classified as supplementary by the contractor because some unidentified animals were dosed for 24 hours rather than the 6 hours recommended by the guidelines. However, the study demonstrates effects on red blood cells analogous to the feeding studies for 90-days in rat and mice (MRID# 418631-01 and 418993-01, respectively), but at higher dose levels. Thus, in the opinion of this reviewer, no new significant toxicity would be demonstrated by another 21-day dermal study in rabbits and the results of such a study would have no impact on regulation of chlorpropham.

Cover memo 21-day dermal toxicity study in rabbits/
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FINAL

DATA EVALUATION REPORT

CHLORPROPHAM

Study Type:
21-Day Dermal Toxicity Study in Rabbits

Study Title:
21-Day Dermal Toxicity Evaluation of Chlorpropham in Rabbits

Prepared for:

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

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

August 31, 1992

Principal Author Regina Mastrangelo Date 8/19/92
Regina Mastrangelo, M.S.

Reviewer John Liccione Date 8/19/92
John Liccione, Ph.D.

QA/QC Manager Sharon Segal Date 8/20/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-43.1
Clement Number: 91-143
Project Officer: James Scott

Guideline Series 82-2:
21-Day Dermal Toxicity Study in Rabbits

EPA Reviewer: Dr. David Anderson
Review Section III, Toxicology Branch I,
Health Effects Division

Signature: David Anderson

Date: 10/8/92

EPA Section Head: Dr. KAREN HAMERIK
Review Section III, Toxicology Branch I,
Health Effects Division

Signature:

Date: 7/30/93

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity Study in Rabbits Tox Chem. Number: 510A

TEST MATERIAL: Chlorpropham (technical grade) MRID Number: 418999-01
Isopropyl N-(3-chlorophenyl) carbamate

SYNONYMS: Chlorprophame; isopropyl-m-chlorocarbanilate; Chloro IPC, CIPC

STUDY NUMBER: 393F-304-231-89

SPONSOR: Chlorpropham Task Force; John M. Wise Associates
Liberty, MO 64068

TESTING FACILITY: Toxicology and Pathology Services, Inc.
10424 Middle Mt. Vernon Road
Mt. Vernon, IN 47620

TITLE OF REPORT: 21-Day Dermal Toxicity Evaluation of Chlorpropham in Rabbits

AUTHOR: R.W. Krohmer, Ph.D.

REPORT ISSUED: July 5, 1990; revised June 4, 1991

CONCLUSIONS: Chlorpropham, administered dermally to New Zealand White rabbits for 21 days at doses of 100, 500, and 1000 mg/kg/day was associated with minimal to slight dermal effects consisting of acanthosis, hyperkeratosis, and focal inflammatory infiltrate of the treated skin. The incidences for each of these effects at doses of 100, 500, and 1000 mg/kg/day were 8/14, 14/14, and 14/14, respectively. These doses also induced dose-related dermal irritation in the form of erythema and scaly skin. In addition, edema and fine transverse cracking were noted, especially in the high-dose group, but these effects were not dose related. Significant increases in reticulocyte counts occurred in the high-dose group but not in the low- or mid-dose groups. There were no treatment-related toxicological effects on mortality, body weight, organ weight, or clinical chemistry.

The no-observed-effect level (NOEL) for systemic toxicity is 500 mg/kg/day. The lowest-observed-effect level (LOEL) is 1000 mg/kg/day for increases in reticulocyte counts [redacted] (possibly related to spleen) KLH 7/30/93 Minimum 10/9/92 weights [redacted] relative to brain weights increased in both sexes were observed.

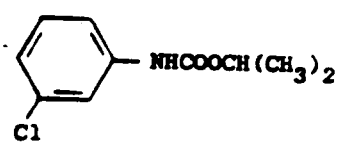
CORE CLASSIFICATION: Core ~~Supplementary~~ Minimum. This study ~~does not~~ satisfies the Guideline Series 82-2 requirements for a 21-day dermal toxicity study in rabbits. The study ~~is~~ was classified as Core ~~Supplementary~~ Minimum because the study reported that some animals were exposed for 24 hours instead of 6 hours. The study ~~must~~ should indicate which animals were exposed for 24-hour periods and what days the 24-hour exposures occurred for each animal. This information should be contained in a "Protocol Deviations" section of the report. A second reason for the classification of Core ~~Supplementary~~ Minimum is that food consumption levels were not reported, as is required by the guidelines. The animals appeared to be healthy throughout the study and there were no adverse effects that could be attributed to changes in food consumption, such as a decrease in body weight or organ weight. Therefore, the reviewers believe that exclusion of the food consumption data did not alter the conclusions of the study. A repeat study would not supply meaningful information. 10/9/92 1000 mg/kg/day is the limit dose for this type of study.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Chlorpropham

Formula:



Lot number: 14065 L 89

Purity: ~~97.1%~~ 96.2% KLH 7/30/93 (Sponsor analysis)

Physical property: White crystalline solid

Stability: Not reported Product stability has been established in previous studies. KLH

2. Test Article Analyses for Purity and Stability

The test material was melted at 45-47°C, recrystallized, and ground to a fine crystalline powder prior to application onto the rabbit skin. The dose was measured by weighing the recrystallized material. Saline (0.9%) was used to moisten the material prior to application.

The test material was not tested for stability or purity by the reporting laboratory. A sample was given to the sponsor for this purpose; however, no stability results were provided or discussed in the report. The purity of the test material was analyzed by an unspecified laboratory and was reported to be 97.1%. The impurities in the sample were not specified.

3. Animals

New Zealand White albino rabbits were received from Lessers Rabbitry, Union Grove, WI. Animals were housed in hanging, metal cages (1 animal per cage) in a room with a 12-hour light/12-hour dark cycle and with temperature and humidity controls set at 64-72°F and 25-70%, respectively. Tap water (automatic water system) and food (Purina Certified Rabbit Chow® #5322) were provided ad libitum.

The period of acclimation, prior to initiation of testing, was described as "adequate" by the author; however, no duration was specified. Rabbits were identified by ear tattoo.

At the time of exposure, body weights ranged from 2.4 to 3.7 kg for males and 2.1 to 3.7 kg for females. No ages were specified for the animals, however, they were described as "young adults" at the time that they were received.

Rabbits received physical and ophthalmological examinations prior to treatment with chlorpropham. Rabbits were randomly grouped (7/sex/dose) utilizing a randomization computer program. Animals were assigned to exposure groups, as shown in Table 1. Exposure doses of the test material were incorrectly based upon a purity of 100% on day one of exposure, and 96.2% chlorpropham, on the remaining days of exposure. Later, the purity of the test material was found to be 97.1%. A group of 14 (7/sex) saline-treated rabbits was used as the vehicle control. The doses used in this study were previously determined by the sponsor, but the rationale for the selection of dose levels was not discussed.

4. Procedure

Hair was removed from the back of each rabbit 1 day prior to treatment with chlorpropham and thereafter, when necessary. Only animals that had abrasion-free skin were used in the study.

Exposures were conducted by spreading the test material, which was moistened with saline, or saline vehicle control, over 10% of the total body surface area of each rabbit. Gauze was used to cover the treated area and rubber damming was taped over the gauze. During exposure, collars were used to prevent each rabbit from contacting the application site. Animals were exposed daily in this manner for at least 6 hours per day (on 3 occasions, maximum exposures of 24 hours were used). Males were exposed in this manner for 21 consecutive days and females were exposed for 22 days. Following each daily exposure, the wrapping was removed, animals were cleaned (the cleaning procedures were not specified), and chlorpropham or saline were reapplied.

TABLE 1. Group Assignment and Dose Levels for Rabbits During 21-Day Dermal Exposure to Chlorpropham

Dose Group[1]	Target Dose Level (mg/kg/day)	Levels of Exposure[2] (mg/kg/day)
Group 1 (Control)	0	0
Group 2 (Low-)	100	104
Group 3 (Mid-)	500	520
Group 4 (High-)	1000	1040

[1] Data are based on 7 animals/dose/sex.
[2] The levels of exposure were reported in the study and were based upon a purity of 96.2%. However, after the exposure period, the actual purity of chlorpropham was found to be 97.1%. Therefore, the actual exposure doses given to the rabbits are slightly higher than those indicated. Also, exposure levels on day 1 were lower than the target doses because the doses were incorrectly based upon a purity of 100% for that day.

5. Statistical Methods

Dunnett's analysis of variance was used to determine the statistical significance of data for treated groups as compared to the controls. Statistical analyses were performed on mean hematologic and clinical chemistry values, body weights, weight changes, growth rates, organ weights, organ/body weight ratios, and organ/brain weight ratios.

6. General Observations

Hematologic and clinical chemistry parameters were measured prior to exposure and at necropsy. Body weights were measured at the initiation of the study, once per week during the exposure period, and just prior to necropsy. It was not reported whether food consumption was measured. Animals were observed twice daily for general health, physical appearance, behavior, and pharmacologic or toxic effects. On the last day of dosing, animals were given physical and eye examinations. Animals were sacrificed 1 day after the termination of exposure. At this time, necropsy and blood collection were performed.

(a) Mortality/moribundity/survival

There was neither mortality nor moribundity in animals prior to termination of the study.

(b) Clinical observations

No pharmacological, toxicological, or behavioral effects were observed during the study. Erythema, edema, fine transverse cracking, and scales, but not scabs, were noted on the skin by clinical observation. Erythema and scales appeared to be dose related and occurred in all exposure groups. Table 2 summarizes these results. Only erythema was noted for all 4 weeks of the observation period in each exposure group; edema was also noted for 4 weeks, but only in the rabbits that received 1000 mg/kg/day. Edema, in the low-dose group (100 mg/kg/day), and the remaining effects in the majority of the exposure groups, were first observed during the second week of treatment. The incidences of these effects remained the same through week 4 of exposure.

(c) Body weights/food consumption

Body weights--There were no significant effects on body weight or body weight gain.

Food consumption--Food consumption data were not reported. The study does not indicate whether food consumption was measured.

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TABLE 2. Summary of the Incidence of Dermal Effects in Rabbits During and Following 21-Day Dermal Exposure to Chlorpropham[a]

Dermal Effect (week of exposure)	Dose Group			
	Group 1 (0 mg/kg/day)	Group 2 (100 mg/kg/day)	Group 3 (500 mg/kg/day)	Group 4 (1000 mg/kg/day)
Erythema (1)	0	1	7	14
(2)	0	6	9	14
(3)	0	6	6	13
(4)	0	6	6	13
Edema (4)	0	2	0	3
Fine transverse cracking (4)	0	0	1	3
Scales (4)	0	1	3	6

[a] Data are based on 7 rabbits/sex/dose.

7. Clinical Pathology

Blood samples were taken from fasted rabbits from the marginal ear vein prior to treatment and from the vena cava at necropsy. The checked (X) parameters were examined.

(a) Hematology

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

* = Recommended by Subdivision F (November 1984) Guidelines

There was a dose-related increase in the mean percent reticulocyte count in the mid- and high-dose males and females. This increase was statistically significant ($p \leq 0.01$) in the high-dose group when compared to controls (Table 3). No other statistically significant hematological effects occurred in rabbits following treatment with chlorpropham.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
X Cholinesterase
X Creatinine phosphokinase
X Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
Gamma glutamyltransferase (GGT)

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
Cholesterol
X Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
Triglycerides

* = Recommended by Subdivision F (November 1984) Guidelines

TABLE 3. Selected Hematology and Clinical Chemistry Values [Mean ±(SD)] for Rabbits Following 21-Day Dermal Exposure to Chlorpropham[a,b]

Hematological and Clinical Chemistry Parameters (Week #4)	Dose Group							
	Group 1 (0 mg/kg/day)		Group 2 (100 mg/kg/day)		Group 3 (500 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female	Male	Female	Male	Female
Reticulocyte count (%)	2.4 (0.5)	2.4 (1.0)	2.5 (0.6)	2.6 (1.2)	3.5 (1.3)	3.3 (1.0)	5.0** (1.9)	5.6** (1.2)
Calcium level (mEq/L)	15.8 (0.6)	15.2 (0.8)	14.2* (1.0)	14.6 (1.3)	14.8 (1.7)	15.4 (0.5)	15.1 (0.5)	15.6 (0.5)
Glucose level (mg/dl)	349.9 (96.7)	162.8 (88.2)	196.6* (72.1)	196.0 103.2	164.9* (65.5)	259.9 (172.1)	240.6* (84.2)	153.4 (38.8)

[a] Data represent parameters measured at termination of the study.
[b] Data are based upon 7 rabbits/sex/dose.
* Significantly different from control value, $p \leq 0.05$
** Significantly different from control value, $p \leq 0.01$

Table 3 summarizes data on selected clinical chemistry parameters. The author reported a statistically significant decrease ($p \leq 0.05$) in calcium levels in males from group 2 (100 mg/kg/day). However, the standard deviations for the values overlap with the control data. Therefore, this effect is not considered to be related to treatment with chlorpropham. Similarly, statistically significant ($p \leq 0.05$) decreases in serum glucose levels were reported in male rabbits from all exposure groups; however, only the standard deviations for these values in rabbits receiving 500 mg/kg/day did not overlap with those of the controls. Since the decrease in serum glucose levels was not dose related, this effect is not likely to be treatment related.

8. Sacrifice and Pathology

No animals died during the study. All animals were sacrificed after a minimum of 21 days of treatment (i.e., on day 21 for males; on day 22 for females), and complete necropsies were performed.

For all animals, histological examination was conducted after tissue fixation in 10% neutral-buffered formalin of those organs checked (X), below. A double-check (XX) denotes organs that were also weighed.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	Aorta	XX Brain
Salivary glands	XX Heart	Peripheral nerve (sciatic nerve)
Esophagus	X Bone marrow	X Spinal cord (three levels)[b]
Stomach	Lymph nodes	XX Pituitary
Duodenum	XX Spleen	X Eyes (Optic nerve)[c]
Jejunum	Thymus	
Ileum		Glandular
Cecum	Urogenital	
Colon		XX Adrenals
Rectum	XX Kidneys*	Lacrimal gland
XX Liver*	Urinary bladder	Mammary gland
Gallbladder	XX Testes*	XX Thyroids
Pancreas	XX Epididymides	XX Parathyroids
	Prostate	X Harderian glands
Respiratory	Seminal vesicle	
	XX Ovaries	
Trachea	Uterus	
X Lung		

Other

X Bone (sternum and femur)*
X Skeletal muscle

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X Skin (treated and untreated)*
X All gross lesions and masses*

* = Recommended by Subdivision F (November 1984) Guidelines
[a]Only the sternum was examined.
[b]Only the cervical and thoracic sections were examined.
[c]It was not reported whether this specific parameter was examined.

(a) Macroscopic

The high-dose rabbits (1000 mg/kg/day) had roughened, thickened skin at the site of treatment. No other gross lesions were noted.

(b) Organ weights and body weight ratios

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weights (both sexes)

There were no statistically significant differences in absolute ~~and~~ organ relative organ weights. Table 4 summarizes data on selected relative organ weights. Heart and spleen weights relative to body weight and spleen weight relative to brain weight in males were reported to be statistically significantly greater than those of controls; however, the standard deviations for these values overlap with the control values. The increased spleen weight may be related to the increased percent reticulocytes at 1000 mg/kg/day. ~~However, these effects may not be related to treatment with chlorpropham.~~ DN 10/8/92

The organ weight changes were not accompanied by histological lesions.

(c) Microscopic

Histological data for selected lesions are summarized in Table 5. Effects on the skin were treatment related since there was a dose-response relationship for each effect and all exposure groups, of both sexes, were affected; but none of the control animals were affected.

Several minimal to slight ~~effects~~ findings, which were not dose related, occurred in male rabbits of all exposure groups in the brain, eye, heart, and kidney (Table 5). These ~~effects~~ findings are not considered to be treatment related since they were not noted in the male control group but did occur in the female control and treated groups at incidences comparable to those of the treated males. KLH 7/30/93

No statistical analyses were conducted for any of the histopathological effects; ~~therefore, it cannot be verified whether the effects are or are not treatment related~~. KLH 7/30/93

TABLE 4. Selected Relative Organ Weight Data for Male Rabbits Following 21-Day Dermal Exposure to Chlorpropham

Organ	Group 1 (0 mg/kg/day)	Group 2 (100 mg/kg/day)	Group 3 (500 mg/kg/day)	Group 4 (1000 mg/kg/day)
		Mean Organ to Body Weight Ratio (%)[a] (SD)		
Heart	0.220 (0.016)	0.247* (0.011)	0.250** (0.020)	0.239 (0.015)
Spleen	0.030 (0.008)	0.045 (0.012)	0.053* (0.024)	0.050 (0.016)
		Mean Organ to Brain Weight Ratio (%)[a] (SD)		
Spleen	10.39 (2.92)	15.57 (3.95)	16.67* (5.51)	16.40* (5.06)

[a] Data are based upon 7 male rabbits/dose; female data not shown.
* Significantly different from control value, $p \leq 0.05$
** Significantly different from control value, $p \leq 0.01$

TABLE 5. Selected Pathological Effects in Rabbits Following 21-Day Dermal Exposure to Chlorpropham[a]

Affected Organ and ~~Effect~~ Finding Noted	Incidence of Effect (Severity)[b]							
	Group 1 (0 mg/kg/day)		Group 2 (100 mg/kg/day)		Group 3 (500 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female	Male	Female	Male	Female
Brain								
Focal encephalitis	0	3 (1-2)	3 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)	2 (1)	0
Eye								
Focal lymphoid infiltrate	0	1 (1)	1 (1)	0	2 (1)	1 (1)	1 (1)	1 (1)
Heart								
Focal myocarditis	0	3 (1)	3 (1)	0	3 (1)	1 (1)	2 (1)	0
Kidney								
Focal interstitial nephritis	1 (1)	3 (1-2)	4 (1-2)	2 (1-2)	2 (1)	3 (1-2)	4 (1)	0
Treated Skin								
Acanthosis	0	0	4 (1)	4 (1)	7 (1-2)	7 (1-2)	7 (1-2)	7 (1-2)
Hyperkerotosis	0	0	4 (1)	4 (1)	7 (1-2)	7 (1-2)	7 (1-2)	7 (1-2)
Focal Inflammatory Infiltrate	0	0	4 (1)	4 (1)	7 (1)	7 (1)	7 (1)	7 (1)
Foot								
Dermatitis	ND	ND	ND	ND	1[c] (2)	ND	ND	ND

[a] Data are based on 7 rabbits/sex/dose, unless otherwise specified.
[b] Severity ratings: (1) = minimal, (2) = slight, (3) = moderate, (4) = marked, (5) = extensive/severe
[c] Only one animal was tested because of abnormal foot effects in this animal.
ND = No data; ~~effect was not tested for these animals~~ apparently was an incidental finding in 1 animal. KLH 7/30/93

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The reviewers have no other comments regarding the materials and methods sections.

A description of the statistical analysis employed was included in the report.

A signed Good Laboratory Compliance Statement, a signed Quality Assurance Statement, and a list of Quality Assurance Inspections were included.

B. DISCUSSION

The study design was acceptable for a repeated dose dermal study. Generally, the study was complete, the data were well reported, and all summary data were supported by individual animal data. However, the report did not indicate whether food consumption was measured, as required by the guidelines, and food consumption data were not reported. Also, on page 11 of the study, it was reported that some animals were exposed for 24 hours instead of 6 hours. However, there was no information as to which animals were exposed for 24-hour periods or on what days the 24-hour exposures occurred. This information should be contained in a "Protocol Deviations" section of the report. Another deviation from the guidelines is that statistical analyses were not conducted for any of the gross or histopathological effects noted in the treated animals.

Although, the food consumption levels were not reported, the animals appeared to be healthy throughout the study. There were no decreases in body weight or organ weights to indicate a reduction in food consumption and there were similar increases in body weight between the treated and control groups. Therefore, it is likely that inclusion of the food consumption data would not alter the findings of the study.

A dose-related increase in reticulocyte count was noted but was statistically significant only in the high-dose group. Although the study author mentioned that the increase in reticulocyte counts may be indicative of a decreased red cell life span and subsequent increase in hemopoiesis, there were no clinical signs of anemia in the rabbits. No other treatment-related changes were noted in other hematological parameters. Chlorpropham did not induce mortality and did not affect organ weight, body weight, or blood chemistry in rabbits (except, possibly, for the increases in spleen weight relative to brain weight observed in both sexes at the HDT). KLH 7/30/93

Minimal to slight dermal effects of acanthosis, hyperkeratosis, and focal inflammatory infiltrations of the skin, were noted at all doses and were treatment related. Also, erythema and scales of the skin were dose-related and treatment-related effects. Edema and fine

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transverse cracking [redacted] in the high dose group may have been related ~~were treatment related only in the high dose animals.~~ to treatment.

In summary, dermal administration of chlorpropham to rabbits at a dose of 1000 mg/kg/day induced a significant increase in reticulocyte count. No other systemic effects were noted. Therefore, the LOEL for systemic toxicity is 1000 mg/kg/day and the NOEL is 500 mg/kg/day. Minimal to slight dermal effects were noted in all treated animals.