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CASWELL FILE

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

JUN 14 1993

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**MEMORANDUM**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**SUBJECT:** Picloram, Potassium Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits, and Picloram, Triisopropanolamine Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits.

Tox.Chem No.: 663C & 663CD
MRID No.: 413849-01 & 413849-02
DP Barcode: D165820
Submission No.: S398435
PC Code: 005104 & 005102

From: John C. Redden, Toxicologist
Section 3
Toxicology Branch 1
Health Effects Division (H7509C)
5/26/93

To: Venus Eagle, Product Manager 71
Reregistration Branch
Special Review and Reregistration Division (H7509C)

Thru: Karen L. Hamernik, Ph.D.
Acting, Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)
5/26/93 KB 6/1/93

**CONCLUSIONS:**

Picloram, Potassium Salt (Caswell No. 663C) MRID 413849-01: NOEL (systemic) ≥ 753 mg/kg/day for male and female New Zealand White rabbits. A LOEL (systemic) was not established for males and females. Dermal irritation, very-slight to well-defined edema and/or erythema, was observed at all doses, in both sexes. The highest dose tested was not the limit dose of 1000 mg/kg/day. However, the study authors stated that 753 mg/kg/day corresponded to a dose volume of 1.7 ml/kg/day which was the maximum amount of test material that could be practically maintained at the test site. The study was classified as Core **Minimum**, and satisfies the guideline requirement (82-2) for a 21-day repeated dermal toxicity study.

Picloram, Triisopropanolamine Salt (Caswell No. 663CD) MRID 413849-02: NOEL (systemic) ≥ 1,320 mg/kg/day for male and female

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New Zealand White rabbits. A LOEL (systemic) was not established for males or females. Dermal irritation, very slight to well-defined edema and/or erythema, was observed at all doses, in both sexes. The study was classified as Core **Guideline**, and satisfies the guideline requirement (82-2) for a 21-day repeated dermal toxicity study.

**ACTION:**

Request review of: 1) MRID 413849-01, "Picloram, Potassium Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits," and 2) MRID 413849-02, "Picloram, Triisopropanolamine Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits." The Sponsor is the Dow Chemical Co.

DOC930152

FINAL

# DATA EVALUATION REPORT

Picloram (Potassium Salt)

Study Type:
Twenty-one Day Repeated-Dose Dermal Toxicity Study

Study Title:
Picloram, Potassium Salt: 21-Day Dermal Toxicity Study
in New Zealand White 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

| | | |
|---|---|---|
| Principal Reviewer | Betty Shindel, M.P.H. | Date 9/21/92 |
| Independent Reviewer | William McLellan, Ph.D. | Date 9/21/92 |
| QA/QC Manager | Sharon Segal, Ph.D. | Date 9/21/92 |

Contract Number: 68D10085
Work Assignment Number: 1-89.1
Clement Number: 93-39
Project Officer: James Scott

Guideline Series 82-2
Twenty-one Day Repeated-Dose Dermal Toxicity Study

EPA Reviewer: Henry Spencer, Ph.D.
Tox. Branch I, Review Section III
Health Effects Division

Signature: Henry Spencer
Date: 9/30/92

EPA Section Head: Karen Hamernik, Ph.D.
Tox. Branch I, Review Section III
Health Effects Division

Signature: K. Hamernik
Date: 5/20/93

# DATA EVALUATION REPORT

STUDY TYPE: Twenty-one day repeated-dose dermal toxicity study

TEST MATERIAL: Picloram-$K^+$

CAS REGISTRY NUMBER: 2545-60-0

SYNONYMS: Tordon $K^+$ Salt Liquor; Picloram, potassium salt

MRID NUMBER: 413849-01

STUDY NUMBER: K-050731-008

PC NUMBER: 005104

SPONSOR: DowElanco, Midland, MI 49674

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI 49674

TITLE OF REPORT: Picloram, Potassium Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits.

AUTHORS: L. Atkin, W.T. Stott and K.E. Stebbins

REPORT ISSUED: January 31, 1990

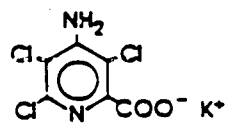
CONCLUSIONS: NOEL (systemic) = ≥753 mg/kg/day for male and female New Zealand White rabbits. A LOEL (systemic) was not established for males or females. KLH 5/20/93
Dermal irritation, very slight to well-defined edema and/or erythema, was observed at all doses, in both sexes.

CORE CLASSIFICATION: Core Minimum. This study satisfies the guideline requirement (82-2) for a 21-day repeated dermal toxicity study. The highest dose tested was not the limit dose of 1000 mg/kg/day. However, the study authors stated that 753 mg/kg/day corresponded to a dose volume of 1.7 ml/kg/day which was the maximum amount of test material that could be practically maintained at the test site.

## A. MATERIALS, METHODS, AND RESULTS

### 1. Test Article Description

**Chemical name:** 4-Amino-3,5,6-trichloropicolinate, potassium salt
**Physical state:** 35.2% (30.4% acid equivalent) aqueous solution
**Molecular formula:** $C_6H_2Cl_3N_2O_2 \bullet K^+$
**Structural formula:**




**Molecular weight:** 241.5 (Acid); 279.6 (potassium salt)
**Lot number:** AGR 276452

Vehicle: Distilled water
Purity: 100%
Stability: Dosage solutions were stable for 68 days.
Density: 1.258

2. Test Article Analyses for Homogeneity and Concentration

Homogeneity analyses of three samples of the 251-mg/kg/day dosing solution indicated that the test article was homogeneous. The homogeneity mean concentration was 129.5 mg/mL (target 127.9 mg/mL), with a 100.4 coefficient of variation*, and a 1.0 standard deviation. The percent recovery for the three samples was 101.6, 101.9 and 100.4% of the target picloram acid equivalent (127.9 mg/mL).

The mean concentrations of the 75.3, 251 and 753 mg/kg/day dose levels (target picloram acid equivalent = 38.3, 127.9 and 382.8 mg/mL) were 36.8, 128.4 and 382.8 mg/mL, respectively. The percent recoveries were 96.1, 100.4 and 89.8% of the target picloram acid equivalents at dose levels of 75.3, 251 and 753 mg/kg/day, respectively.

* This CV may have been an error in the study report because it could not be calculated from the mean & std. dev. supplied. The variability in the homogeneity mean values for top, middle & bottom positions appeared to be acceptable (i.e. CV's < 5%). KLH 5/20/93

3. Test Animals

Species: Rabbits
Strain: New Zealand White
Source: Hazleton Research Products, Inc., Denver, PA
Sex and numbers: 20 Males and 20 females
Age at study initiation: Approximately 5 months
Initial body weights: 3,460-4,369 g males; 2,989-3,579 g females

Animals were examined for health status upon arrival. Prior to dosing, rabbits were acclimated to laboratory conditions for four weeks. All rabbits were housed in individual cages. Animals were identified by a unique alphanumeric metal ear tag. The animal room was designed to maintain an adequate temperature, humidity, and photocycle. Feed (Purina® Certified Chow #5322) was provided at a rate of 4 ounces/day/rabbit. Tap water was provided ad libitum throughout the acclimation and study period. Rabbits were assigned to groups based on body weight using a computer-generated randomization procedure. For at least four days during the week prior to dosing, animals were acclimated to an elastic jacket used to hold the test material dressing in contact with the skin.

Dose administration: Groups of five rabbits of each sex were dermally administered Picloram-K+ at doses of 75.3, 251 or 753 mg/kg/day (65, 217 or 650 mg/kg/day acid equivalent) at a volume of 1.7 mL/kg/day. Five rabbits of each sex served as a vehicle control group and were administered distilled water (vehicle) at a volume of 1.7 mL/kg/day. Each animal received 15 applications during a 21-day study period.

An area of fur approximately 10x15 cm on the back of each rabbit was clipped prior to study initiation and as needed throughout the study period. The test material was held in contact with the test site by absorbent gauze and non-absorbent cotton secured with an elastic jacket. At the end of the 6-hour exposure period, the test site was

wiped with a water-dampened disposable towel to remove any residual test material.

Dose selection was based on the absence of treatment-related effects in a prior dose range-finding study in which 1 New Zealand White male rabbit was administered 753 mg/kg/day of undiluted picloram-$K^+$ for 4 days.

4. Statistical Methods

Equality of variance for body weight, clinical chemistry and hematology (except WBC differential), and absolute and relative organ weight data were evaluated using Bartlett's test (Winer 1971)[1].

Body weight data were evaluated using a three-way measures ANOVA for a time-sex-dose interaction (Winer 1971)[1]. If a time-sex-dose interaction was present, analysis was repeated for each sex, and data were then examined for a significant sex-dose interaction. If a sex-dose interaction was identified, data were examined for each sex separately. The presence of a time-dose interaction was evaluated after accounting for the factor of sex (sex was controlled for or statistical significance was lacking). If a time-dose interaction was statistically significant, analysis was repeated for each dose level against controls.

A two-way ANOVA with the factors of sex and dose (Winer 1971)[1] was used to evaluate hematology (except WBC differential), clinical chemistry, terminal body weight, and relative and absolute organ weight (except testes) data. Data were first examined for a significant sex-dose interaction; if present, each sex was analysed separately using a one-way ANOVA. If no sex-dose interaction was identified but a dose effect was, separate ANOVAs were used for each dosage group with control. A Bonferroni correction was used to control for multiple comparisons with control.

Data for absolute and relative testes weights were analyzed using a one-way ANOVA; if significant, each dose was compared to controls using one-way ANOVA with Bonferroni's Correction.

5. General Observations

(a) Mortality/moribundity/survival

Each animal was observed at least once daily for mortality and moribundity during the study period. No mortality was reported for any of the animals.

[1]Winer, B.H. 1971. Statistical Principles in Experimental Design. McGraw-Hill Book Company, Inc., New York, NY.

(b) Clinical observations

Animals were observed prior to each test material application for clinical signs of toxicity. No clinical signs of toxicity were observed in any of the animals.

The severity of dermal irritation was evaluated prior to the second application and following each application using a modification of the acute dermal irritation scoring system recommended by the OECD (1981b)[2]. No dermal irritation was reported for vehicle control animals; however, dermal irritation was reported at each dose level for males and females. At a 75.3 mg/kg/day dose level, very slight erythema was observed in 1 male on test days 15-21 and 1 female on test day 20. At a 251 mg/kg/day dose level, very slight erythema was observed in from 1 to 3 males on test days 15-21 and 2 females on test days 7-20. At a 753 mg/kg/day dose level, very slight-to-well-defined erythema was observed in from 1 to 4 males on test days 13-21 and in 2 females on test days 13-20. A dose-related increase was observed in the incidence and severity of edema (from very-slight-to-[redacted] well-defined) in treated males. Very slight edema was observed at doses of 75.3, 251, and 753 mg/kg/day in from 1 to 2 males on days 16-21, 3 males on days 13-20, and from 1 to 5 males on days 3-15, respectively. Well-defined edema was observed at doses of 75.3 and 251 mg/kg/day in 1 male at day 21 and in from 1 to 3 males on days 15-21, respectively. Edema was not observed in females.

(c) Body weight/body weight gain/food consumption

Body weights were measured prior to the first application and approximately once a week throughout the study. Food consumption was not measured since each rabbit consumed its entire food ration of 4 ounces/day.

There were no effects on absolute body weights or body weight gains that were attributable to the test material. Body weight gains were comparable between treated and vehicle control animals. There was a statistically significant time-dose-interaction (p value = 0.0110) for all doses combined for in-life body weights; however, the results were not statistically significant when each dose level was analysed separately. There was no significant sex-dose or time-sex-dose interaction for all doses combined or for each dose analysed separately.

6. Clinical Pathology

Hematology and clinical chemistry parameters were examined in all animals at the end of the study. Blood samples were collected one day prior to necropsy from the ear vein of each animal. The study report

[2]OECD. 1981b. Organization for Economic Co-Operation and Development. OECD Guidelines for Testing of Chemicals, Section 4-Health Effects, No. 404: Acute Dermal Irritation/Corrosion.

did not indicate if animals were fasted overnight prior to blood collection. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Leukocyte differential count*
X Erythrocyte count (RBC)*
X Platelet count*

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related findings were observed for hematology parameters.

(b) Blood (clinical) chemistry

Electrolytes

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

Other

X Albumin*
X Glucose*
X Blood creatinine*
X Blood urea nitrogen (BUN)*
X Total bilirubin*
X Total protein*
X Globulin

Enzymes

X Serum alanine aminotransferase (ALT)*
X Serum aspartate aminotransferase (AST)*
X Alkaline phosphatase (ALK)

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related findings were noted for clinical chemistry parameters.

(c) Urinalysis

No urinalysis was performed. Urinalysis is not suggested by Subdivision F (November 1984) Guidelines unless there is a need based on expected or observed toxicity.

7. Sacrifice and Pathology

A gross necropsy was performed on all rabbits at the end of the study. Checked (X) tissues were examined microscopically for each rabbit in the control and high-dose groups. For rabbits from the low and intermediate dose groups, microscopic examination was performed on treated and untreated skin, and any masses or lesions. Those tissues marked with "w" were also weighed.

| Digestive | Urogenital | Other |
|---|---|---|
| X Liver*w | X Kidneys*w | X Treated and untreated skin |
| Testes* | | X Gross lesions |

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic pathology

No remarkable gross pathological findings were observed in any of the tissues from treated animals with the exception of the skin. In the skin of animals from the 753-mg/kg dose group, hyperemia was reported in 2/5 females and slight thickening was reported for 3/5 males.

(b) Organ weights, and organ/body weight ratios

No treatment-related effects on absolute or relative organ weights were observed.

(c) Microscopic pathology

Skin: At the dermal test site, very slight epidermal hyperplasia and dermal inflammation were observed in treated males and females at each dose level. Epidermal parakeratosis and epidermal microabscesses were observed in treated males at each dose level. Focal muscle inflammation was observed in females at 75.3 and 251 mg/kg/day dose levels, and epidermal necrosis was observed in females at a 251 mg/kg/day dose level. On untreated skin adjacent to the dermal test site, histopathologic lesions were observed but they were attributed to repeated contact with the elastic jackets.

Other organs: Incidence of histopathologic observations in the liver and kidneys was comparable between treated and vehicle control animals.

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A signed Good Laboratory Practice Compliance Statement and a signed Quality Assurance Statement were included.

B. DISCUSSION

The design of this study was reasonable for a 21-day repeated dermal toxicity study and the data summaries accurately reflected the individual data. No study limitations were noted by the reviewers.

In conclusion, there was no evidence of systemic toxicity in rabbits administered picloram-$K^+$. However, dermal irritation, very slight to well-defined edema &/or erythema was observed in males and females at each dose level (75.3, 251 and 753 mg/kg/day). The highest dose of picloram-$K^+$ administered (753 mg/kg/day) corresponded to a dose volume of 1.7 mL/kg/day which represented the maximum amount of test material that could be practically maintained at the application site. The NOEL for systemic toxicity was $\geq$753 mg/kg/day for male and female rabbits.

KLH 5/20/93

DOC 930151

FINAL

DATA EVALUATION REPORT

Picloram (Triisopropanolamine salt)

Study Type:
Twenty-one Day Repeated-Dose Dermal Toxicity Study

Study Title:
Picloram, Triisopropanolamine Salt: 21-Day Dermal Toxicity Study in New Zealand White 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

Principal Reviewer Carrie Robe for Betty Shindel, M.P.H. Date 9/21/92

Independent Reviewer William L. McLellan William McLellan, Ph.D. Date 9/21/92

QA/QC Manager Sharon A. Segal Sharon Segal, Ph.D. Date 9/21/92

Contract Number: 68D10085
Work Assignment Number: 1-89.1
Clement Number: 93-39-2
Project Officer: James Scott

Guideline Series 82-2
Twenty-one Day Repeated-Dose Dermal Toxicity Study

EPA Reviewer: Henry Spencer, Ph. D. Signature: Henry Spencer
Tox. Branch I, Review Section III Date: 9/30/92
Health Effects Division

EPA Section Head: Karen Hamernik, Ph.D. Signature: Karen L. Hamernik
Tox. Branch I, Review Section III Date: 5/20/93
Health Effects Division

# DATA EVALUATION REPORT

STUDY TYPE: Twenty-one day repeated-dose dermal toxicity study

TEST MATERIAL: Picloram-triisopropanolamine salt

SYNONYMS: Picloram-TIPA; Tordon TIPA Salt Liquor

CAS REGISTRY NUMBER: 6753-47-5

STUDY NUMBER: K-049877-011

MRID NUMBER: 413849-02

SPONSOR: DowElanco, Midland, MI 49674

PC NUMBER: 005102

TESTING FACILITY: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI 49674

TITLE OF REPORT: Picloram, Triisopropanolamine Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits.

AUTHORS: L. Atkin, W.T. Stott and K.E. Stebbins

REPORT ISSUED: January 31, 1990

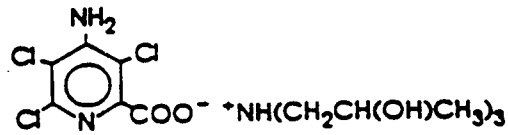
CONCLUSIONS: NOEL (systemic) ≥ 1,320 mg/kg/day for male and female New Zealand White rabbits. A LOEL (systemic) was not established for males or females. Dermal irritation, very slight to well-defined edema and/or erythema, was observed at all doses, in both sexes.

CORE CLASSIFICATION: Core Guideline. This study satisfies the guideline requirement (82-2) for a 21-day repeated dermal toxicity study.

## A. MATERIALS, METHODS, AND RESULTS

### 1. Test Article Description

Chemical name: 4-Amino-3,5,6-trichloropicolinate, triisopropanolamine salt
Physical state: 61.0% (34.1% acid equivalent) aqueous solution of picloram-TIPA
Molecular formula: $C_6H_2Cl_3N_2O_2^- \bullet C_9H_{22}NO_3^+$
Structural formula:




Molecular weight: 241.5 (Acid); 433 (triisopropanolamine salt)
Lot number: AGR 276453
Vehicle: Distilled water
Purity: 100.0% pure within analytical limits
Stability: Picloram stable for at least 45 days (Kropscott and Kluck 1989)[1]; TIPA stable for 57 days (Markham 1989)[2].
Density: 1.273

### 2. Test Article Analyses for Homogeneity and Concentration

Homogeneity analyses of three samples from the 132-mg/kg/day dose level resulted in percent recoveries of 98.1, 97.1 and 93.5% of the target picloram acid equivalent concentration (43.3 mg/mL). The homogeneity mean concentration was 41.70 mg/mL (target 43.3 mg/mL), with a 2.4 coefficient of variation, and a 1.02 standard deviation.

The mean concentrations of the 132- (43.3 mg/mL target picloram acid equivalent) and 440-mg/kg/day (144.5 mg/mL target picloram acid equivalent) dose levels were 94.7 and 96.5%, respectively, of the target picloram acid equivalent concentration.

### 3. Test Animals

Species: Rabbits
Strain: New Zealand White
Source: Hazleton Research Products, Inc., Denver, PA
Sex and numbers: 20 Males and 20 females
Age at study initiation: Approximately 5 months
Initial body weight: 3434-4428 g males; 2964-4020 g females

Animals were examined for health status upon arrival. Prior to dosing, rabbits were acclimated to laboratory conditions for at least

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[1]Kropscott BE and Kluck B. 1989. Determination of Stability for Picloram (Acid Equivalent) in Dosing Solutions. Report of the Dow Chemical Company, Midland, MI.

[2]Markham DA. 1989. Picloram-TIPA Analysis for Concentration, Homogeneity, and Stability. Report of the Dow Chemical Company, Midland, MI.

14 days. All rabbits were housed individually in cages. Animals were identified by a unique alphanumeric metal ear tag. The animal room was designed to maintain an adequate temperature, humidity, and photocycle. Feed (Purina® Certified Chow #5322) was provided at a rate of 4 ounces/day/rabbit. Tap water was provided ad libitum throughout the acclimation and study period. Rabbits were assigned to test groups based on body weight using a computer-generated randomization procedure. For at least four days during the week prior to dosing, animals were acclimated to an elastic jacket used to hold the test material dressing in contact with the skin.

Dose administration: Groups of five rabbits of each sex were dermally administered Picloram-TIPA at doses of 132, 440 or 1,320 mg/kg/day (73.8, 246 or 738 mg/kg/day acid equivalent) at a volume of 1.7 mL/kg/day. Five rabbits of each sex served as a vehicle control group and were administered distilled water (vehicle) at a volume of 1.7 mL/kg/day. Each animal received 15 applications during a 21-day study period.

An area of fur approximately 10x15 cm on the back of each rabbit was clipped prior to study initiation and as needed throughout the study period. The test material was held in contact with the test site by absorbent gauze and non-absorbent cotton secured with an elastic jacket. At the end of the 6-hour exposure period, the jacket and dressing were removed and the test site was wiped with a water-dampened disposable towel to remove any residual test material.

Dose selection was based on the absence of erythema, edema or signs of systemic toxicity in a probe study in which 1 New Zealand White male rabbit was administered 1,320 mg/kg/day of undiluted picloram-TIPA for four days.

4. Statistical Methods

Equality of variance for body weight, clinical chemistry and hematology (except WBC differential), and absolute and relative organ weight data were evaluated using Bartlett's test (Winer 1971)[3].

Body weight data were evaluated using a three-way measures ANOVA for a time-sex-dose interaction (Winer 1971)[3]. If a time-sex-dose interaction was present, analysis was repeated for each sex, and data were then examined for a significant sex-dose interaction. If a sex-dose interaction was identified, data were examined for each sex separately. The presence of a time-dose interaction was evaluated after accounting for the factor of sex (sex was controlled for or statistical significance was lacking). If a time-dose interaction was statistically significant, analysis was repeated for each dose level against controls.

A two-way ANOVA with the factors of sex and dose (Winer 1971)[3] was used to evaluate hematology (except WBC differential), clinical

[3]Winer B.H. 1971. Statistical Principles in Experimental Design. McGraw-Hill Book Company, Inc., New York, NY.

chemistry, terminal body weight, and relative and absolute organ weight (except testes) data. Data were first examined for a significant sex-dose interaction; if present, each sex was analyzed separately using a one-way ANOVA. If no sex-dose interaction was identified but a dose effect was, separate ANOVAs were used for each dosage group with control. A Bonferroni correction was used to control for multiple comparisons with control.

Data for absolute and relative testes weights were analyzed using a one-way ANOVA; if significant, each dose was compared to controls using one-way ANOVA with Bonferroni's Correction.

5. General Observations

(a) Mortality/moribundity/survival

Each animal was observed at least once daily for mortality and moribundity during the study period. No mortality was reported for any of the animals.

(b) Clinical observations

Animals were observed prior to each test material application for clinical signs of toxicity. No clinical signs of toxicity were observed in any of the animals.

The severity of dermal irritation was scored prior to the second application of the test material and following each application of the test material. The laboratory evaluated the test site based on its modification of the acute dermal irritation scoring system recommended by the Organization for Economic Cooperation and Development (OECD 1981)[4]. No dermal irritation was reported for vehicle control animals; however, dermal irritation was reported at each dose level for treated males and females.

At a dose of 75.3 mg/kg/day dose level, very slight erythema was observed in from 1 to 2 males on test days 16-21 and 1 female on test day 20. At a 251 mg/kg/day dose level, very slight erythema was observed in from 1 to 3 males on test days 15-21 and 2 females on test days 7-20. At a 753 mg/kg/day dose level, very slight-to-well- defined erythema was observed in from 1to 4 males on test days 13-21 and in 2 females on test days 13-20. Very slight-to-well-defined edema was only observed in from 1 to 3 treated males at 75.3 and 753 mg/kg/day dose levels.

(c) Body weight/body weight gain/food consumption

Body weights were measured prior to the first application and approximately once a week throughout the study. Food consumption was not measured since each rabbit consumed its entire food ration of 4 ounces/day.

[4]OECD. 1981. Organization for Economic Co-Operation and Development. OECD Guidelines for Testing of Chemicals, Section 4-Health Effects, No. 404: Acute Dermal Irritation/Corrosion.

There were no effects on absolute body weights or body weight gains that were attributable to the test material. Body weight gains were comparable between treated and vehicle control animals.

6. Clinical Pathology

Hematology and clinical chemistry parameters were examined in all animals at the end of the study. Blood samples were collected one day prior to necropsy from the ear vein of each animal. The study report did not indicate if animals were fasted overnight prior to blood collection. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Leukocyte differential count*
X Erythrocyte count (RBC)*
X Platelet count*

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related findings were observed for hematology parameters.

(b) Blood (clinical) chemistry

Electrolytes

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

Other

X Albumin*
X Glucose*
X Blood creatinine*
X Blood urea nitrogen (BUN)*
X Total bilirubin*
X Total protein*
X Globulin

Enzymes

X Serum alanine aminotransferase (ALT)*
X Serum aspartate aminotransferase (AST)*
X Alkaline phosphatase (ALK)

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related findings were noted for clinical chemistry parameters. The mean value for alanine aminotransferase (ALT) was statistically significantly higher ($p = 0.0294$) in high-dose females (1,320 mg/kg/day) as compared to the vehicle control group. The mean values for ALT in females from the 0-, 132-, 440- and 1,320-mg/kg/day dose groups were 32, 36, 37, and 50 mU/mL, respectively. The increase in ALT in high-dose females was not considered to be treatment related by the study authors or the reviewers because there were no treatment related histopathological findings in the liver.

(c) Urinalysis

No urinalysis was performed. Urinalysis is not suggested by Subdivision F (November 1984) Guidelines unless there is a need based on expected or observed toxicity.

7. Sacrifice and Pathology

A gross necropsy was performed on all rabbits at the end of the study. Checked (X) tissues were examined microscopically for each rabbit in the control and high-dose groups. For rabbits from the low- and intermediate-dose groups, microscopic examination was performed on treated and untreated skin, and any masses or lesions. Those tissues marked with "w" were also weighed.

| Digestive | Urogenital | Other |
|---|---|---|
| X Liver*w | X Kidneys*w | X Treated and untreated skin |
| Testes w | | X Gross lesions |

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic pathology

No gross pathological findings were considered to be treatment related.

Gross pathology findings in the kidney consisted of a cyst observed in 1 female from the low-dose (132 mg/kg/day) group. In the liver, a multifocal accentuated lobular pattern was observed in 1 male from the 440-mg/kg dose group and in 1 vehicle control female. A pale liver focus was observed in 1 vehicle control female and in 1 male and female from the 440-mg/kg dose group. In the uterus, a cyst was observed in 1 female from the 440-mg/kg dose group.

Very slight-to-slight erythema was reported in 1 animal/dosage group with the exception of the female vehicle control group for which no erythema was reported.

(b) Organ weights, and organ/body weight ratios

No treatment-related effects on absolute or relative organ weights were observed.

(c) Microscopic pathology

Skin: Treatment-related microscopic findings of treated skin at the test site consisted of multifocal hyperplasia of the epidermis and multifocal inflammation of the dermis. Very slight multifocal hyperplasia of the epidermis was observed in males and females receiving applications of picloram-TIPA at a concentration of 132 mg/kg/day (2 males; 1 female), 440 mg/kg/day (4 males; 5 females) and 1,320 mg/kg/day (5 males; 3 females). Very slight

inflammation of the dermis was observed in males and females receiving applications of picloram-TIPA at concentrations of 132 mg/kg/day (2 males; 1 female), 440 mg/kg/day (1 male; 3 females) and 1,320 mg/kg/day (2 males; 4 females). None of the vehicle control animals exhibited these findings.

Microscopic findings were observed in untreated skin adjacent to the test site. However, these findings were comparable between vehicle control animals and animals receiving applications of the test article, and were considered by the reviewers to be attributable to contact with the jackets.

Other organs: Incidence of histopathologic observations in the liver and kidneys were similar between treated and vehicle control animals.

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A signed Good Laboratory Practice Compliance Statement and a signed Quality Assurance Statement were included.

B. DISCUSSION

The design of this study was reasonable for a 21-day repeated dermal toxicity study and the data summaries accurately reflected the individual data. No study limitations were noted by the reviewers.

There were no treatment-related signs of systemic toxicity in rabbits administered picloram-TIPA. However, treatment-related dermal irritation (very slight to well-defined erythema) was observed at each dose level for males and females administered picloram-TIPA. The mean value for alanine aminotransferase (ALT) was statistically significantly higher (p value = 0.0294) in high-dose females (1,320 mg/kg/day) as compared to the vehicle control group. However, the increase in ALT in high-dose females was not considered to be treatment related by the reviewers because there were no histopathological findings in the liver that were attributable to treatment. The mean ALT values in females from the 0, 132, 440 and 1,320 mg/kg/day dose groups were 32, 36, 37, and 50 mU/mL, respectively.

The appearance of erythema and edema at all treatment levels after approximately 2 weeks on study, despite a 10-fold difference between the low and high dose, is suggestive of sensitization. Additional work directly examining the dermal sensitization potential of the triisopropanolamine salt of picloram could resolve this question.

In conclusion, there were no signs of systemic toxicity in rabbits administered picloram-TIPA. The highest dose of picloram-$K^+$ administered (1,320 mg/kg/day) was higher than the limit dose of 1,000 mg/kg/day. The NOEL for systemic toxicity was $\geq$1,320 mg/kg/day for male and female rabbits.