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May 9, 1968

Mr. Kenneth E. Kash
Pesticides Regulation Division
Agricultural Research Service
U. S. Department of Agriculture
Washington, D. C. 20250

Reg. No. 100-471
Referral Date - 3/15/68

Dear Mr. Kash:

We have reviewed the toxicological data of Prometryne and we have no objection to registration with the suggested label changes.

Sincerely,

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

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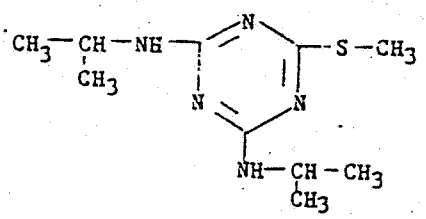
Paul D. Baron, M.D.:mw
May 14, 1968

Trade Name	:	Prometryne
Chemical Name	:	2-methylthio-4,6-bis-(isopropylamino)-S-triazine
Empirical Formula	:	$C_{10}H_{19}N_5S$
Structural Formula	:	



Physical - chemical properties

m.p. - 118 - 120°C

Solubility - 48 ppm @ 20°C in water

easily solubie in organic solvents

Colorless

Non-flammable

Use	:	Herbicide ✓
Company	:	Geigy
Tolerances	:	1 ppm, cotton forage; 1/2 ppm, celery; 1/4 ppm, fresh corn, fodder, forage, grain
Formulations	:	a.i. 80% related products 2.50% [redacted] 100%

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Acute Rabbit Dermal (80W)	:	No irritation up to 10.2 g/kg (highest dosage)
Acute Rat Inhalation (80W)	:	26.9 mg/L [redacted] of the active ingredient. 0.1345 mg/L (calculated in terms of the 80W).
Acute Rabbit Eye Irritation (80W	:	Mildly irritating, no sign of irritation at 72 hours after instillation
Raw Data Not In Our Files on following through Subacute Rat Oral (50% WP) (28 days)*		
Acute Mouse Oral (tech.)	:	LD_{50} = 3750 mg/Kg
Acute Rat Oral (tech.)	:	LD_{50} = 3750 mg/Kg
Acute Rat Oral (50% WP)	:	LD_{50} = 2500 mg/Kg
Subacute Rat Oral (tech.) (28 days)	:	No effect level 250 mg/Kg/day Weight loss at 500 mg/Kg and greater 500 mg/Kg and greater gave fatty degeneration of the liver, congestion following severe circulatory disorders.
Subacute Rat Oral (50% WP) (28 days)*	:	Same results as wit active ingredient doses calculated in terms of active ingredient.
Subacute Rabbit Dermal (80) (21 days)	:	No significant changes noted with dosages to 2.0 g/Kg except for mild inflammatory reactions in the skin.
Three generation Rat reproductive study (50W)	:	No adverse effect noted in 3 generations.
Chronic Dog Feeding (2 years) (80W)	:	No consistent changes which could be attributable to drug toxicity to 150 ppm. At 1500 ppm histopathologic examination of liver, kidney and bone marrow revealed degenerative changes.

Chronic Rat Feeding (2 years) (50W)	:	Slight fatty changes of livers of males at 1250 and 250 ppm at one (1) year. No differences noted at 2 years. No other changes noted.

COMMENTS

The toxicological data on Prometryne has been reviewed. The data is complete and indicates a wide margin of safety for the indicated usage patterns for the product.

The material is only mildly toxic when administered by the various routes. Chronic feeding studies reveal toxicity only at high dosage levels.

This reviewer has no objection to registration of this product.

TOXICOLOGICAL EVALUATION OF PROMETRYNE

Acute Rabbit Dermal (80W)

Two (2) each male and female rabbits were dosed at 0, 3.0, 4.6, 6.8, and 10.2 gm/Kg of the test material applied on closely clipped intact backs of albino New Zealand strain rabbits. After each application the exposure site was covered by wrapping the trunk of the animal with impervious plastic sheeting for a period of twenty-four hours. Observations were continued for 14 days.

Results:

No deaths or untoward behavioral reactions were observed among animals receiving the single dermal dose of the test material at all levels used. There was no evidence of local skin irritation as a consequence of the dermal application of the material at these dosage levels.

Acute Rabbit Inhalation (80W)

Five (5) each male and female Sprague-Dawley albino rats were exposed to an aerosol concentration of 26.9 mg/L of air of a 0.5% (W/V) aqueous suspension of the test material. Particle sizes generated by the nebulizer were in the range of 0.5 to 20 microns. The exposure period was 4 hours.

Results:

No deaths or untoward behavioral reactions were observed among the animals exposed for 4 hours at the concentration.

Acute Rabbit Eye Irritation (80W)

50 mgs of undiluted test material was instilled into the conjunctivival sac

of the right eye of each of 5 albino test rabbits. The left eye of each animal served as control. The cornea, iris, conjunctivae were examined at 1, 24, 48, 72, 96 hours and 7 days following the instillation.

Results:

The material is considered mildly irritating to the cornea, iris, conjunctivae lasting approximately 48 hours and no sign of irritation at 72 hours.

Subacute Rabbit Dermal (80W)(21 days)

Five each male and female albino rabbits were divided into groups of those with intact and abraded skins each group containing 10 animals and dosed at levels of 1.0 and 2.0 gm/Kg/day of the test material. A treated control was used utilizing 5 male and 5 female animals with intact skin and treated with 2.0 gm/Kg/day of the wettable powder without the active ingredient. The animals were tested with a 50% (W/V) aqueous suspension which was applied for 7 hours a day, 5 days per week for three weeks. At the end of the test period survivors from each test and control group were sacrificed for pathological studies. The usual hematological clinical blood chemistry determinations and urinalyses were conducted.

Results:

The body weight gains of the test animals were not significantly different than those of the control group. There was no significant mortality or untoward behavioral reactions in any of the test or treated control groups. The local skin reactions were characterized by mild erythema, drying, desquamation, and thickening of the skin at the application site. These were noted in all test groups. There was no remarkable changes from normal ranges found in either the hematological or the clinical blood chemistry

parameters (WBC,RBC,HGB,HCT,BUN,ALK.PHOS.). The only tissue disclosing any significant pathological alterations was the skin of all the test group animals. In the skin there was evidence of local inflammatory reactions seen both grossly and microscopically. There was no other significant pathological changes which could be attributed to toxicity of the test material. There was no significant differences between organ weights and organ to body weight ratios noted between test and control animals.

Three Generation Rat Reproductive Study (50W)

For the F sub 0 generation 10 males and 20 females were fed dosage levels of 0, 100, and 50 ppm of a 50% wettable pwoder in the feed. After 79 days of dietary administration the rats in each group were paired for mating during a 10 day period. The males in each group were then immediately paired for mating with the unmated females from the same group during the next consecutive 10 day period. The number of births, stillbirths, physical condition of the new-born and general condition of the mothers were ~~XXXX~~ recorded at the birth of the first litters (F sub 1A). The first litters were sacrificed after weaning and weighing and examination of the young for any evidence of abnormalities. Approximately 10 days after weaning of the first litters each female was remated with a different male from the same group by reversing the order of the males. The procedures outlined above were repeated for the rats and the second (F sub 1B) litters through weanling. The F sub 0 parent generations were then sacrificed. The weanlings were fed controlled diet until 10 days after the last F sub 1B litter was weaned. One or two weanlings of each sex were selected from each of a number of the F sub 1B litters to give 10 males and 20 females from each

group. These F sub 1B weanlings were grouped according to the same protocol as the F sub 0 parents. These animals were in groups containing control 100 ppm and 50 ppm of the test material in their diets, respectively. This F sub 1B generation were fed their respective diets for 79 days before being paired for mating as in the previous part of the experiment. Likewise the F sub 2B generation was subjected for the 3 dietary levels.

Results:

F sub 0 Generation

All of the animals in the F sub 0 group survived during the experimental period. The general appearance and behavior of the test and control groups were comparable. The body weight gains of the test and control groups of animals were comparable. Comparable results were seen in the F 2B and the F 3B litters. No malformations or increase in fetal resorbtion was noted. No change in gross or histopathologic studies of the animals on the highest dosage level were noted in any of the litters.

Chronic Dog Oral (2 years) (80W)

Three (3) each male and female purebred beagle dogs were fed dietary levels of 15, 150, 1500, and 0 ppm of the test material in their diets. Weekly detailed physical examinations were carried out during the study period. Neurologic and ophthalmic examinations were conducted monthly. Each dog was weighed weekly. General observations were made at the time of feeding and daily food intake was recorded. Complete hemograms consisting of HGB, HCT, sed rate, and total and differential white cell counts were determined initially and at 4, 8, 13, 19, 27, 40, 52, 68, 80, 91 and 104 weeks.

blood glucose, BUN, serum alkaline phosphatase, and SGOT evaluations were conducted at the same intervals as the hemogram. Urinalyses were also done. Gross autopsies of the animals were performed after

after 106 weeks on the drug. Histopathologic observations were conducted on the tissues of animals in the control and 1500 ppm. Fewer observations were conducted on the lower dosage groups.

Results:

Dogs given the test material at all dosage levels showed normal body weight gains. Food consumption was decreased slightly during the first six weeks of the study for the dogs at 1500 ppm, 2 at 150 ppm and 2 at 15 ppm. The behavior of treated dogs could not be distinguished from that of controls. A slightly increased sedimentation rate was noted for a few control and treated animals, otherwise hematological values were generally within normal limits. The serum alkaline phosphatase, SGOT and blood glucose levels were noted for all animals in control and test groups. There was slight elevation in BUN levels at week 8 for 2 dogs, 1 on 15 ppm and the other on 1500 ppm. Urinalyses showed no differences between treated and control groups. Organ weights and the organ to body weight ratio showed no distinction between treated and control dogs. There were no changes on gross autopsy that could be attributed to toxicity of the test material. There were no histological changes of significance in the control 150 and 15 ppm levels, however at 1500 ppm degenerative changes in the liver, renal tubules and slight bone marrow atrophy were noted for each/2 of the 6 dogs.

Chronic Rat Feeding (2 years)(50W)

25 each male and female albino rats were fed dietary levels of 0,50,250, and 1250 ppm of the test material in their diets. Hemagrams consisting of hemaglobin, hematacrit total and differential white cell counts were

determined for a specified number of animals at each of the dosage levels. 5 males and 5 females from each dosage group were sacrificed at 52 weeks. All the survivors were sacrificed after 104 weeks of dosage. Gross necropsy and histopathological observations were made on the tissue.

Results:

Mortality of treated rats were indistinguishable from that of controls except for males at 50 ppm level. Body weight gains of the experimental animals varied only slightly from control weights throughout the first 77 weeks of study. Gradual but steady weight losses were noted for all animals after this time. Complete hemagrams showed no changes related to the administration of the test material. Organ weights and the organ to body weight ratios showed slightly heavier livers for all animals at the 1250 ppm and 250 ppm levels as well as for the 50 ppm females at the 52 week sacrifice. At termination slightly heavier livers were noted only for 1250 ppm males. No changes in gross autopsy findings for the treated groups as compared to controls were found. Histopathologic observations at the 52 week partial sacrifice of 5 males and 5 females revealed an increased frequency of very slight fatty changes in the liver of the male rats given 1250 and 250 ppm. Histopathological observations made for all surviving rats at termination failed to indicate any effect of compound administration and all changes were such as commonly seen in aging rats.