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

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SEP 15 1993

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Triforine. Acute toxicity and chronic feeding (dog) toxicity data review.
Tox Chem No. 890AA
Shaughnessy No. 107901
Submission No. S4221326
MRID Nos. 423804-07, 423804-08, 423804-09, 423804-10,
Case No. 816127
DP Barcode No. [illegible]
Action No. 627

From: Alberto Protzel, Ph.D. 9/13/93
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

To: Mr. Ron Kendall
Accelerated Reregistration Branch
Special Review and Registration Division (H7508W)

Thru: James N. Rowe, Ph.D., Head 9/13/93
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief 9/14/93
Toxicology Branch II
Health Effects Division (H7509C)

ACTION:
Review of the following studies on the chemical TRIFORINE submitted by Shell Forschung-GmbH, Schwabenheim, Germany:

1. W524-XX (Triforine) 104 Week Oral Toxicity Study in Dogs (102AB-437-017, MRID 423804-10).

2. Primary Eye Irritation Study with Triforine Technical in Rabbits (102AB-466-019, MRID 423804-07).

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3. Primary Skin Irritation Study in Rabbits (4-hour semi-occlusive application) [102AF-465-016, MRID 423804-08].

4. Delayed Contact Hypersensitivity in Albino Guinea Pigs. The Maurer Optimization Test (Triforine) [102AD-467-007, 423804-09].

CONCLUSIONS:

Study 1. W524-XX (Triforine) 104 Week Oral Toxicity Study in Dogs (102AD-467-017, MRID 423804-10).
Triforine was administered in the diet to groups of four beagle dogs/sex for 104 weeks at dosage levels of 0, 10, 40, 100, or 1000 ppm (approximately 0, 0.24, 0.96, 2.48, and 23.05 mg/kg/day, respectively). Chronic toxicity was reported at 1000 ppm as manifested by increased hemosiderosis in the Kupffer cells, siderosis of the bone marrow (no data submitted for verification), and minor increases in erythropoiesis. Based on these results, the LOEL is 1000 ppm (23.05 mg/kg/day) and the NOEL is 100 ppm (2.56 mg/kg/day).

This Study is classified as CORE Supplementary. This study does not meet the minimum requirements set forth under EPA FIFRA Guideline Series 83-1 for a chronic toxicity study in dogs. Inadequate reporting of the histopathology data (to support findings of hemosiderosis and increases in erythropoiesis) constitutes a major deficiency.

Study 2. Primary Eye Irritation Study with Triforine Technical in Rabbits (102AF-466-019, MRID 423804-07).
Based on the presence of conjunctival redness in one rabbit at 24 hours (score = 1) which cleared by 48 hours (score = 0), triforine technical is placed in Toxicity Category III for eye irritation. The Study is classified as CORE Minimum and satisfies Guideline 81-4.

Study 3. Primary Skin Irritation Study in Rabbits (4-hour semi-occlusive application) [102AF-465-016, MRID 423804-08].
Based on the absence of observable skin irritation, triforine technical is placed in Toxicity Category IV for skin irritation. The Study is classified as CORE Minimum and satisfies Guideline 81-5.

Study 4. Delayed Contact Hypersensitivity in Albino Guinea Pigs. The Maurer Optimization Test (Triforine) [102AD-467-007, 423804-09].
The skin sensitization potential of this material cannot be ascertained pending submission of the additional data indicated below.

This Study is classified as CORE Supplementary. This study does not meet the minimum requirements set forth under EPA FIFRA Guideline Series 81-6 for a dermal sensitization study. Although the authors indicated that "In a separate test (June 1984) the incidence of the guinea pig strain to allergic reactions was tested", no information was given on the conditions of the test, the dermal sensitizer used, the results obtained, or the corresponding incidences supporting the results of the positive test. This study may be upgraded to CORE Minimum if the above information is submitted and is considered satisfactory to the Agency.

FINAL

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DATA EVALUATION RECORD

TRIFORINE

Study Type: Chronic Feeding in Dogs

Prepared for:

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

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer: Pia Lindström, DrPH — Date: 8/24/93

Independent Reviewer: William McLellan, Ph.D. — Date: 8/24/93

QA/QC Manager: Sharon Segal, Ph.D. — Date: 8/24/93

Contract Number: 68D10075
Work Assignment Number: 2-68
Clement Number: 193
Project Officer: Caroline Cordon

Guideline Series 83-1: Chronic Toxicity

EPA Reviewer: Alberto Protzel, Ph.D.
Review Section III, Toxicology Branch II/HED

Signature:
Date: 9/2/93

EPA Section Head: James Rowe, Ph.D.
Review Section III, Toxicology Branch II/HED

Signature: James N. Rowe
Date: 9/13/93

DATA EVALUATION RECORD

STUDY TYPE: Chronic Feeding Study (Dog); Guideline Series 83-1

EPA IDENTIFICATION NUMBERS

TOX CHEM NUMBER: 890 AA

MRID NUMBER: 423804-10

TEST MATERIAL: N,N'-[1,4-piperazine diylbis(2,2,2-trichloro-ethylidene)]-bis-[formamide]

SYNONYMS: W524-XX; Triforine; CME74770; Funginex

SPONSOR: Stoll Forschung GmbH, Schwabenheim, Germany

STUDY NUMBER: 102AB-437-017

TESTING FACILITY: Inveresk Research International, Musselburgh, Scotland

TITLE OF REPORT: W524-XX (Triforine) 104 Week Oral Toxicity Study in Dogs

AUTHORS: R. Goburdhun and R.J. Greenbough

REPORT ISSUED: August 1973

CONCLUSIONS: Triforine was administered in the diet to groups of four beagle dogs/sex for 104 weeks at dosage levels of 0, 10, 40, 100, or 1000 ppm (approximately 0, 0.24, 0.96, 2.48, and 23.05 mg/kg/day, respectively). Chronic toxicity was reported at 1000 ppm as manifested by increased hemosiderosis in the Kupffer cells, siderosis of the bone marrow (no data submitted for verification), and minor increases in erythropoiesis. Based on these results, the NOEL and LOEL were 100 and 1000 ppm, respectively (2.56 and 23.05 mg/kg/day).

CORE CLASSIFICATION: Core Supplementary Data. This study does not meet the minimum requirements set forth under EPA FIFRA Guideline Series 83-1 for a chronic toxicity study in dogs. Inadequate reporting of the histopathology data (to support findings of hemosiderosis and increases in erythropoiesis) constitutes a major deficiency in this study.

A. MATERIALS

Test Compound

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Purity: 96.6%
Description: Not reported
Stability: Not reported
Batch number: T 3/70
Received: August 22, 1971

Vehicle: None was used. The test material was administered in the diet.

Test Animals

Species: Dog
Strain: Beagle
Source: C.H. Boehringer Sohn, Rhein, Germany
Age: 10 Months at start of study
Weight: Males---11.0-14.8 kg at start of study
Females--8.7-13.2 kg at start of study

B. STUDY DESIGN

Animal Assignment

Animals were acclimated to laboratory conditions for 8 weeks. During this time, they were vaccinated against distemper, hepatitis, leptospirosis, and parvovirus and were also dewormed twice. Animals were assigned by sex to the following test groups:

Test group	Dosage level (ppm)	Number of Animals Males	Females
I	0	4	4
II	10	4	4
III	40	4	4
IV	100	4	4[a]
V	1000	4	4

[a]One female died on day 225 of the dosing period.

The study authors did not indicate how randomization of the animals was achieved in the test groups.

Animal Husbandry

Animals were housed individually. Environmental conditions were not reported.

Dosage Rationale

Dosages were selected based on the results of two subchronic feeding studies in beagle dogs (study numbers not provided). The exact dosage levels used in the first subchronic study were not reported but the study authors stated that dosages ranging from 3500 to 30,000 ppm were associated with significant reductions in erythrocytes and hematocrit values. At 3500 ppm, reduced hemoglobin values and increased reticulocyte counts were observed. At dosage levels ≥10,000 ppm, increased levels of alkaline phosphatase, bilirubin, and cholesterol were observed. Histopathological changes (drop-like fatty infiltrations in myocardial fibers and liver cells and siderosis of the Kupffer cells) were also observed at all dosage levels. A NOEL was not established.

In the second subchronic study, animals received dietary concentrations of 100, 600, or 3500 ppm. Iron deposits were detected in the spleen, liver, and bone marrow among animals at 600 and 3500 ppm. Significant reductions in hemoglobin, red blood cell count, hematocrit, total proteins, albumin, and globulin and increased relative spleen weight were observed at 3500 ppm. The NOEL was 100 ppm.

Dosage Preparation

Diets were prepared weekly by mixing the test substance with the standard diet and 900 ml of water. This mixture was ground for 20 minutes and then mixed in a Turbulla mixer.

Analyses for test-article concentrations, for the highest dose only, were reported in association with treatment dates of approximately 9 months (5/15/71) and 17 months (1/23/73 and 1/30/73). It is unclear if these dates correspond to dates of diet preparation or diet analyses. Reported values for 5/15/71, 1/23/73, and 1/30/73 for nominal 1000 ppm were 934, 947, and 947 ppm, respectively. Additionally, test-article concentrations, were analyzed at the end of the study at all treatment levels. Results were reported for prepared diet prior to mixing with meat (nominal: 15, 60, 150, and 1500 ppm) and presumably for prepared diet after mixing with meat (nominal: 10, 40, 100, and 1000 ppm). The results for nominal 15, 60, 150, and 1500 ppm (no meat) were 15.3, 63.0, 146.3, and 1468.7 ppm, respectively. The results for nominal 10, 40, 100, and 1000 ppm (with meat) were reported to be 10.4, 39.8, 102.6, and 979.9 ppm, respectively. The authors did not specify if the results obtained after adding the meat were obtained right after mixing with the meat or after 4 weeks of storage. No analytical data for lower doses during treatment were available.

The authors also provided data on samples from a different study (at 15, 60, 150, and 1500 ppm) which was completed in December 1969. In this study, analyses for stability (after 7, 14, 21, and 28 days) revealed mean values from 79% to 109% of nominals with coefficient of variation ranging from 1.8% to 14.9%. Analyses for concentration and homogeneity revealed mean values from 99% to 105% of nominals with coefficients of variation ranging from 1.8% to 12.4%.

Food and Water Consumption

Animals received 300 g of food (200 g standardized powdered 'Haltungs-futterfur Hunde 42H' [Jacob ZAHN II] with 100 g 'Latz-Purin' Argentine dried beef [source not stated]) daily throughout the study. Tap water was available ad libitum except during the urine collection.

Statistics

The following procedures were used in analyzing hematology, clinical chemistry, organ weights and body weights: F-max test for homogeneity of variance; ANOVA and Student's t-test for homogeneous data; and Kruskal-Wallis test for heterogeneous data. Organ weight data were also analyzed by covariance with body weight.

Compliance

- A signed Statement of No Data Confidentiality Claims, dated June 25, 1992, was provided.
- A signed Statement, dated June 29, 1992, indicating that the study was not in compliance with EPA GLPs, was provided. The study was completed prior to the date that GLP standards were issued.
- A signed Statement of Quality Assurance, dated March 1, 1990, was provided.

C. METHODS AND RESULTS

Observations

Animals were observed at regular intervals throughout the day for clinical signs and morbidity and twice a day for mortality.

Results: No compound-related mortalities or clinical signs were observed in either sex at any dosage level. One female at 100 ppm died on day 225. Prior to death, a purulent nasal discharge was observed. Necropsy revealed acute pneumonia as the cause of death. Incidental clinical signs, observed in all groups, included liquid feces, vomiting, ectrova, salivation, mild trembling, and moderate ataxia. Data for individual clinical signs were not presented.

Body Weight

Body weight data were recorded weekly throughout the study.

Results: No compound-related effects on body weight were observed in either sex at any dosage level. A summary of body weight data at selected intervals is presented in Table 1. Total weight gains for weeks 0-104 were similar in all groups.

Food Consumption and Compound Intake

Food consumption data were recorded daily throughout the study and group mean food consumption was calculated weekly. Food efficiency was not reported.

Results: No compound-related effects on food consumption were observed in either sex at any dosage level. Nearly all males consumed the 300 g of food with which they were provided. A few females consistently failed to eat all of their food. Mean test material intake for weeks 1-104 were 0.23, 0.93, 2.39, and 22.50 mg/kg/day in males and 0.25, 0.99, 2.56, and 23.60 mg/kg/day in females at 10, 40, 100, and 1000 ppm, respectively.

Ophthalmological Examinations

The fundus of the eyes of all animals was examined prior to study initiation and during weeks 13, 26, 52, 78, and 104 using a Kowa Fundus Camera. Prior to examination, pupils were dilated with 1-2 drops of Roche mydriatic agent.

Results: No compound-related lesions were observed in either sex at any dosage level. Incidental findings included one male at 10 ppm with discoloration of the retina at all eye examinations; one female at 100 ppm and one male at 1000 ppm with keratitis with vascularization and pigmentation during week 104; and one male at 1000 ppm with an intra-retinal hemorrhage during week 52.

Hematology and Clinical Chemistry

Hematology and clinical chemistry parameters were determined at the start of the study and during weeks 6, 13, 26, 52, 78, and 104. The study authors did not indicate from where the blood was collected or if the animals were fasted prior to collection. The following checked (X) parameters were determined.

Hematology

- X Hematocrit (HCT)[a]
- X Hemoglobin (HGB)[a]
- X Erythrocyte count (RBC)[a]
- X Leukocyte count (WBC)[a]
- X Leukocyte differential count
- X Lymphocyte count
- X Monocyte count
- X Reticulocyte count
- X Mean cell hemoglobin (MCH)
- X Mean cell hemoglobin concentration (MCHC)
- X Mean cell volume
- X Thrombocytes[a]
- X Prothrombin time
- X Blood sedimentation rate
- X Osmotic resistance
- X Siderocytes

[a]Recommended by Subdivision F (October 1982) Guidelines

~~In addition, femoral bone marrow smears, taken at necropsy, were evaluated.~~

Results: No significant compound-related effects were observed on any hematological endpoint. Incidental differences from control were

noted. However, no consistent dosage-, sex-, or time-related pattern was noted for any endpoint. The study authors report [illegible] and for a dose-related reduction in red blood cell parameters (RBC, and HCT) and associated cell indices in the treated groups during week 6...". The reviewers note, however, that even though there was a generally dose-related decrease in Hb, RBC, and HCT at 6 weeks, especially in females, there were no statistically signficant pairwise decreases and all mean values were within 8% of controls with the exception of Hb in females at 100 and 1000 ppm, which decreased by 10% and 14%, respectively. At 6 weeks, the individual animal values for high-dosage females (but not males) were all below pretest values. They were, however, similar to pretest values at week 13 and thereafter. Reticulocyte counts were not affected. A slight increase was noted in treated males at week 13; however, no consistent time- or dosage-related pattern was observed.

Bone marrow smears demonstrated a shift towards erythropoiesis in the granulopoietic-erythropoietic ratio at the high-dosage level in two males and three females. Additionally, the mitotic index in the erythropoietic system of one high-dose female was also above normal limits.

Clinical chemistry

Electrolytes

X Calcium[a]
X Chloride[a]
Magnesium
X Inorganic phosphate[a]
X Potassium[a]
X Sodium
X Iron

Other

X Albumin[a]
X Albumin/globulin ratio
X Creatinine[a]
X Blood urea nitrogen[a]
X Total cholesterol[a]
X Globulins
X Glucose
X Total bilirubin[a]
X Total protein[a]
X Carbon dioxide

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
Creatine kinase[a]
X Alanine aminotransferase (ALT/SGPT)[a]
X Aspartate aminotransferase (AST/SGOT)[a]

[a]Recommended by Subdivision F (October 1982) Guidelines

Results: No significant compound-related effects were observed in clinical chemistry parameters. Although bilirubin levels were increased with statistical significance versus controls for weeks 13, 26, and 104 in males and weeks 13 and 104 in females, there was no clear dosage- or time-related trend. Individual values in treated groups were generally within the range of pretest values (0.04-0.11 mg/dL). Although mean cholesterol levels tended to be higher than controls in both males and females receiving 1000 ppm, at most intervals, the increases were slight, none were statistically significant, and there was no trend over time. Most values for

individual animals were within the range of pretest values which were 108-224 mg/dL. These increases in bilirubin and cholesterol may have been compound related; however, they were not biologically significant since they were within the normal ranges for this species (as reported by the study authors; no historical control data were submitted). For all other endpoints, no consistent dosage-, sex-, or time-related pattern was noted.

Urinalysis

Urinalysis was performed on all animals prior to treatment and during weeks 6, 13, 26, 52, 78, and 104 . Urine samples were collected over a 24-hour period while the animals were housed in metabolism cages. The following checked (X) parameters were determined.

	Volume[a]		Ketones[a]
	Appearance[a]	X	Acetone
X	pH	X	Bilirubin[a]
X	Specific gravity	X	Sediment (microscopic)
X	Protein	X	Occult blood[a]
X	Glucose[a]		

[a] Recommended by Subdivision F (October 1982) Guidelines

Results: No compound-related effects were observed for any urinalysis endpoint in either sex at any dosage level.

Sacrifice and Pathology

All animals were subjected to gross pathological examination. The method of sacrifice comprised deep anesthesia followed by exsanguination via the carotid arteries. Gross examination consisted of external and internal examinations including a recorded description of all gross lesions. The following checked (X) tissues were preserved in 10% calcium-buffered formalin for histological examination. Additional sections of adrenals, kidneys, heart, and liver were stained with fat red 7 b and the Berlin blue method was used for detection of iron in the heart, lung, liver, kidneys, and spleen. In addition, the double checked (XX) organs were weighed.

Digestive system

X Tongue
X Salivary gl.[a]
X Esophagus[a]
X Stomach[a]
X Duodenum[a]
X Jejunum[a]
X Ileum[a]
X Cecum[a]
X Colon[a]
X Rectum
XX Liver[a]
X Pancreas[a]
- Gall bladder

Glandular system

XX Adrenals[a]
Lacrimal
X Mammary[a]
XX Thyroids[a]
Parathyroids[a]
Harderian

Urinary system

XX Kidneys
X Urinary bladder
XX Testes (with epididymides)
XX Prostate gland
Seminal vesicles
XX Ovaries
Uterus
Cervix
Renal pelvis
Vagina

Cardiovascular and hematologic systems

X Aortic arch
XX Heart[a]
X Bone marrow[a]
X Lymph nodes[a]
XX Spleen
X Thymus

Respiratory System

X Trachea[a]
XX Lungs[a]
Larynx
Pharynx

Neurologic System

XX Brain w/stem
X Peripheral nerve[a]
Spinal cord
XX Pituitary[a]

Other

X Skeletal muscle[a]
X Skin[a]
X All gross lesions
Bone[a]

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

Results

Organ weights: No compound-related effects on unadjusted organ weights or weights adjusted by covariance with body weights were observed in either sex at any dosage level.

Gross pathology: No compound-related gross findings were observed in either sex at any dosage level. Incidental findings included hematocyst of the tricuspid, hematoma on the edge of the spleen, and parasitic changes.

Microscopic pathology: The authors stated that compound-related histopathological findings were observed at 1000 ppm. The authors stated that the effects were manifested as increased iron content of Kupffer cells in the liver of animals receiving 1000 ppm and siderosis of the bone marrow in two animals at 1000 ppm. However, histopathology data in support of these assertions were not present in the summary tables or in the individual histopathology sheets. Therefore, they can not be verified. A summary of the incidence of Kupffer cell

siderosis, as extracted from a text table, is presented in Table 2. Severity of this effect was increased at 1000 ppm.

D. STUDY AUTHOR'S CONCLUSIONS

Triforine was administered in the diet to beagle dogs at dosage levels of 1, 10, 40, 100, or 1000 ppm for 104 weeks. Chronic toxicity was observed at 1000 ppm as evidenced by increased Kupffer cell hemosiderosis, siderosis of the bone marrow, and minor increases in erythropoiesis. The absence of any consistent reductions in red blood cell parameters indicated that the effect was mild. The NOEL and LOEL were 100 and 1000 ppm, respectively.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The animals may have tolerated a higher dose of triforine as evidenced by unaffected body weights and no clinical signs. Body weight in all groups of males, including controls, tended to decrease during the first 26 weeks of the study compared to body weight at initiation. This is not unusual for mature dogs (10-months-old). Younger dogs (4-6-months-old) should have been used in this study (guideline recommendation). The reviewers agree with the study authors that no compound-related toxicity was observed in clinical signs, food consumption, body weight, urinalysis, organ weights, and gross findings. Sporadic deviations from control in these parameters were within the normal variation for this species and strain of dogs. Slight effects were observed in selected hematology and clinical chemistry parameters. However, these effects do not appear to be biologically significant and were frequently within the historical control range (as reported by the study authors; historical control data were not provided). Compound-related histopathological findings were observed. Both individual pathology sheets and summary pathology tables were provided. However, these sources (Table 20 and Appendix 33, CBI) did not support the reported findings of increased hemosiderosis in the bone marrow or in the Kupffer cells of the liver. This major reporting deficiency is the basis for classifying the study as Supplementary. In addition, the following deviations from EPA Guidelines were noted:

- Stability, concentration (except sporadically), and homogeneity were not reported for the actual dosages in this study.
- Data on individual clinical observations were not submitted.
- Standard deviations were not included in the summary tables of body weights and food consumption.
- Animals were 10-months-old at initiation of the study. Therefore, body weights (particularly females) were near their maximum and body weight gain data in this duration are not a good effect indicator.

- Page 13 of the report is missing.

- Protocol and protocol deviations were not submitted.

GLPs were not completely followed as the study was conducted before this requirement, which may explain why the data reporting is insufficient.

Based on the above deficiencies, this study was classified as Core Supplementary Data.

TABLE 1. Mean Body Weight (kg) at Representative Intervals in Dogs Fed Triforine for 104 Weeks[a,b]

Study Week	Dietary Level (ppm) 0	10	40	100	1000
			Males		
1	13.1	13.2	12.9	13.0	13.3
13	11.7	12.2	12.3	11.9	12.5
26	12.2	12.2	12.4	12.0	12.9
52	12.6	12.8	13.1	12.3	13.8
78	12.2	12.7	12.8	11.5	13.2
104	12.9	13.5	13.5	12.4	13.9
Mean weight gain Weeks 0-104	-0.4	0.1	0.5	-0.7	0.5
			Females		
1	10.8	10.9	10.8	10.9	11.2
13	10.6	10.7	11.1	10.8	11.6
26	11.0	11.1	11.3	11.1	11.8
52	11.9	12.0	11.9	12.2	13.2
78	12.0	12.6	11.5	11.6	12.8
104	13.5	13.8	12.3	12.8	14.2
Mean weight gain Weeks 0-104	2.6	2.9	1.4	1.9	3.1

[a]Data were extracted from Study No. 10248-137-017, Table 2.

[b]Standard deviations were not provided.

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TABLE 2. Incidence of Kupffer Cell Hemosiderosis in Dogs Fed Triforine for 104 weeks[a,b]

Degree of Siderosis	Dietary Level (ppm)				
	0	10	40	100	1000
0	3/8	---	---	---	---
+[c]	1/8	6/8	4/8	2/6[d]	1/8
++	3/8	2/8	2/8	1/6[d]	3/8
+++	1/8	---	2/8	---	4/8

[a]Data were extracted from Study No. 10288-437-017, p. 34

[b]The study authors did not provide individual or summary data to support this nor did they define the various degrees of severity.

[c]Degree of siderosis

[d]Only six animals available; one female died and one animal was not examined.

Reviewed by: Alberto Protzel, Ph.D.
Section III, Tox. Branch II(H7509C)
Secondary reviewer: James N. Rowe, Ph.D.
Section III, Tox. Branch II(H7509C)

Alberto Protzel 9/13/93
James N. Rowe 9/13/93

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation in rabbits; EPA Guideline 81-4 TOX. CHEM NO: 890AA

MRID NO: 423804-07

TEST MATERIAL: Triforine Technical

SYNONYMS: U524-XX; CME74770; Funginex

STUDY NUMBER: Shell 102AF-466-019

SPONSOR: SHELL AGRAR GMBH. & CO. KG. Postfach. D-6507 Ingelheim/Rhein. Germany.

TESTING FACILITY: Research and Consulting Company AG. Itingen / Switzerland.

TITLE OF REPORT: Primary Eye Irritation Study with Triforine Technical in Rabbits.

AUTHOR(S): L. Ullmann, T. Ferricello.

REPORT ISSUED: July 8, 1988

CONCLUSION:

Toxicity Category: IV

Core Classification: Minimum

Primary Eye Irritation Rating: Not a primary eye irritant.

MATERIALS:

1. Test compound: Triforine Technical, Description: Colorless to cream powder or crystals, Batch #: 2764, Purity: 98.1 ±0.9% a.i.

2. Test animals: Species: rabbit, Strain: New Zeland White KFM (SPF-Quality); Age: 14 weeks (males) & 13 weeks (females); Weight: 2.5-2.9 (males) & 2.5-2.7 (females); Source: Kleintierfarm Madoerin AG. CH 4414 Fuellinsdorf / Switzerland.

METHODS:

After a 4-day acclimatization, six rabbits (3 males, 3 females) received a single 0.1 g. dose of the test material in the conjunctival sac of the left eye. The eyelids of treated eyes were were held together for about 1 second; the

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right eyes were left untreated and served as controls. Treated and untreated eyes were examined for lesions at 1, 24, 48, and 72 hours after treatment and then the animals were sacrificed. The cornea (opacity), iris and conjunctive (redness, chemosis and extent of discharge) were scored as specified in Guideline §81-4. In addition, the animals were examined for toxic symptoms/ mortality and body weights. Individual eye irritation scores for each rabbit were presented.

RESULTS:

Individual results and irritation grades were presented. No corneal opacities (score 0) or iris irritation (score 0) were observed in the six rabbits. All treated conjunctivae showed signs of redness (grade 1) after 1 hour and were clear, except for one (grade 1), at 24 hours. All treated conjunctivae showed swelling (grade of 1) after 1 hour and were normal (score = 0) by 24 hours. All treated conjunctivae showed discharge (grades 1-2) by 1 hour and no discharge by 24 hours (score = 0). No eye irritation effects were present after 24 hours (score = 0).

No mortality or signs of systemic toxicity were observed.

Based on the presence of conjunctival redness in one rabbit at 24 hours (score = 1) which cleared by 48 hours (score = 0), the chemical is placed in Toxicity Category III for eye irritation.

Signed and dated statements of quality assurance and GLP compliance were present.

Reviewed by: Alberto Protzel, Ph.D. 9/13/93
Section III, Tox. Branch II(H7509C)
Secondary reviewer: James N. Rowe, Ph.D. 9/13/93
Section III, Tox. Branch II(H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation in rabbits; EPA Guideline 81-5

TOX. CHEM NO: 890AA

MRID No.: 423804-09

TEST MATERIAL: Triforine Technical

SYNONYMS: US24-XX; CME74770; Funginex

STUDY NUMBER: Shell 102AF-465-016

SPONSOR: SHELL AGRAR GMBH & CO. KG. Postfach. D-6507 Ingelheim/Rhein. Germany.

TESTING FACILITY: Research and Consulting Company AG. Itingen / Switzerland.

TITLE OF REPORT: Primary Skin Irritation Study in Rabbits (4-hour semi-occlusive application).

AUTHOR(S): L. Ullman, T. Porricelle.

REPORT ISSUED: June 24, 1988

CONCLUSION:

Toxicity Category: IV

Core Classification: Minimum

Primary Skin Irritation Rating: Not a primary dermal irritant.

MATERIALS:

1. Test compound: Triforine Technical, Description: Colorless to cream powder or crystals. Batch #: 2764. Purity: 98.1 ± 0.9%

2. Test animals: Species: rabbit. Strain: New Zeland White. Age: 14-15 weeks. Weight: 2.2-3.0 kg. Source: Kleintierfarm Madoerin AG. CH 4414 Fuellinsdorf / Switzerland. Acclimation period: 4 days.

METHODS:

Six rabbits (3 males, 3 females) were shaved (10 cm X 10 cm dorsal area) and 24 hours later were dermally treated with a single application of the test material. The test material (0.5 g) was moistened with tap water, applied to the shaved area of skin and covered with surgical gauze. The gauze was covered with

a semi-occlusive dressing and anchored to the abdomen with an elastic bandage. Four hours after treatment, dressings were removed and test areas were flushed with lukewarm tap water for scoring for erythema and edema as specified in Guideline §81-4. Treated sites were scored for erythema and edema at 1, 24, 48, and 72 hours after removal of the dressing and test article. In addition, the animals were examined for toxic symptoms/mortality and body weights.

RESULTS:

Individual results and irritation grades were presented. No signs of skin irritation were observed at any time: all individual skin irritation scores were 0 at all times. No mortality or signs of systemic toxicity were observed.

Based on the absence of observable skin irritation, triforine technical is placed in Toxicity category IV for skin irritation.

Signed and dated statements of quality assurance and GLP compliance were present.

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Reviewed by: Alberto Protzel, Ph.D.
Section III, Tox. Branch II(H7509C)
Secondary reviewer: James N. Rowe, Ph.D.
Section III, Tox. Branch II(H7509C)

Alberto Protzel 9/13/93
James N. Rowe 9/13/93

DATA EVALUATION REPORT

STUDY TYPE: Dermal sensitization in ~~[illegible]~~ Guinea pigs; EPA Guideline 81-6

I. Y. CHEM NO: 890AA

MRID No.: 423804-09

TEST MATERIAL: Triforine Technical

SYNONYMS: W524-XX; CME74770; Funginex

STUDY NUMBER: Shell 102AD-467-007

SPONSOR: CELAMERCK GMBH & CO. KG. D 6507 Ingelheim / Rheim. Federal Republic of Germany.

TESTING FACILITY: Research and Consulting Company AG. Itingen / Switzerland.

TITLE OF REPORT: Delayed Contact Hypersensitivity in Albino Guinea Pigs. The Maurer optimization Test (Triforine).

AUTHOR(S): L. Ullman and B. Suter

REPORT ISSUED: August 10, 1984

CONCLUSION:

The skin sensitization potential of this material cannot be ascertained pending submission of the additional data indicated below.

CORE CLASSIFICATION: CORE Supplementary. Although the authors indicated that "In a seperate test (June 1984) the incidence of the guinea pig strain to allergic reactions was tested", no information was given on the conditions of the test, the positive control used, the results obtained, or the corresponding incidences supporting the results of the positive test. This study may be upgraded to CORE Minimum if the above information is submitted and is considered satisfactory to the Agency.

MATERIALS:

1. Test compound: Triforine Technical. Description: white powder. Batch #: 2230. Purity: 99.9%.

2. Test animals: Species: guinea pigs, Strain: Dunkin-Hartley albino (DUNA KEN). Age: approximately 7-8 weeks; Weight: 395-433 g (males) and 400-445 g (females) g. Source: Kleintierfarm Madoerin AG. CH 4414 Fuellinsdorf /

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Switzerland. Acclimatization period: 1 week.

METHODS:

Group Assignment
Sensitization testing was done with the Maurer optimization re... Twelve males and 12 females were assigned to vehicle control groups and 12 males and 12 females were assigned test article-treatment groups. Positive controls (10 males and 10 females) were tested for sensitization in a separate experiment dated June 1984. These controls were nearly contemporaneous with the test article treatments/observations, which were done from June 25 to August 10, 1984.

Treatment
Treatment involved induction doses during weeks 1, 2 and 3, followed by two challenge treatments:

Week 1: A 0.1 ml dose of the test article (a 0.1% solution in saline with polypropylene glycol 1:1) was injected intradermally into the shaven flank and back on Monday and into the back on Wednesday and Friday.

Weeks 2 and 3: A 0.1 ml dose of the test article (prepared as above and mixed 1:1 with Freund's adjuvant) was injected into the nuchal skin on Monday, Wednesday and Friday.

Challenge 1: 13 days after the last induction dose, 0.1 ml of the test article (prepared as for week 1) was injected in an area of untreated flank.

Challenge 2: 13 days after the first challenge, a filter patch with test article as a 30% dilution in vaseline, was applied to untreated, shaven skin, and anchored with an occlusive bandage for 24 hours.

Animals were observed for mortality and toxicity symptoms daily; body weights were taken at acclimation, on day 1 and at termination of the study. No necropsies were performed.

Scoring

The animals were examined for erythema formation 24 hours after injection on week 1 and for Challenge 1, and 24 hours after patch removal for Challenge 2. Erythema reaction after injection was assessed by measuring the diameter of the erythematous area and the skin fold thickness to compute a "reaction volume" (in μl). A positive Challenge 1 was obtain if the reaction volume observed after the challenge exceeded the mean + 1 standard deviation of the reaction volumes obtained for the animal during week 1. A positive Challenge 2 was indicated if there was clearly discernible reddening at the site of challenge; no erythema received a score of 0.

RESULTS

As shown below and in Attachment 1, ~~2/12 males~~ and 1/12 females showed a positive response after intracutaneous challenge (Challenge 1); these results did not differ significantly (Fisher's exact test) with control values (2/12 positive in

males and 0/12 in females). No positive responses were observed in any animal after epicutaneous (patch) testing (Challenge 2).

No toxic symptoms attributable to the test article were observed; body weight gain was not affected by the test procedure.

Table 1. Number of animals with a positive sensitization reaction.

Challenge	Vehicle Controls		Triforine Treated	
	Male (N=12)[a]	Female (N=12)	Male (N=12)	Female (N=12)
Challenge 1 (Intracutaneous)	2	0	2	1
Challenge 2 (Skin patch)	0	0	0	0

[a] N is the Total number of animals in the test group.

Signed and dated Quality Assurance and GLP Compliance statements were present.

Although the authors indicated that "In a separate test (June 1984) the incidence of the guinea pig strain to allergic reactions was tested", no information was given on the conditions of the test, the positive control used, the results obtained or the corresponding data supporting the results of the positive test.

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Attachment 1.- Dermal sensitization test in guinea pigs. Individual irritation scores. From pp. 24 and 25 of the Study Report (102AD-467-007, MRID 423804-09).

Trifloxysulfuron Tox Review

Page 24 is not included in this copy.

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