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November 15, 1968

11-19-68

Registration Division
Research Service
Department of Agriculture
Washington, D. C. 20250

Reg. Nos. 1256-ET, 1250-RI
Referral Date - 12/1/64

Dear Mr. [redacted]:

We have completed our review of the toxicological data on Finc
Oxaline and have no objection to registration of these labels.

We suggest, however, that the following changes be made on each
label:

- 1) Omit the word "Prolonged" from the caution statement
- 2) Place the statement "Keep out of reach of children in
a prominent place on the front panel"

Sincerely yours,

Paul D. Baron, M. D.
Medical Officer
Registration Section
Pesticides Program

Enclosures

PDBaron:ecv

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Common Name

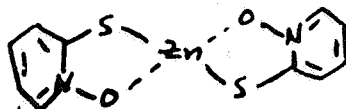
: Zinc Omadine

Chemical Name

: Zinc 2-pyridine thiol 1-oxide

Structural Formula

:



Empirical Formula

: $C_{10}H_8N_2O_2S_2Zn$

Physical-Chemical Constants

: Powder

Colour - off white

Melting Point - $240^{\circ}C$

pH - 10% in water 6.5-7.5

2% in water 6.8-7.3

Solubility - in water 10-20 ppm

Water Dispersion

Colour - off white, grey

pH - 48% - 6.5 to 8.0

10% - 7.0 to 8.0

Use

: Cosmetic Preservation

Cutting Fluid Systems - bactericide

Company

: Olin Mathieson Chemical Corp.

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DATA SUMMARY

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Acute Dog Oral (tech) : $LD_{50} = 600$ mg/kg

Acute Rabbit Eye Irritation (tech) : Severe reversible irritation.

Acute Rabbit Dermal (tech) : $LD_{50} \approx 8$ g/kg

Acute Rabbit Eye Irritation (tech) : Severe corneal, iridal and conjunctival irritation at 72 hours.

Acute Rabbit Eye Irritation (0.025% in cream base) : Slight irritation when eye unrinsed, eyes appeared normal at 48 hours.

Rat Skin Irritation (0.025-0.1% in cream base) : Slight irritation in abraded or unabraded skins, healing within 7-15 days.

Rabbit Skin Irritation (0.025% in cream base) : Slight irritation, healing in 10 days.

Subacute Rabbit Dermal (tech) (5 days) : 25 and 40 mg/kg produced no signs other than bladder atonia.

Subacute Rat, Rabbit, Dog, Monkey Oral (3 weeks) (10% formulation) : Rat - no-effect level 10 mg/kg
Rabbit (feeding) no-effect level 3.5 mg/kg
Rabbit (s.t) - No-effect level 80 mg/kg
Dog - 25 mg/kg produced blindness (only species)

Human Patch Test (0.5 % suspension) : No skin sensitization or irritation.

PDBaron:bjc
November 19, 1968

ZINCPYRIDINETHIONE

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Acute Dog Oral (Tech)

Groups of 5 mongrel dogs of both sexes were intubated and fed dietary levels of 200, 400, 600, and 800 mg/kg. The material was made up as a 10% w/v suspension in a 1% aqueous solution of methocel. Because of the marked ^{emetic} ~~medic~~ properties of the test material 20 mg/kg of morphine sulphate was given subcutaneously prior to its administration to reduce the vomiting.

Results

LD₅₀ = 600 mg/kg. All deaths occurred within 48 hours. No effects on the vision were noted on these or the surviving animals. Development of marked weakness and stupor preceded death. Despite the heavy dosing with morphine a vomiting tendency still persisted in some of the dogs.

Acute Rabbit Eye Irritation (Tech)

A few drops of the test material were placed in the eye of a rabbit.

Results

Marked erythema resulted and a watery discharge persisted for several days. No permanent damage was noted. The precise amount of the test material instilled into the rabbit's eye was not elucidated.

Acute Rabbit Dermal (Tech)

Three groups of 4 albino rabbits were dosed at levels of 2, 4, and 8 gm/kg. The test material was administered at a 50% aqueous paste. The trunk was encased in a sleeve and the animal restrained in stock during application. The material was applied for a 24-hour continuous period. Observations

including body weight, appearance, behavior, skin irritation and mortality were made over a 14-day period. 003932

Results

No deaths occurred at any level in 14 days except for 1 animal that died of a traumatic injury. No noteworthy findings were observed at autopsy. The acute dermal toxicity of the test material >8 gm/kg.

Acute Rabbit Eye Irritation

Six albino rabbits were dosed with 10 mg of a powdered sample of the test material in the right eye without washing. The animals were maintained in stocks 6 hours after dosage and observations with respect to the degree of eye irritation were made at 24, 48 and 72 hours.

Results

There ^{was} severe opacity of the cornea, severe iridial irritation and severe lid redness, chemosis and discharge of the conjunctiva. The data does not indicate whether the severe irritations were at all reversible.

Acute Rabbit Eye Irritation (0.025% in Cream base)

50 mg of the test material was instilled in the conjunctival sac of 1 eye in each of 4 rabbits once every 24 hours for 3 days. The eye was held shut for 1 minute. The control sample was similarly placed in the other eye. The control consisted of a 1% quinolor cream. The eyes were examined for irritation at 1, 3, 6 and 24 hours after the first treatment and 3 and 24 hours after the second and third treatments. There was a slight irritation produced by the test material in the unrinsed eyes, which was slightly less than caused by the control. Those eyes treated with the zinc salt and rinsed showed evidence of slight irritation during the test period.

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the eyes appeared normal 48 hours after the last treatment and there was no evidence of corneal damage in any case.

Rat Skin Irritation

Groups of 4 albino rats were exposed to 250 mg of each of 4 test samples for 5 days. The materials (0.1, 0.05, 0.025% zinc pyridinethione and 1% quinolor cream as control) were applied to closely clipped abraded and unabraded skin of 5 or 6 rats (3 or 4 abraded, 2 unabraded sites per sample). Comparable sites on the opposite side of the animal were treated with the control samples or another test samples and all sites were rebandaged after treatment and the rats were observed for 20 days.

Results

No evidence of skin irritation was observed on the unabraded skin of rats treated with either the test or control samples. In rats treated on abraded sites without either zinc pyridinethione or the control, degree of irritation was only slight (erythema) and time for healing ranged from 7-15 days. Moderately excessive drying was observed with the 0.1% and 0.05% zinc formulations causing the scabs to curl upwards, exposing the underlying epidermis and thereby prolonging the healing process. Healing required from 4-8 days in animals treated with the control materials. The abraded skin of rats treated with 0.025% zinc pyridinethione generally remained soft and the scabs showed no evidence of excessive drying during the healing period.

Rabbit Skin Irritation (0.025%-0.1% in cream base)

A comparable study to the previous report-250 mg of the test material was applied to the backs of abraded and unabraded skins of 3 rabbits. The materials were applied daily for 2 days.

Results

At 0.025% 1 rabbit showed a slight erythema occurring for 7 days but the drying and the cracking of the scab caused some delay in healing which did not occur until the 10th day. In the 1% quinolor cream control there was very slight erythema occurring for the first 3 days after the initial application with complete healing being observed within 1 week.

Subacute Rabbit Dermal (Tech)

Groups of 4 New Zealand white rabbits, each group containing 5 animals, were dosed with either 20 or 40 mg/KG of the test material for a period of 5 days. The skin was prepared so that a 225 sq cm area was clipped. The doses were covered and the rabbits harnessed so as to prevent oral attack over the intended duration of 5 days. Two groups had the pH adjusted so as to correspond with a comparable sodium salt solution and 2 groups had the solution non-adjusted.

Results

There were no deaths or signs of compound effects grossly in any of the 4 groups of 5 rabbits during the course of the study. The only symptom or sign noted was bladder distension. One rabbit showed bladder atonia and it received 40 mg/kg daily of the non-adjusted suspension material. Food consumption in all instances were slightly reduced over pre-test levels but not inordinately in view of the restraint during applications. Body weights declined slightly but unremarkable.

Subacute Rat Oral (3 weeks) (10% formulation)

Two male and 2 female rats received the daily dose by stomach tube of a shampoo containing 10% zinc pyridinethione at a level of a 100 mg/kg of shampoo per day for 15 daily doses during a 3-week period. Additional

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studies were carried out on groups of 13 rats. A control group received a ground basal diet and a second group received 1 mg of the test material per 20 gm of diet and a third group received 5 mg of the test material per 20 gm of diet. The zinc pyridinethione was incorporated in the diet in the form of a shampoo and was fed on an interrupted schedule over a 9-week period. Four groups of 2 rabbits each received 10% zinc pyridinethione shampoo formulation incorporated in the diet at levels supplying 0, 3.5, 17.5, and 70 mg/kg in terms of the zinc pyridinethione. These animals were fed for a period of 21 days. Four groups of 6 rabbits each received the same product at levels supplying zinc pyridinethione at levels of 0, 20, 40 and 80 mg/kg/day for 21 days. The material was administered in single daily doses with the stomach tube. One group of 4 rabbits was given daily doses of 15 mg/kg/day. This material was given in 10 divided daily doses by mouth for 28 days.

In an additional study, 2 mongrel dogs (1 male and 1 female) were given oral doses of zinc pyridinethione as a w/o emulsion at a level of 25 mg/kg/day for 14 days. The dose was administered in a gelatin capsule. As a control for this experiment 1 mongrel dog was given oral doses of hydroxy pyridinethione at the same level for the same period of time.

A 10 mg/kg dose of the test material was administered by stomach tube to a monkey 5 times a week for 16 weeks.

Two monkeys (^{Reese}~~Reese's~~) were given oral doses of zinc pyridinethione (as a w/o emulsion) at a level of 25 mg/kg for 8 days to gain an indication of the ocular toxicity in the species.

The effect on dogs of the oral administration of shampoo containing 2%

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zinc pyridinethione was also studied. The material was administered by stomach tube or in capsules. Doses ranged from 50 mg to 5 gm of shampoo/kg. One dog was given 1 gm of shampoo/kg 3 times weekly for 8 weeks; other animals received only single doses. The eyes of the dogs were examined histologically when appropriate after being fixed, embedded in paraffin, cut and stained.

Results

Rats tolerated a daily dose for 15 days of shampoo containing 10% zinc pyridinethione at a level of 10 mg of zinc pyridinethione/kg/day without apparent effect.

Rats fed the diet containing 5 mg of the test material/20 gm of diet showed typical skeletal muscle paralysis in 1 week after consuming an average of about 20 mg of the test material/day. Six weeks after being returned to the basal diet their body weights were within 15 gm of the control group. At that time they were put back on the diet containing zinc pyridinethione. In about 2 weeks, signs of paralysis were once again observed. The animals were again put on the basal diet and again recovered from the paralysis. The group fed the diet containing 1 mg of zinc pyridinethione/20 gm of feed gained about 100 gm less during the 9 week period than the control. These animals did not develop a rigid paralysis but a muscle relaxation was observed. At the end of the experiment the animals were placed on a basal diet, and the borderline symptoms of paralysis again disappeared.

Rabbits showed no effect when fed a diet containing shampoo (10% zinc pyridinethione) at a level supplying 35 mg of shampoo/kg/day for 2 weeks. At levels of 175 and 700 mg of shampoo (17.5 and 70.0 mg of zinc pyridine-

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thione)/kg/day the animals developed gross signs of toxicity within 2 weeks. They became listless and disinclined to move, unable to sit in a normal position and were frequently observed half sitting and half lying; after several days they could no longer get up to drink or eat and appeared to be in a condition very similar to curare paralysis; accommodation to light was slow, and the animals moved sluggishly when stimulated, becoming quite illtempered and irritable. Death was assumed to be due to starvation. No signs were observed when rabbits were given oral doses of 200, 400, or 800 mg of shampoo/kg/day as a single dose, 5 doses a week for 3 weeks. Then when a dose of 150 mg of shampoo was divided into 10 equal doses during the day, 3 rabbits died during the first week, without developing signs of paralysis. A fourth rabbit remained in apparent good health during the 4 week period. None of the animals developed paralysis or muscle relaxation.

Of the 2 mongrel dogs that received 14 daily oral doses of zinc pyridine-thione (25 mg/kg), 1 male generally showed normal appetite, elimination and muscle tone throughout the experimental period. Emesis occurred within 1 hour following dosage on the first day, but subsequent doses were retained. Ocular effects consisting of dilating pupils and lack of response to light were observed in this animal after 7 daily doses. The animal appeared blind after 9 doses. These effects persisted without change throughout the observation period. The dog showed a weight loss of 600 gm during the experimental period. At autopsy no gross pathology was noted. Microscopic examination of the excised eyeball showed detachment of the retina.

The other dog (female) receiving zinc pyridinethione showed normal appetite

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muscle tone and pupil response, and gained 500 gm during the experimental period. Emesis occurred after dosage on the 4th day, but the remaining doses were retained. Scattered instances of diarrhea and slowed light reflexes were observed, although a persistent eye discharge and a relaxed nictitating membrane made observation of the pupil difficult. Sections made of the eyeball showed retinal detachment upon microscopic examination. A female dog receiving identical oral doses of hydroxy pyridinethione showed normal appetite with the exception of days 4, 7 and 8 and gained 100 gm. Muscle tone appeared normal at all times. Emesis occurred on days 1, 2, 3 and 5. The remaining doses were retained. Salivation was observed on days 6 and 8. Ocular signs including slight constricted pupils and slow light reflex on days 6, dilated pupils and slow light reflex on day 8 and constricted pupils and negative light reflex on day 9. Cloudiness of the eyes was observed beginning on day 6. The cloudiness gradually increased until day 10, when it became impossible to observe the pupils, and the dog appeared to be blind. Blindness persisted throughout the remainder of the study. The cloudiness diminished somewhat and observation of the pupils was resumed on day 17 at which time the pupils were dilated and had a negative light reflex. At autopsy the cortex of the kidneys appeared pale and possible formation of fibrous tissue and the eyeballs were abnormally soft to the touch. Microscopic examination of sections prepared from the eyeball showed retinal detachment. These findings are in agreement with those of other workers. The time lapse before blindness was observed differed from the 2 compounds, HPT being faster, adumbrating the conversion of zinc pyridinethione to hydroxy pyridinethione before any ocular effects are observed.

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The monkey receiving 10 mg/kg of zinc pyridinethione as a shampoo containing 10% zinc pyridinethione by stomach tube 5 times weekly for 16 weeks showed no apparent signs of muscle weakness, paralysis, or damage to the retina.

Neither monkey given daily oral doses of 25 mg/kg of zinc pyridinethione by stomach tube showed signs of ocular toxicity at the end of the 8-day feeding study. Emesis and diarrhea were observed in both animals after the 6th dose. Emesis was regularly produced in mongrel dogs given shampoo containing 2% zinc pyridinethione at doses of 50 mg/kg and above. Doses as high as 5 gm/kg well above the LD₅₀ level for rodents, produced emesis, but no other effects were seen over a 2-week observation period. To determine possible cumulative effects under these conditions a single dog was given oral doses of the test material at levels of 1 gm/kg 3 times a week for 8 weeks and a 5 gm/kg during the 9th week. Emesis occurred after each dose at intervals between 30 minutes and 200 minutes. Despite the relatively long retention times there were no apparent neurological or ocular effects. Body weight was maintained and the animal appeared healthy.

Human Patch Test (0.5% Suspension)

A 1/2 in. sq. of clean white blotting paper was impregnated with the test material and was applied to the backs of a 100 female volunteers. The material was applied to previously cleansed skin sites and covered with an elasto-patch plaster and allowed to remain in contact with the skin for 48 hours. When the patches were removed the test areas were observed for immediate reaction. A final examination for delayed reactions was made 72 hours after application of the patch test. All examination of the test sites were made by 2 experienced dermatologists.

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Four days after re-examination of the skin of the back the patch test procedure was repeated.

Results

Throughout the entire test program no instances of any skin reactions were observed. The subject produced no evidence of producing primary skin irritation and there was a low index of skin sensitizing potential for the test material in man.

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COMMENTS

The toxicological data on zinc pyridinethione has been reviewed.

" The material appears to have a low order of acute oral and dermal toxicity. Severe eye irritation was noted with the technical material, however.

The only finding of merit was production of blindness in dogs after low dosages. This was the only species so affected. The effect apparently is on the tapetum lucidum, a structure found only in dogs' eyes.

The use of the material is limited, as is suggested by the enclosed labels.

The reviewer has no objection to registration of these product labels.