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'ITED STATES ENVIRONMENTAL P[illegible]TECTION AGENCY

CASWELL FILE

DATE: March 13, 1978

SUBJECT: Triadine - 10 - New Route

EPA Registration No. 1258-990
Shaughnessy#1088004, 105601, Caswell#790A, 481C

FROM: Larry Anderson, Ph.D
Toxicology Branch

TO:
J. H. Banks
Product Manager #33

THRU: Acting Branch Chief

Recommendations:

Acute oral LD_{50}, acute dermal LD_{50}, acute inhalation LC_{50}, skin and eye irritation studies and the potentiation study are adequate. The TOX I Category label proposed by the registrant requires the following change :

"Harmful or fatal if swallowed" to "Harmful if swallowed, inhaled or absorbed through the skin."

The formulation is a skin sensitizer and appears to induce phototoxicity. However, the phototoxicity study is classified "Invalid" until further clarified according to reasons stated in the review.

*The formulation is a candidate for the Restricted Use classification because corneal opacities which were not reversible during 7 days post-treatment were observed in the eye irritation study.

**No RPAR criteria have been exceeded.

***Studies by Industrial Bio-Test Laboratories, Inc. were submitted and will require validation prior to registration of the product.

Review:

I. Acute Oral Potentiation Study with Onyxide - 200 and Sodium Omadine, 40% in Albino Rats (Industrial Bio-Test Laboratories, Inc., IBT No. 8530-10054, 3/11/77, submitted by Olin Corp., 10/5/77, Acc.#232145).

A. Acute Oral Potentiation Study

1. Procedure

a). Young albino rats (COBS), 150-262g, were divided into 12 groups of 10 animals each (5 males and 5 females) and were administered the following by gavage: 400, 600, 900, or 1350 mg/kg of Onyxide - 200, 900, 1350, 2025, or 3038 mg/kg of Sodium Omadine, 40%; 900, 1350, 2025 or 3038 mg/kg of a mixture of 24.19% Omyxide - 200 and 75.81% Sodium Omadine, 40%.

Animals were fasted 24 hours prior to treatment. Observations of mortality, body weight changes, and reactions were continued during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortality: Onyxide - 200 LD_{50} = 710.77 (234.51-954.43) mg/kg; Sodium Omadine, 40% LD_{50} = 2125.8 (1692.9-2669.4) mg/kg; Equitoxic mixture of Onyxide - 200 and Sodium Omadine, 40% LD_{50} = 1464.1 (1187.6-1804.9) mg/kg.

b). Body Weight Changes: Unremarkable

c). Toxic Symptoms: Onyxide-200 - Hypoactivity, salivation, lacrimation, muscular weakness, prostration, labored breathing, diarrhea; Sodium Omadine, 40% - Lacrimation, cyclic running, vasodilation, hypoactivity, ptosis, labored breathing, salivation, diarrhea, excretion at nostrils, diuresis, intermittent convulsions, muscular weakness, prostration; Mixture of Onyxide-200 and Sodium Omadine, 40% Same as for Sodium Omadine, 40% less ptosis.

d). Necropsy:

i. Decedents: Onyxide -200 - Red lungs, gastrointestinal hemorrhages, slightly pale kidneys, abnormally dark spleens; Sodium Omadine, 40% - Same as for Ony ide - 200 plus pale areas on livers; Mixture of Onyxide-200 and Sodium Omadine, 40% - Same as for Sodium Omadine, 40%.

ii. Survivors: Unremark able except for necrotic stomach lini gs in 3 anima l given the mixture of Onyxide-200 and Sodium Omadine, 40%.

3. Conclusions

a). Classification: Core Guidelines

b). Neither sample potentiated acute oral toxicity of the other, i.e., the observed LD_{50}, 1.464 g/kg and the theoretical LD_{50}, 1.418 g/kg, values of the equitoxic mixture are approximately equal.

II. Acute Aerosol Inhalation Toxicity Study with Triadine-10, 70% Active, Sample No. 873158 in Rats (Industrial Bio-Test Laboratories, Inc., IBT No. 8562-10345, 3/14/77, submitted by Olin Corp., 10/5/77, Acc.#232145).

A. Acute Aerosol Inhalation Toxicity Study

1. Procedure

a). Ten (5 males and 5 females) albino rats (Charles River) were exposed for 1 hour in an 80L inhalation Chamber to 7.44 mg/l air of test material (nominal concentration) generated as aerosol in clean dry air (6 l/min). After exposure, animals were bathed, dried, and observed for mortality, body weight changes, and toxic symptoms during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortality: None: LC_{50} > 1.44 mg/ air.

b). Body Weight Changes (Gain): Males, 81 g, Females, 22 g.

c). Toxic Symptoms: Unremarkable

d). Necropsy: Unremarkable

3. Conclusions

a). Classification: Core-Minimum Data

i. Although only 1 dosage level was used, results show that it was adequately high to show low toxicity of the test compound.

b). TOX Category: III.

III. Acute Toxicity Studies with Triadine-10, 70% Active (Industrial Bio-Test Laboratories, Inc., IBT No. 8530-10344, 7/14/77, submitted by Olin Corp. 10/5/77, Acc.#232145).

A. Acute Oral Toxicity Study - Albino Rats

1. Procedure

a). Young albino rats (COBS), 174-296g, were divided into 6 groups of 4 animals each (2 males and 2 females) and were administered 266.7, 400, 6(900, 1350 or 2025 mg/kg of test material by gavage. Observations for mortality, body weight changes, and reations were recorded during 14 days post-treatment. Necropsies were done.

2. Results

a). Mortality: LD_{50} = 734.86 (485.99-1176.5) mg/kg.

b). Body Weight Changes: Unremarkable

c). Toxic Symptoms: Hypoactivity, salivation, muscular weakness, diarrhea, labored breathing, prostration,diuresis, emaciation.

d). Necropsy

i. Survivors: Necrosis in stomach lining.

ii. Decedents: Pale kidneys, gastrointestinal hemorrhages, chemical burns in stomach linings, a red lung in one animal, pale liver, pale spleen, fat depletion in one animal, distended gastrointestinal tract.

3. Conclusions

a). Classification: Core-Minimum Data

i. Only 2 animals/sex/dose were used, but use of 8 dose levels improves acceptability of the study.

b). TOX Category: III

B. Acute Dermal Toxicity Study - Albino Rabbits

1. Procedure

a). Thirty-two young adult albino rabbits (New Zealand), 2.3-3.46 kg, were divided into 8 groups of 4 animals each (2 males and 2 females) which received dermal applications of 177.8, 266.7, 400, 600, 900, 1350, 2025 or 3038 mg/kg of undiluted test material under occlusive dressing. Backs were shaved 24 hours before application. Test sites of (1 male and 1 female)/dose were abraded. Dressing and residual test material were removed at 24 hours post-treatment. Observations of mortality, local reactions, toxic symptoms, and body weight changes were continued during 14 days after treatment. Necropsies were done.

2. Results

a). Mortality: LD_{50} = 854.4 (409.2-1784.2) mg/kg.

b). Body Weight Changes: Unremarkable

c). Toxic Symptoms: Diarrhea, tonic convulsions, hypoactivity, diuresis, prostration.

d). Local Reactions: Erythema, edema, second degree burns, focal third degree burns, subdermal hemorrhages at 24 hours post-treatment; erythema and edema at 7 days post-treatment; second degree burns, escharosis, and focal necrosis at 7 and 14 days post-treatment.

e). Necropsy

i. Survivors: Pale kidneys, enlarged gall bladder, body fat depletion, discolored large intestine, red lung, emaciation, pale liver, pale spleen, lung edema.

ii. Decedents: Moderate and advanced post-mortem autolysis.

3. Conclusions

a). Classification: Core-Minimum Data

i. Only 2 animals/sex/dose were used, but use of 8 dose levels improves acceptability of the study.

b). TOX Category: II

C. Eye Irritation Study - Albino Rabbits

1. Procedure

a). Into each right eye of 6 young albino rabbits (New Zealand), 10-13 weeks old, was instilled 0.1 ml of undiluted test material. Untreated left eyes were controls. Eyes were not washed after treatment. Injuries were scored according to Draize et al (1944) at 1, 24, 48, and 72 hours and 7 and 14 days after treatment.

2. Results

a). Corneal damage, iritis, and conjunctivitis were evident throughout 14 days' post-treatment. Corneal opacity was observed in all rabbits throughout 14 days' post-treatment.

3. Conclusions

a). Classification: Core-Minimum Data

i. Effect of washing eyes after treatment was not evaluated.

b). TOX Category: I

D. Primary Skin Irritation Test - Albino Rabbits

1. Procedure

a). Onto intact and abraded test sites, each of 6 young albino rabbits (New Zealand), 10-13 weeks old, received dermal applications of 0.5 ml of undiluted test material under occulsive dressing. Test sites were shaved prior to application. Dressing and residual test material were removed at 24 hours post-treatment. Injuries were scored according to Draize et al. (1944) at 24 hours and 72 hours post-treatment.

2. Results

a). P.I. Index = 6.3/8.0

b). Local Reactions: Erythema, edema, subdermal hemorrhages, second degree chemical burns.

3. Conclusions

a). Classification: Core Guidelines

b). TOX Category: II

IV. Skin Sensitization Test with Triadine-10 (70%) in Albino Guinea Pigs (Industrial Bio-Test Laboratories, Inc., IBT No. 8530-10667, 8/25/77, submitted by Olin Corp., 10/15/66, Acc.#232145).

A. Skin Sensitization Test

1. Procedure

a). Irritation Range - Finding Test

i. Eight guinea pigs were divided into groups of 2 which were insulted with 0.5 ml of 0.1% (w/v), 1%, 10% or undiluted test material for 5 hours. Irritation was scored at 24 and 48 hours following application of test material onto each of 2 test sites/animal .

b). Skin Sensitization Test

i. Ten guinea pigs were insulted with .5 ml of undiluted test material for 5 hours. Four animals from the same population were controls. Each treated animal was insulted 3 times/week/3 weeks with a single closed patch containing 0.5 ml of test material. Four weeks after final exposure, test and control animals were challenged with test material. Test sites were depilated, 24 hours post-challenge, and were scored for irritation 3-5 hours after depilation. Irritation was scored, 24 and 48 hours after initial insult, 24 hours after each intermediate insult, and 24 and 48 hours after challenge. Test animals and new controls were rechallenged (challenge 2), and irritation was scored 24 and 48 hours post-challenge.

2. Results

a). Results of the range - finding test were unremarkable except for minimal erythema at 24 hours post-treatment on 1 test site.

b). Skin reactions included edema, erythema, chemical burns, and fissures. Erythema and edema were evident following challenges 1 and 2 before and after depilation. Escharosis was observed after challenge 2. Reactions of control animals were unremarkable except for minimal erythema on 1 test site through 48 hours after challenge. Local reactions similar to those exhibited by animals exposed to Triadine-10 were reported for another group of test animals challenged with 0.05% (w/v) DNCB in ethanol.

3. Conclusions

a). Classification: Core Guidelines

b). Test material is a skin sensitizer.

V. Phototoxicity Test with Triadine-10 (70%) in Albino Guinea Pigs (Industrial Bio-Test Laboratories, Inc., IBT No. 8530-10667, 8/25/77, submitted by Olin Corp., 10/5/77, Acc.#232145).

A. Phototoxicity Test

1. Procedure

a). Sixteen albino guinea pigs were divided into 2 groups of 8 which were designated Irradiated and Nonirradiated test groups. Test sites were depilated at 24 hours before dosing. Topically applied was 0.5 ml of 0.1% (w/v), 1%, 10%, or undiluted test material. Each concentration of test material was applied to 4 animals. Local reactions were evaluated at 24 and 48 hours post-treatment. Irradiated animals were exposed to irradiation (2900-3200A) for 15 minutes at a distance of 35 cm from the source.

2. Results

a). Test data were reported for each test material concentration evaluated on 4 animals/group for both Irradiated and Nonirradiated groups. Erythema was evident on irriadiated and nonirriadiated animals receiving undiluted test material and on 1 irradiated animal receiving 10% test material.

3. Conclusions

a). Classification: Invalid (Provisional).

i. Numbers of animals divided into dosage and treatment groups are not clearly reported and require further explantation.

ii. Control data should be included with the results.

b). The test material is shown to be a skin photosensitizer.

VI. Final Conclusions

1. Use of the signal word "Danger" proposed by the registrant is supported as follows:

Test Indicator	Tox. Category
Acute oral LD_{50}	III
Acute inhalation LC_{50}	III
Acute dermal LD_{50}	II
Eye irritation	I
Skin irritation	III

Larry Henderson
E 3/24/78