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<th>L register</th>
<th>L other (explain)</th>
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TOX recommends addition of the word 'Corrosive' before the statement 'causes eye damage.' TOX also notes that because of the severe eye irritant characteristics of the formulation, the product is registered for restricted use only.

<table>
<thead>
<tr>
<th>Acute Oral (Rat)</th>
<th>LD50</th>
<th>Toxic signs:</th>
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Comments: For review of toxicology data, see that of June 9, 1975 (attached).

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<th>Acute Dermal (Rabbit)</th>
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Comments: 

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Comments: 

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Comments: 

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Comments: 

Other Studies: 

BEST AVAILABLE COPY

1/13
SUBJECT: Label safety review for registration of the fungicide 'ORTHO Rose Disease Control' (6.5% Triforine – H,N'-[1,4-piperazineadiyl-bis-(2,2,2-trichloro-ethylidene)]-bis-[formamide] to be sprayed on roses, crape myrtle, phlox and zinnias.

FROM: TB

TO: Product Manager

File Symbol: 239-EUGL
Applicant: Chevron Chemical Company
Ortho Division
940 Hensley Street
Richmond, California 94804

Chemical Name: H,N'-[1,4-piperazineadiyl-bis-(2,2,2-trichloro-ethylidene)]-bis-[formamide].

Other Names: Triforine
H-524

Trade Name: Funginex® is a registered trademark for Triforine, a compound of Celanese

Recommendation:

The toxicity data does not support the labeling as submitted.

The eye irritation study with the undiluted 6.5 EC formulation produced corneal opacity which persisted for fourteen days. This necessitates the use of the signal word 'DANGER' on the front panel and the precautionary wording as follows:

1. Causes eye damage
2. Do not get in eyes
3. Wear goggles or face shield
4. First Aid
   In case of contact flush eyes with plenty of water. Call a physician.

TB further recommends that this product be registered only for non-domestic uses and that the front panel of the label indicate this restriction.

Note:

With the exception of the three-generation rat study (C. H. Boehringer Sohn, May 31, 1974) and the mutagenicity study with albino mice (IBT No. 622-05459, October 15, 1974), which were not reviewed for this registration.
the remaining studies submitted (including long-term studies), were reviewed by R. Coberly of TB, 2/26/75, in conjunction with Registration No. 279-EOON-2990.

6.5 EC Formulation

Active Ingredient
Triforine
Percent by Wt.
6.5

Inert Ingredients

| Total | 100.0% |

Toxicological Review

**Mouse, acute oral, W-524, Lot No. X479**
C. H. Boehringer Sohn, 2/5/68
0/10 dead at 6,000 mg/kg
LD50 >6g/kg

**Rat, acute oral, Triforine (W-524)**
Celamerck, 3/20/73
LD50 >16,000 mg/kg

Administered orally by gavage in suspension (20 grams Triforine + 100 ml demineralized water and 015 g of carboxymethyl cellulose. (5 males and 5 females/dose)

Staggering and slower deeper breathing noted at 30 minutes. All animals normal at 48 hours. All animals survived the 14-day observation period.

**Rat, acute oral, W-524, Lot No. 51**
C. H. Boehringer Sohn, 11/4/68
0/10 dead at 5,658 mg/kg
LD50 >5,658 mg/kg

**Rat, acute oral, W-524 (Triforine) EC 20%, Celamerck, 3/29/73**

Rat LD50 = 6,600 mg/kg
5 males and 5 females used per dose level. 80 animals used in study.

INERT INGREDIENT INFORMATION IS NOT INCLUDED.
Rat, acute oral CELA W-524 6.5% EC (CC5443), Chevron, 9/25/74

Doses ranged from 1500 mg/kg to 7600 mg/kg for males and from 1500 mg/kg to 5060 mg/kg for females. At autopsy, no gross pathological changes were observed that could be attributed to the test material.

The LD50 was 4.450 mg/kg for males
95% confidence limits 2300-8590 mg/kg

The LD50 was 3.760 mg/kg for females
95% confidence limits 1400-9920 mg/kg

Rat, Intraperitoneal LD50, W-524, Lot No. T1/70, C. H. Boehringer Sohn, 4/16/771

Preparation - 20% suspension (+tylose)
0/10 dead at 4000 mg/kg
LD50 34000 mg/kg

Rat, acute dermal, W-524 Technical, Lot No. T1, C. H. Boehringer Sohn, 11/4/768

One hour prior to application of the test material, the dorsal and ventral areas of the animals were shaved with electric clippers. The skin remained intact. Triforine was diluted 1:1 with demineralized water and applied to an area 6 X 6 cm for 24 hours. Five males and 5 females were used in this study.

No signs of irritation occurred. One male and one female were found dead on the morning of the day following treatment. Death was thought to be caused by animals trying to free themselves of the rubber cuff. Other animals survived the observation period.

LD50 >10,000 mg/kg

Rat, acute dermal, W-524 (Triforine) EC 20%, Celamerck, 3/29/73

Rat LD50 = 2,500 mg/kg

Rabbit, male, acute dermal, CELA W-524 6.5% EC (CC5443), Chevron, 9/25/74

Six male New Zealand white rabbits were used in the study. At 2.9 g/kg CELA W-524 6.5% EC (CC5443) (undiluted) deaths were noted. Caused moderate erythema and edema.

Dermal LD50 >2.0 g/kg

Rabbit, Eye Irritation, Triforine (W-524), Technical, Celamerck, 3/20/73, reference 3.

0.1 g of Triforine was instilled into the conjunctival sac of the left eye of 3 animals. No signs of irritation were noted during the one-week observation period.
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<th>RABBIT NUMBER</th>
<th>CORNEA</th>
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<th>REDNESS</th>
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A. Cornea sloughing
B. Cornea roughened
C. Fannus observed
Primary mucosal irritation caused by Triforine EC 20% in the rabbit (Draize method of assessment) after bathing after instillation.

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<th>d No. 971</th>
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</table>
Rabbit, Eye Irritation, CELA W-524, 6.5% EC Formulation (CC4263) (Coded SX 569, Chevron, 11/16/73)

0.1 ml of the undiluted test substance was administered into the conjunctival sac of one eye of each of six rabbits.

Slight corneal opacity developed in most eyes by the two-day reading.
At 14 days, three eyes had moderate opacity and three eyes were normal.
Sloughing and roughened corneas were observed at the three-day reading.
Pannus was observed at the ten- and fourteen-day readings.

The test compound is a severe eye irritant.

[Table 1]

Rabbit, Eye Irritation, W-524 (Triforine) EC 20%, Celamerck, 3/29/73

Nine New Zealand White rabbits were used in this study:

3 males in which the eye was not washed
3 males in which the eye was washed after 2 seconds
3 males in which the eye was washed after 4 seconds

0.1 ml of Triforine EC 20% was instilled into the eyes.

In the unwashed group, moderate to severe symptoms occurred in the conjunctiva, and cornea. After 2-3 days the whole of the cornea was slightly opaque; it became more pronounced towards the end of the observation period. Corneal opacity persisted for more than 14 days. Washing considerably lessened irritation. Triforine (W-524) EC 20% causes severe eye irritation. The signal word DANGER is necessary. See Table 2.

Rabbit, Skin Irritation, CELA W-524 6.5% EC (CC5443) Coded SX 636
Chevron, 9/25/74

Slight erythema was noted in 3 of 6 animals at 24 hours. No other skin irritation was observed. The primary skin irritation score was 0.1.

Rat, Acute Inhalation, CELA W-524 6.5% EC (CC5443), Chevron 9/25/74

Five Sprague-Dawley rats of each sex were exposed to vapors for one hour. No deaths or signs of toxicity were noted.

Vapor exposure - 3.7 grams of CELA W-524 6.5% EC were put into 300 liters of air or 12.3 mg/l. (No effects).

Aerosol exposure - 23.4 grams of diluted CELA W-524 6.5% EC were aerosolized in 300 liters of air or 78 mg/l. (No effects noted).
Rat, 21-day subacute dermal. W-524 20% EC Celamerck, 4/4/72

The test compound was applied to the intact and abraded skin of 80 Sprague-Dawley rats over a period of 21 days. Five males and females, intact and abraded skin were observed without treatment for another 21 days after the treatment period (recovery period).

W-524 20% emulsion concentrate was dissolved in water to final concentrations of 0.5 and 1.5% and applied to 1/10 of the body surface.

Following each application very slight reddening and swelling were seen in test and control animals. (Maximum degree 1 [Draize] subsided within 30-60 minutes and are most probably to be associated with the hyperthermia occurring in consequence of covering.

The following parameters did not reveal any definite indication of incompatibility reactions after application of 0.5 or 1.5% emulsion:

1. General and cleaning behavior
2. Food and water consumption
3. Body weight development
4. Hematological (after 3 weeks)
   A. Hemoglobin
   B. Erythrocytes
   C. Leucocytes
   D. Differential blood count
   E. Hematocrit
   F. Prothrombin time
   G. Thrombocytes
   H. Reticulocytes
   I. Osmotic resistance of the erythrocytes
5. Clinical Chemistry (after 3 weeks)
   A. SGPT
   B. Liver function test
   C. Cellulose acetate electrophoresis
   D. Inorganic phosphorus
   E. Total cholesterol
   F. Glucose
   G. BUN
   H. Total bilirubin
   I. Total protein
   J. SGOT
   K. Calcium
   L. Sodium
   M. Potassium
   N. Chloride
6. Urinalysis (after 3 weeks)
   A. Color
   B. Specific gravity
   C. pH
   D. Protein
   E. Glucose
   F. Hemoglobin
   G. Bilirubin
   H. Ketone bodies
   I. Acetic acid boiling test
   J. Epithelial cells
   K. Leucocytes
   L. Erythrocytes
   M. Bacteria, worm eggs
   N. Inorganics

7. Visual and hearing functions

8. Inspection of teeth

9. Macroscopic examination of the organs and comparison of organ weights

Histological examination of the following organs (from 5 male and 5 female animals at the 3-week autopsy) revealed no test-substance-related pathological findings:

Heart
Lung
Liver
Spleen
Kidney
Adrenal
Thymus
Pituitary
Gonads
Thyroid
Brain
Prostate
Uterus
Stomach
Small Intestine
Large Intestine
Salivary gland

Bladder
Bone marrow
Trachea
Aorta
Esophagus
Pancreas
Peripheral nerve
Skeletal muscle

Skin - site of application - Slight infiltration predominantly with lympho- and monocytes in the upper third of the corium. In addition to that, a slight reactive acanthosis with hyper- and parakeratosis was observed. No marked differences between intact and abraded skin were noted. These changes were noted in 3 test and 2 control animals (2 ml water/kg). Since these changes occurred in controls, this suggests that the method of treatment was involved. At the end of the 3-week observation period, no pathological changes could be detected at the sites of application.

No effects noted at 1.5% test material in water.
Rat, 14-day, subacute vapor inhalation, 6.5% EC CELA H-524 (Triforine);

Ten albino rats were exposed to the test material vapor for six hours per day, five days per week, for 14 days (ten exposures). The average vapor concentration was 5.0 mg/l air. Ten rats served as controls.

Observations were made with respect to:

1. Incidence of mortality
2. Body weights
3. Hematology and blood chemistry (conducted before and at the end of the testing period)
4. Behavior

All surviving animals were sacrificed after completion of the test.

Other than 3 rats that died during bleeding procedures, there were no other deaths or untoward behavioral reactions.

Body weight gain suppression was noted in both males and females.

### Mean Weights (grams)

<table>
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<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Final</th>
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<td>Male</td>
<td>320</td>
<td>369</td>
<td>.351</td>
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<tr>
<td>Female</td>
<td>209</td>
<td>241</td>
<td>.230</td>
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Guinea Pig, Skin Sensitization Potential, H-524 (Triforine) EC 20%,
Celamerck, 3/29/73

<table>
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<tr>
<th>Pretreatment</th>
<th>No. of Animals</th>
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<tbody>
<tr>
<td>Triforine EC 20% undiluted</td>
<td>5 males &amp; 5 females</td>
</tr>
<tr>
<td>Triforine EC 1.25% dilution</td>
<td>5 males &amp; 5 females</td>
</tr>
<tr>
<td>Dinitrochlorobenzene 2% in ether</td>
<td>5 males &amp; 5 females</td>
</tr>
<tr>
<td>Demineralized water</td>
<td>5 males &amp; 5 females</td>
</tr>
<tr>
<td>No treatment</td>
<td>10 males &amp; 10 females</td>
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</tbody>
</table>

Application to skin of trial groups and control Group I was 5 times per week (total of 10 times). The liquids were applied in the shape of a cross to the left flank. The comparative group received pretreatment for 5 days only.
After pretreatment the guinea pigs received no treatment for two weeks. The doses in the final challenge were 1/10 of the concentrations used in pretreatment, and applied to the right flank.

No reactions were noted in either trial groups, while the comparative group demonstrated an evident reaction.

Laurence D. Chitlik, Toxicologist
Toxicology Branch
Registration Division (WH-567)

cc: Branch Reading File
LChitlik:boa
NCG:O.E.Paynter
Triforine

RIN 0051-90

Page_____ is not included in this copy.

Pages 12 through 13 are not included.

The material not included contains the following type of information:

___ Identity of product inert ingredients.
___ Identity of product impurities.
___ Description of the product manufacturing process.
___ Description of quality control procedures.
___ Identity of the source of product ingredients.
___ Sales or other commercial/financial information.
___ A draft product label.
___ The product confidential statement of formula.
___ Information about a pending registration action.
___ FIFRA registration data.
___ The document is a duplicate of page(s) ________.
___ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.