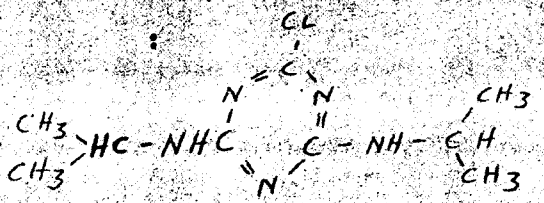
8-7-68/184

RDCoberly:bjc
August 7, 1968

001376

Chemical Name	:	**2 - Chloro-4,6-bis-(isopropylamino) s-triazine.**
Trade Name	:	**Propazine**
Chemical Structure	:	
Physical State	:	**Solid**
Use	:	Herbicide
Company	:	Geigy

SUMMARY

These data indicate that the material has a low degree of acute lethal toxicity by the oral dermal and inhalation routes of exposure. The subacute studies also indicate a low degree of toxicity.

This material should not create an undue hazard when used as a herbicide.

Acute Mouse Oral	:	LD_{50} = >5.0 gm/KG
Acute Rat Oral	:	LD_{50} = >5.0 gm/KG
Acute Rabbit Dermal (80W)	:	LD_{50} = >10.2 gm/KG No effects noted.
Acute Rat Inhalation (80W) (4 hrs.)	:	LC_{50} = >0.07 mg/L of active ingredient
Rabbit Eye Irritation (80W)	:	Mildly irritating
Acute Rat Inhalation (80W)	:	LC_{50} = >3.3 mg/KG
Subacute Rat Dermal (50W) (5 days)	:	No effects were noted at levels tested ie: 60 and 130 mg/KG.
21 Day Rabbit Dermal (80W)	:	Levels tested were 1.0 and 2.0 gm/KG. Effects noted at 2.0 gm/KG.
28 Day Rat Oral	:	Levels tested were 1250 and 2500 mg/KG. Weight retardation noted at both levels.
90-180 Day Rat Oral (50W)	:	Mortality at 2500 mg/KG. Possible effects at 250 mg/KG.
90 Day Dog Feeding (80W)	:	Levels tested were 50, 200, and 1000 ppm. Body weight loss at 1000 ppm.
90 Day Rat Feeding (80W)	:	Levels tested were 50, 200, and 1000 ppm. Body weight loss at 1000 ppm.
Metabolic Study (Rats)	:	Propazine is absorbed and excreted mainly in the urine and feces.
Metabolism Study (Rat)	:	See Report.

PROPAZINE

Acute Mouse Oral

10 mice were tested per dosage level of 2.5 and 5.0 gm/KG. Both male and female mice were used. Observation period was 8 days.

Results

LD_{50} = >5.0 gm/KG. The 2.5 gm/KG level produced slight dyspena and mild drowsiness. The high level produced 30% death accompanied by spasms, dyspena, drowsiness, irregular breathing.

Acute Rat Oral

10 animals were tested per dosage level of 2.5 and 5.0 gm/KG. Both male and female animals were used. Animals were observed for 8 days.

Results

LD_{50} = >5.0 gm/KG. Neither level showed toxic symptoms.

Acute Rabbit Dermal (80W)

2 male and 2 female rabbits were tested per dosage level of 3.0, 4.6, 6.8, and 10.2 gm/KG. The test material remained in contact with the skin for 24 hours.

Results

No deaths or untoward behavioral reactions were observed. No evidence of local skin irritation was noted.

Acute Rat Inhalation (80W)

5 males and 5 females were tested at a concentration of 14.1 mg/L of air of a 0.5 aqueous suspension. Particle sizes varied from 0.5 to 20 microns in size. Exposure was for 4 hours.

Results

No deaths or untoward behavior reactions were noted at the aerosol concentration of 14.1 mg/L of air of a 0.5% aqueous suspension (equal to 0.07 mg/L of active ingredient).

Rabbit Eye Irritation (80W)

Exactly 50 mg of undiluted test material was instilled into the conjunctival sac of the right eye of 5 rabbits. Animals were observed at interim times up to and including 7 days.

Results

The material was mildly irritating to the eye.

Acute Rat Inhalation (80W)

10 rats were exposed to an aerosol concentration of 3.3 mg/L of the 8% wettable powder. Exposure time was 1 hr. The apparatus used in this study allowed the animal to be outside the chamber with only their nostrils exposed to the dust within the chamber.

Results

No deaths or signs of toxicological or pharmacological effects were noted. Thus the LC_{50} = >3.3 mg/L.

5 Day Rat Dermal

Suspensions in gum arabic were prepared with the active ingredient and also with the 50% wettable powder, the concentrations being 5% and 2.5% propazine respectively. 0.4 ml of the suspension was applied for 5 consecutive days on 5 animals per dosage level. This corresponds to 60-70 mg/KG and 130-140 mg/KG of active ingredient.

Results

No symptoms were noted in any of the animals. No local irritation or systemic toxic effects were noted.

21 Day Rabbit Dermal (80W)

10 males and 10 females (half abraded) were tested per dosage level of 1.0 and 2.0 gm/KG. The skin applications of the test material were made in the form of a 50% aqueous suspension on a 7 hours/day 5 days/wk for 3 weeks. The control received the inerts contained in the test material.

Results

The animals receiving 2.0 gm/KG/day showed severe body weight loss. This group also showed 20% mortality in the intact group and also 20% mortality in the abraded group. The lower dosage level showed no mortality.

No significant untoward behavioral reactions were noted in the animals receiving 1.0 gm/KG/day. Generalized inactivity, anorixea and diarrhea were noted at the 2.0 gm/KG/day level.

These reactions appeared after 3-6 applications and progressed to severe within 21 days.

Local skin reactions first became evident after the 3rd or 4th application. These reactions were characterized by mild erythema, drying, desquamation and thickening of the skin at the application site.

The only tissue disclosing any significant pathologic alteration was the skin of all the test animals. This was confined to local inflamatory reactions.

No significant differences were noted between the control and test groups with respect to the organand body weight ratio data.

28 Day Rat Oral

The active ingredient was given by stomach tube to 2 groups of 5 male and 5 female rats on a 6 day a week basis for 4 weeks. The dosage levels employed were 1250, and 2500 mg/KG/day.

Results

No deaths occurred in the low level and only 1 death occurred in 2500 mg/KG/day level. Both test levels showed a distinct retardation in the rate of weight increase but exhibited no symptoms. Histological examination of the liver, kidney, spleen, pancreas, lung, intestines and gonads revealed no pathological changes which could be attributed to the

administration of the test material.

90-180 Day Rat Oral (50W)

12 males and 12 females were tested per dosage of 250 and 2500 mg/KG/day. 2 control groups were used, 1 received the inactive excipients at the dosage level of 2500 mg/KG/day and the 2nd control group received water at 5 ml/KG/day.

This high level group was terminated after 90 days, the remaining animals were continued for 180 days.

Results

The animals receiving the test material at the dosage level of 2500 mg/KG/day showed a marked reduction in food intake. Up to the 90th day the weight gain in the control groups was practically identical. The animals receiving 250 mg/KG/day showed a slight retardation in weight gain and those of the high level showed a distinct retardation in weight growth. However by the end of the 180th day there was a slight difference in weight gain between the 2 control groups. This may indicate an effect of the inactive excipients. There was no difference between the low level and the control receiving the inactive excipients.

There were 3 deaths in 1 control group and 1 death in the 2nd control group. There were 3 deaths in the low level animals and 16 deaths in the high level animals.

Histological examination revealed that the administration in the daily dose of 250 mg/KG produced no degenerative modifications in the major parenchymatous organs. There were however indications of atrophy in 6 out of the 11 animals with 1 exhibiting severe edema. The ovaries of the corresponding females appeared normal. It should be noted that testicular atrophy was also observed in 1 of the control animals which received the inactive excipients.

Of the 8 surviving animals of the 2500 mg/KG group only 1 exhibited perilobular fatty degeneration of the liver. All other organs appeared to be unchanged.

Note - The testicular atrophy noted in the 250 mg/KG does not appear to extend into the high level. Thus we have the possibility that this effect is not dose related. We must also consider that 1 animal in the control group also showed testicular atrophy.

90 Day Dog Feeding (80W)

12 male and 12 female adult dogs were tested per dosage level of 50, 200 and 1000 ppm.

Results

No compound related pharmacodynamic signs were noted. 4 dogs receiving the 1000 ppm dietary level showed body weight loss during the course of the study. There appeared to be nocorresponding reduction in their food intake.

No compound related alterations and hematology, plasma biochemistry, liver function tests or urinalyses were seen.

No compound related gross or microscopic pathologic lesions or variations in organ weights were noted.

90 Day Rat Feeding (80W)

20 males and 20 females were tested per dosage level of 50, 200, and 1000 ppm.

Results

The male and female rats receiving 1000 ppm in their diet showed hyperirritability to handling during the 8th and 11th weeks of the study. No other pharmacodynamic effects were noted. Only 1 female death occurred at this level.

The body weight gains of the 1000 ppm animals were significantly lower than the corresponding control animals.

No compound related alterations in hematology, plasma biochemistry, liver function tests or urinalysis were noted.

No compound related gross or microscopic pathologic lesions or variations in organ weights occurred in any test rat.

Metabolic Fate C^{14} - Propazine

The results of a radiotracer study in albino rats to determine the metabolic fate of propazine following oral administration

indicated that propazine was absorbed. The administered C^{14} propazine was recovered from urine, feces, selected tissues and organs of the test animals, whereas nothing was recovered from the expired air samples.

The amount of the dose recovered from the urine was between 28.9 and 42.2% and from the feces between 14.2 and 28.1%. Radioassays of selected tissues and organs accounted for an additional 2.6-8.6% of the given dose.

The selected tissues included blood, kidney, liver, heart, reproductive organs, muscle and fat.

Metabolism of Propazine and Prometryne in Rats

The metabolic breakdown products of C^{14} propazine and C^{14} prometryne fed orally to rats were compared using extraction, ion exchange gradient elution and paper chromatographic techniques.

3 common metabolites, other than hydroxy-propazine, were found in the urine of rats fed either propazine or prometryne. Both the urine and feces from rats fed either compound contained hydroxy-propazine. Unchanged propazine or prometryne was found in the feces but not in the urine. It can be concluded that propazine and prometryne follow similar metabolic pathways.