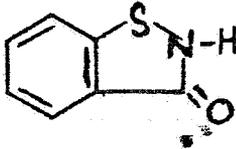


REPittman:mw
September 30, 1969

Trade Name : Proxel PM Paste

Chemical Name : 1,2 Benzisothiazolin-3-one

Chemical Structure : 

Empirical Formula : $C_7H_5N_1S_1O_1$

Company : Imperial Chemical Industries,
America Inc.

Use : Industrial preservative (water-based paints).

Properties : Physical Form - Semi-fluid
pourable paste
Color - fawn
Stability - chemically stable

Proxel PM Paste

2

- Subacute Rat Subcutaneous (tech)(11 days): 2 animals with increased WBC counts at 20 mg/KG
- Rat Skin Irritation (tech)(12.5% Solution): Rat Skin Irritant
- Rabbit Eye Irritation (tech)(12.5% Solution): Irritant with corneal ulceration
- Acute Rat Oral (paste) : LD₅₀ (males) = 4 gm/KG
LD₅₀ (females) = 2-4 gm/KG
- Acute Mouse Oral (paste) : LD₅₀ (males) ~ 4 gm/KG
LD₅₀ (females) ~ 2 gm/KG
- Acute Rat Intraperitoneal (paste) : LD₅₀ (males) = 62.5-125 mg/KG
LD₅₀ (females) = 31.25-62.5 mg/KG
- Rat Skin Irritation (paste) : No irritation at levels up to a 0.5% paste in water
- Rabbit Eye Irritation (paste) : No irritation as a 0.5% paste in water
- Guinea Pig Sensitization (paste) : No sensitization
- Subacute Rat Feeding (paste)(21 days) : No effect at 250 mg/KG for 21 days

The toxicological data available on Proxel PM Paste (23% 1,2 Benzisothiazolin-3-one) has been reviewed.

The product is moderately toxic orally, but is an eye and skin irritant.

We have no objection to registration of this product as a preservative for water-based paints.

Subacute Rat Subcutaneous (tech)(11 days)

Five female rats were given 9 daily injections of 20 mg/Kg of the test material over a period of 11 days.

Results:

All animals increased normally in weight during the test period and showed no toxic signs apart from subcutaneous edema at the site of injection. On examination of the blood at the end of the period hemoglobin concentrations were within the normal range. In 3 animals the white cell count was within the normal range. In 2 of the animals increased white blood cell values were found. Nothing abnormal was found at post-mortem examination and no pathological changes were found on subsequent histological examination of liver, kidneys, and lungs.

Rat Skin Irritation (tech)(12.5% solution)

Pieces of lint six square centimeters were soaked in 0.2 ml of a 12.5% solution in polyethylene glycol and applied for 24 hours under adhesive plaster to dehaired skin of the backs of 3 rats on alternate days.

Results:

No change was seen after the first application, after the second there was some thickening of the area, and after the third application areas of ulceration appeared followed by scab formation in the whole area. No systemic effects were observed when an amount equivalent to 1 gm/KG (0.5 ml of a 25% solution) was maintained in contact with the skin for 48 hours under adhesive plaster, and no local irritant action was found.

Rabbit Eye Irritation (tech)(12.5% solution)

One drop of a 12.5% solution in polyethylene glycol placed in the rabbit conjunctival sac produced signs of irritation at once and lachrymation followed by intense edema and hemorrhages of the nictitating membrane and conjunctivae. Within an hour there was corneal clouding and signs of iritis. Ulceration of the cornea developed later and was still present after one week.

Acute Rat Oral (paste)

Three groups of 3 male and 3 female albino rats each were administered the undiluted test material by stomach tube at the following dose levels: 1, 2, and 4 gm/KG. The animals were observed for 7 days following dosage. Animals that died during the observation period and survivors sacrificed at the end of the observation period were submitted to gross necropsy.

Results:

The acute oral LD₅₀ for male rats equals 4 gm/KG. The acute oral LD₅₀ for female rats equals 2-4 gms/KG. Only the animals receiving the highest dose were affected, and these developed ^pylor^ection, abdominal distension, body tremors and unsteadiness commencing four hours after dosing. Death occurred in coma. The only significant findings noted at necropsy were gastric hemorrhages in animals which died during the experiment and gastric ulcers in animals which were sacrificed at the end of the observation period.

Acute Mouse Oral (paste)

Three groups of five male and five female mice each were administered the test material as an aqueous ~~dispersion~~ dispersion by stomach tube at the

following dose levels: 1, 2, and 4 gms/KG. The animals were observed for 7 days after dosing.

Results:

The acute oral LD₅₀ for male mice is approximately 4 gm/KG. The acute oral LD₅₀ for female mice is approximately 2 gm/Kg. General signs of toxicity leading to prostration and death in coma were noted. At post-mortem there was severe gastric irritation and hemorrhage.

Acute Rat Intraperitoneal (paste)

Five groups of 3 male and 3 female albino rats each were administered the test material intraperitoneally at the following dose levels: 31.25, 62.5, 125, 250, and 500 mg/KG. The animals were observed for 7 days following dosing.

Results:

The acute intraperitoneal LD₅₀ was found to be between 62.5 and 125 mg/KG for male rats and between 31.25 and 32.5 mg/KG for female rats. The compound caused peritoneal irritation, the severity of which appeared to be dose dependent and post-mortem examinations showed varying degrees of peritonitis. Histological examinations of major organs from animals that died and from those that survived for 7 days following injection revealed only non-specific lesions, such as cloudy swelling in the liver and kidney consistent with the degree of peritonitis present.

Rat Skin Irritation (paste)

The skin irritant properties were assessed by an occlusive technique in which 6 alternate 24 hour applications were made under polythene/shorn backs of
to the

groups of 3 female rats, the skin being cleansed during the intervening periods; and by ^a non-occlusive technique in which similar applications are left uncovered, the animals being prevented from cleansing the treated site by means of plastic collars being fastened around the neck. The material was tested as an 0.5%, 0.15%, 0.02% paste in water.

Results:

No abnormality was detected, except for slight hyperkeratosis after the fifth application of the 0.5% concentration by the occlusive technique. This had resolved after the 6th application.

Rabbit Eye Irritation (paste)

0.1 ml of the 0.5% suspension was instilled into the right eye of 3 male rabbits, with observation of the animals for the subsequent 3 days.

Results:

No abnormality was detected at any time, and the fluorescein test for corneal ulceration was consistently negative.

Guinea Pig Sensitization (paste)

Six guinea pigs were given 3 daily applications of the undiluted test material to the ears followed at 7 days by a challenge in which the material was applied to the flank. A group of 4 untreated guinea pigs served as a control, and sensitivity is indicated by increased erythema at the site of challenge compared with the control animals.

Results:

No difference between the amount of erythema at the site of challenge between the control and animals previously treated was found. Therefore the

test material cannot be considered a sensitizer in guinea pigs. The erythema which was recorded was due to skin irritation at this concentration.

Subacute Rat Feeding (paste)(21 days)

7 male and 7 female albino rats were fed 21 consecutive daily doses of the test material at ^athe dose level of 250 mg/KG. A complete blood study was done on each animal before the feeding began and at the conclusion of the experiment. Two females and one male rat were killed 24 hours after the last dose, the remainder were observed for 7 days before being killed.

Results:

All the animals gained weight over the period of treatment and adverse effects were mild. Occasionally animals salivated excessively after a dose and one female showed signs of mild abdominal irritation. Rats killed 24 hours after the last dose showed some gastritis. Those killed 6 days later showed increased amounts of keratin^{and an} apparent excess of mucin production in the glandular stomachs. A comparison of pre and post treatment hematological findings failed to reveal any adverse effect of treatment.