002369

DATE: 1/31/78

SUBJECT: EPA Reg. No. 239-EULL, Ortho Triforine EC
(N,N'-[1,4-piperazinediylbis(2,2,2-trichloroethylidene)]bis[formamide]

FROM: R.B.Jaeger
TB

TO: Eugene Wilson
PM 21

Data submitted are reviewed as follows:

1. "The Acute Oral Toxicity of Ortho Triforine EC", Environmental Health & Toxicology, Standard Oil Co. of California, 10/19/77, Study No. S-1113 (SOCAL 1065/31:48); submitted by Chevron Chem. Co., 1/3/77 (Acc#232564).

   a. Protocol: Acute Oral LD50

   Substance Tested: Orhto Triforine EC (laboratory analysis of composition of materialttested was included)

   Species: Sprague-Dawley rats

   Sex and Age: Adult M/F

   Number of Animals: 5M/5F per each of 4 and 6 dosage groups, respecti

   Conduct of Test:

   Dosing/Duration: Animals housed individually; fasted overnight prior to dosing; free access to food and water during study. Single intragastric doses ranging from 3.3 to 10 g/kg (males), or 2.2 - 15 g/kg (females) of the undiluted test material were administered to groups of 5 fasted rats. Five fasted animals of e sex served as controls.

   Observations: Animals weighed prior to treatment and 7 and 14 day after treatment. Mortality observed up to 14 days.

   Necropsy: After 14 days, the surviving animals were sacrificed a examined for gross pathological changes. The following organs and

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tissues were examined: salivary glands, thymus, heart, lungs, kidneys, adrenal glands, spleen, liver, gonads, pancreas, G-I tract, bladder, lymph nodes, body fat, teeth, skeletal muscle, eyes and skin.

b. Results:

Mortality:

Dose (g/kg)	Sex	14-Day Mortality	Time to Death	Time to Recovery (i
2.2	Female	0/5	---	---(a)
3.3	Male	0/5	---	<4
	Female	2/5	<1 - 1 days	2
5.0	Male	2/5	<1 - <2 days	<2 - <7
	Male	1/5	<4 days	<4
	Female	5/5	1 - 2 days	---
7.5	Male	5/5	<1 - <4 days	---
	Female	5/5	~3 hrs-< 2 days	---
10	Male	5/5	<1 day	---
	Female	5/5	~3 - 4 hrs	---
15	Female	5/5	~2 - 3 hrs	---

(a) No signs of toxicity were observed at this dose level.

	LD_{50} (95% Limits)	Slope (95% Limits)
Males	5.7 (4.0 - 8.2) g/kg	1.5 (0.98 - 2.2)
Females	3.8 (1.9 - 7.6) g/kg	2.1 (1.0 - 4.2)

Toxicological Symptoms: At higher doses the following were noted: depression, weakness, collapse, convulsions, diarrhea, reduced food consumption and death.

Necropsy: "No gross pathological changes attributed to the test material were observed."

Body Weight: Individual wts., etc. were not reported.

c. Conclusions:

Study is considered CORE:Guidelines.

Toxicity Category: III "CAUTION"

2. "The Acute Dermal Toxicity of Ortho Triforine EC"; Environmental Health & Toxicology, Standard Oil Co. of California, 10/19/77, Study Number S-1114 (SOCAL 1066/29:44), submitted by Chevron Chem. Co., 3/3/77 (Acc#232564).

a. Protocol: Acute Dermal LD50

Substance Tested: Same as 1. above

Species: New Zealand White Rabbits

Sex and Age: M (wt 2.11 to 2.77 kg)

Number of Animals: 6

Conduct of Test:

Dosing/Duration: Animals housed individually; given daily ration of commercial lab. feed and free access to water. Fur on the trunks of each rabbit was clipped free of hair on the day prior to testing. 3/6 rabbits had their skin abraded. 5g/kg of test material were applied to the trunk of each animal and held in contact by plastic sheeting. 6 control rabbits were also used. After 24 hrs material was removed from the animals.

Observation: Animals observed for 14 days and sacrifieed. Animals were weighed prior to treatment, and at 7 and 14 days after treatment; weights compared to controls.

Necropsy: The following organs and tissues were examined: thymus heart, lungs, liver, kidneys, adrenal glands, spleen, gonads, G-I tract, pancreas, salivary glands, lymph nodes, bladder, body teeth, skeletal muscle, eyes and skin.

b. Results:

Mortality:

1/6 died 5 days after treatment.

Observations: Less than normal food intake with accompanying wt. loss observed in 5/6 up to 8 days post treatment. Eleven days post treatment survivors were eating normally, gaining wt. and appeared normal, except for severe skin irritation. The wts. of the treated and control groups were significantly different at 7 and 14 days ($p < 0.01$) and ($p < 0.05$), respectively.

Necropsy: Anatomy of expired rabbit showed an enlarged, granular congested liver and leather-like necrotic skin. Survivors showed less than normal amounts of body fat and areas of sloughing, necrotic skin, and eschar formation.

c. Conclusions:

Study is considered CORE: Minimum Data. However, since only male rabbits were tested the study does not satisfy the requirement for an Acute Dermal LD50 evaluation by itself; female rabbits would need to be tested as well. See comments at conclusion of registration review.

An LD50 evaluation was not conducted or reported. It can be reasonably concluded that ~~Ef~~/X the LD50 is greater than 5g/kg for the male rabbit.

3. "The Eye Irritation Potential of Ortho Triforine EC", Environmental Health & Toxicology, Standard Oil Co. of California, 10/20/77, Study Number S-1115, (SOCAL 1067/30:72), submitted by Chevron Chem. Co., 1/3/77 (Acc#232564)

a. Protocol: Primary Eye Irritation

Substance Tested: Same as 1. above

Species: New Zealand White Rabbit

Sex and Age: M; age not stated

Number of Animals: 6

Conduct of Test:

Dosing/Duration: Animals housed individually; daily ration of commercial lab. feed and free acess to water. 0.1 ml of test material was palced in the conjunctival sac of one eye in each of 6 rabbits. Untreated eye served as control. Eyes were examine at 1, 24, 48, and 72 hrs, and at 7, 10, and 14 days using the modified Draize method.

b. Results:

- 5/6 rabbits demonstrated increased severity of corneal opacity up to 14 days (complete corneal opacity, with roughened cornea and pannus).
- mild iritis reversible to 0 at 10 days
- severe redness of conjunctiva (6/6 at 3 days, 5/6 at 7 days, 1/6 at 14 days), conjunctival sloughing was evident
- severe to moderate discharge and chemosis reversible to slight at 7days and 14 days.

c. Conclusions:

Study is considered CORE:Minimum Data.

Toxicity Category: I "DANGER"

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The following were noted:

(1) irritation index not reported

(2) length of time material was on contact with eyes was not reported

(3) used only 6 animals with no indication that the effects of washing were evaluated.

4. "The Skin Potential of Ortho Triforine EC", Environmental Health & Toxicology, Standard Oil Co. of California, 10/20/77, Study Number S-1116, (SOCAL 1068/30:73), submitted by Chevron Chem. Co., 1/3/77 (Acc# 232564)

a. Protocol: Primary Dermal Irritation

Substance Tested: Same as 1. above

Species: New Zealand White Rabbit

Sex and Age: Male; age not stated

Number of Animals: 6

Conduct Of Test:

Dosing/Duration: Animals housed individually and given daily ration of commercial lab feed; water available ad lib. The fur on the backs of 6 rabbits was clipped free of hair. 0.5 ml of test material was applied to an intact and abraded site on the back of each rabbit. Treated area was then covered with a gauze patch, secured by adhesive tape. The trunkof each animal was then loosely wrapped in a plastic sheet. After 24 hr exposure the wrappings and test material were removed. Irritation was scored at 24, 48, 72 hrs and at 7 days using the modified Draiz

b. Results:

Primary Irritation Index 5.5/8.0

There was virtually no difference between intact or abraded skin areas. Erythema remained severe (beet redness) with

eschar formation (injuries in depth) at 7 days. Also noted was white necrotic skin. Edema was moderate to severe at 7 days.

c. Conclusions:

Study is considered CORE:Minimum Data.

Toxicity Catefory I "DANGER"

5. "About the Acute Inhalation Toxicity of 20% Emulsion-Concentrate of W-524 in SPF Rats", Laboratorium Für Pharmakologie Und Toxikologie, 3/3/72, Submitted by Chevron Chem. Co., 1/3/77 (Acc# 232564)

a. Protocol: Acute Inhalation LC50

Substance Tested: Unknown?

Species: SPF-Wistar Rats (Farbwerke HOECHST AG., Frankfurt/Main)

Sex and Age: M/F, 60 and 82 days old, reppectively.

Number of Animals: 5M/5F per each of 5 doses (0, 5.1, 9.8, 20.6 and 37.8 mg/l)

Conduct of Test:

Dosing/Duration: 10 rats were housed in glass tubes with respiratory tubes within a 39 liter glass container. The air was dried in three grades (potassium dichromate-sulphuric acid, sodium hydroxide, calcium chloride) before applying the W-524 emulsion-concentrate. Exposure was 1 hr. Afterwards animals were housed individually and the cages illuminated and darkened at 12 hr intervals during the 21 day observation period. Food and water available ad lib. Sixe of droplets were determined to be: 70% < 5 µ; 95% < 20 µ .

Observations: General behavior and condition and food comsumption determined weekly (at same day and hour of the day).

Necropsy: All animals sacrificed by decapitation, exsanguinated, dissected and microscopically examined: heart, liver, lungs, spleen and kidneys.

b. Results:

Behavior: Increased salivation, serous rhinitis and sedation as dose increased. Ataxia noted after 40 minutes of inhalation.

Fodd Consumption/Body Wt.: No change from control

Mortality: None.

LC50 (21 days obs.) > 37.8 mg/l

Necropsy: No significant pathogical findings.

c. Conclusions:

Study is considered INVALID because the material tested was not completely, clearly, and sufficiently identified. Is it the same as the formulation for EPA Reg. No. 239-EULL? Once this information is received the study will be upgraded to CORE: Minimum Data and will satisfy the requirement for an Acute Inhalation LC50 study.

As noted above, Acute Dermal LD50 data is lacking with regard to the female. However, sufficient toxicity data are available which indicate: (1) the female is not sufficiently more sensitive than the male (i.e. Acute Oral LD50); (2) this information together with the AD LD50 value for males indicate it is suffiently great (i.e. >5 g/kg) to preclude further testing in the female; and (3) the product will be required to carry maximum precautionary labeling for avoidance of skin contact based on the Primary Dermal Irritation Study in male rabbits (i.e. "DANGER. Do not get on skin, etc., etc.").

Further, TB notes the Inhalation LC50 evaluation is unacceptable until the questions raised above have been adequately addressed, with regard to that specific study.

TB notes also, the Registrant's label statement pertaining to emesis if

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material is swallowed. TB questions this statement based on the apparent corrosiveness of the material. As such, emesis may produce further complications and ulceration of the mucoid lining of the esophagus and other associated tissues. Consequently, TB will require justification from the Registrant that emesis of ingested material is a proper and safe statement of practival treatment. Until such information is received, proper precautionary labeling cannot be prescribed and therefore, TB recommends against registration until items addressed above are clarified.

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Toxicology Branch

for WHB 2/3/78

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