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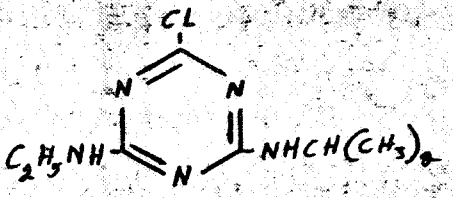
Releasable

RDCoberly:bjc
July 10, 1968

Name	:	Atrazine
Chemical Name	:	2-Chloro-4-ethylamino-6-isopropylamino-s-triazine
Chemical Structure	:	
Physical State	:	White crystalline solid
Melting Point	:	173-175° C
Solubility	:	Almost insoluble in water, soluble in methanol, ether, and chloroform
Use	:	Herbicide (crop)
Co.	:	Geigy (1963)
Patent No.	:	2,891,855

ATRAZINE

Two Year Rat Feeding (50 W)	:	Levels tested 1.0, 10, and 100 ppm (raised to 1000 ppm). No effect level is >1000 ppm. Changed in 1981 by Colby to read NOEL = 100ppm due to change in attitude + not in error.
Two Year Dog Feeding (80 W)	:	Levels tested were 15, 150, and 1500 ppm of active ingredient. No mortality, muscular tremors or stiffness in the rear limbs was noted at the 1500 ppm level.
Three Generation Rat Reproduction (80 W)	:	Levels tested were 50 and 100 ppm of active ingredient. No effects were noted.
Acute Rat Oral (80 W)	:	LD_{50} = 5.1 gm/KG ✓ LD_{01} = 3.8 gm/KG
Acute Rabbit Dermal (80 W)	:	LD_{50} = 9.3 gm/KG ✓ LD_{01} = 6.9 gm/KG Mild erythema and edema noted.
Rabbit Eye Irritation (80 W)	:	Mildly Irritating. ✓
Primary Rabbit Skin Irritation (80 W)	:	Minimal irritation noted. ✓
Acute Rat Inhalation (80 W)	:	LC_{50} = >2.0 mg/L ✓
21 Day Rabbit Dermal (80 W)	:	Levels tested were 1.0 and 2.0 gm/KG. Effects noted at both levels. Paralysis at 2.0 gm/KG/day. ✓
28 Day Sheep Oral (80 W)	:	Levels tested were 50, 100, 400 mg/KG/day of active ingredient. Death occurred at 400 mg/KG/day in 2 days and in 16 days at 100 mg/KG/day. Weight loss at 50 mg/KG/day.
35 Day Sheep Oral (80 W)	:	Levels tested were 1.0, 5.0, and 25 mg/KG/day. No pathological effects were noted.

28 Day Sheep Feeding (80 W)	:	Levels fed were 10, 30, and 100 ppm.
21 Day Cattle Feeding (80 W)	:	Levels fed were 3.0, 15, and 100 ppm. No effects were noted.
Metabolism of Atrazine C^{14}	:	Majority of radio - activity eliminated within 48 hours.

ATRAZINE

Two Year Rat Feeding (50 W)

Thirty males and thirty females were tested per dosage level of 1.0, 10, and 100 ppm. After completion of 65 weeks, the 100 ppm group was raised to 1000 ppm. The following tissues from each sacrificed animal were preserved in 10% Formalin: brain, pituitary, tyroid, heart, lung, liver, kidney, adrenal, spleen, stomach, pancreas, small and large intestines, urinary bladder, testis or ovary, bone marrow, skeletal muscle, and peripheral nerve. The following tissues, were examined microscopically; thyroid, liver, stomach, small and large intestines, kidney, adrenal, gonads, and urinary bladder.

Results

The physical appearance and behavior of the test animals of both sexes were comparable with those of the controls throughout the two year period. None of the test rats showed signs of systemic toxicity which could be attributed to the ingestion of the test material. Body weight gain, food consumption, and survival were comparable among the control and test groups throughout the first 18 months. Mortality was unusually high during the first six months of the study in all groups, including the controls.

Hematological studies and urine analyses performed on the rats after 26, 52, and 104 weeks showed no unusual values.

The mean terminal body weights, organ weights, and organ to body weight ratios determined for male and female rats sacrificed after 26 or 52 weeks were comparable among the control and the various test groups. The small number of

survivors at 104 weeks precluded statistical evaluation.

Histopathological examination of selected tissues from control and high level test rats sacrificed after 52 weeks, from animals which died during the second year, and from all survivors sacrificed after 104 weeks showed no consistent deviation in the tissues and no unusual lesions which could attributed to the consumption of the test material.

In considering the aforementioned results it appears evident that the toxic effect of the test material is ≥1000 ppm.

Comment - It should be noted that the dosage levels employed in this study are based on the active ingredient.

Two Year Dog Feeding (80 W)

Three male and three female beagles were tested per dosage level of 15, 150, and 1500 ppm of active ingredient. Hemograms consisting of hemoglobin, hematocrit, sedimentation rate, and total and differential white cell counts were obtained for all dogs initially and at frequent intervals up to and including 104 weeks.

Clinical chemistry determinations at the same intervals included blood urea nitrogen, serum alkaline phosphatase and serum glutamic oxalacetic transaminase.

The following tissues were examined microscopically; thyroid, heart, lung, liver, adrenals, kidney, spleen, gonads, prostate or uterus, brain, putuitary, gall bladder, trachea, tonsil, urinary bladder, spinal cord, skin, stomach, large intestine, small intestine, mesenteric lymph node, bone marrow, eye, pancreas, peripheral nerve, thymus, parotid salivary gland, esophagus and skeletal muscle.

Results

No signs of toxicity were seen at the 15 ppm level. A slight reduction in food intake at the 150 ppm level. A convulsive spasm was also noted in one dog at this level.

At the 1500 ppm level toxic signs were limited to a reduction in food intake, a failure to gain weight, slightly increased adrenal weight, and an increased frequency of reduced hemoglobins and hematocrits. Signs of pharmacological effects consisted of muscular tremors or stiffness in the rear limbs and also lacrimation.

The NO effect level is located between 150 ppm and 1500 ppm.

Three Generation Rat Reproduction (80 W)

Ten males and twenty females were tested per dosage level of 50 and 100 ppm.

Results

The test and control animals were comparable throughout the study in survival, mean body weights, general appearance and behavior, and reproductive performance.

The test and control litters were comparable in number of litters per group, number of live births, physical condition, mean weights at birth and weaning, per cent young alive at weaning, and gross autopsy observations.

No malformations were observed in the test animals. No effect of the test material was detected by histopathological observations on tissues of weanlings.

Acute Rat Oral (80 W)

Five male rats were tested per dosage level of 3.0, 4.6, 6.8, and 10.2 gm/KG. Animals were fasted for 16 hours prior to treatment.

Results

LD_{50} = 5.1 gm/KG. LD_{01} = 3.8 gm/KG. The animals at each level showed some toxic symptoms. Those exhibited by the 6.8 gm/KG level were hypoactivity, ptosis, and ruffled fur.

Necropsy of the animals which died during the study revealed no significant gross pathologic abnormalities in the tissues and organs examined.

Acute Rabbit Dermal (80 W)

Four animals were tested per dosage level of 4.6, 6.8, 10.2, and 15.4 gm/KG. The test material was applied in the form of a 75% aqueous suspension.

Results

LD_{50} = 9.3 gm/KG. LD_{01} = 6.9 gm/KG.

No significant untoward behavioral reactions were noted among the rabbits in the 4.6 and 6.8 gm/KG dosage groups. Three of four animals receiving 10.2 gm/KG became lethargic and emaciated and died within 3 to 10 days.

Slight to mild erythema and etema were noted in all those groups.

Rabbit Eye Irritation (80 W)

Exactly 50 mg. of undiluted test material was instilled into the conjunctival sac of the right eye of each test rabbit. The left eye served as control.

Results

The test material was mildly irritating.

Primary Rabbit Skin Irritation (80 W)

Two sites on each rabbit were used, one was abraded. The test material was applied undiluted to the skin of the prepared exposure sites on each of four rabbits. Applications were the form of square gauze patches containing 0.5 gm of test material moistened with 0.5 mls. of water.

Results

The test material proved to be minimally irritating.

Acute Rat Inhalation (80 W)

Eight animals were exposed to an air concentration of 2.0 mg/L.

Results

No deaths or signs of toxicological or pharmacological effects due to exposure were noted. LC_{50} = >2.0 mg/L.

21 Day Rabbit Dermel (80 W)

Ten males and ten females (half abraded) were tested per dosage level of 1.0 and 2.0 gm/KG/day. The test material was applied to the skin in the form of a 50% aqueous suspension. The test material remained in contact with the skin for seven hours a day for five days per week for three weeks.

The dosages are expressed in terms of atrazine 80 W and not in terms of the 50% aqueous suspension.

Results

The animals receiving the dose of 1.0 gm/KG/day caused 6 deaths. The high level caused 9 deaths.

All animals receiving 1.0 gm/KG/day appeared listless after the third application of the test material. This reaction continued throughout the remainder of the test period or until death intervened. Animals receiving the 2.0 gm/KG/day dosage level appeared listless and exhibited partial paralysis of the entire body after 3 applications of test material. Complete paralysis was noted in approximately 1/2 of the surviving animals after 10 to 12 applications.

All test animals exhibited slight erythema of the skin at the application sight after 3 applications. Dryness, cracking and desquamation were noted after 6-8 applications.

These data indicate that the subacute no effect level is ≤1.0 gm/KG/day in rats.

28 Day Sheep Oral (80 W)

One sheep was tested per dosage level of 50, 100, and 400 mg/KG/day of active ingredient. The animals were 7-8 months of age and weighed approximately 50-60 pounds.

Results

The animal receiving the 400 mg/KG/day dosage level became affected in one day and died during the second day. The animal receiving the dosage of 100 mg/KG/day died on day 16. The animal receiving the 50 mg/KG/day dosage

level was able to survive the 28 days showing only weight loss.

35 Day Sheep Oral (80 W)

One sheep was tested per dosage level of 1.0, 5.0, and 25 mg/KG/day. Treatment was conducted on a six day a week basis for 5 weeks.

Results

No death or abnormal symptoms were observed. No pathological effects were noted.

28 Day Sheep Feeding (80 W)

The formulation was fed to sheep in a diet for 4 weeks at the dosage levels of 10, 30, and 100 ppm.

Results

No effects were noted.

21 Day Cattle Feeding (80 W)

Two cows were tested per dosage level of 3.0, 15, and 100 ppm of active ingredient.

Milk production records were maintained for each milking for each cow. For residue analysis, two morning and two evening milk samples of approximately 750 ml. each were collected from each cow on various days.

Results

The physical condition and behavior of all cows remained uniformly good. The appetite was unaffected. The test material did not appear to have any affect

on milk production.

Metabolism of Atrazine C^{14}

Three male and three female rats were utilized in this study. The radio-analyses of the urine,feces, and exhaled carbon dioxide was conducted.

Results

These assays indicated that the majority of the radio activity was eliminated from the body within 48 hours. As an example, several rats eliminated the following percentages, 71.55%, 71.84%, 67.8%, and 67.79%.

ATRAZINE
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July 15, 1968

COMMENTS

On an acute oral, inhalation, or dermal basis, this material produces toxic effect at high dosage levels. These levels are sufficiently high enough to ensure safe use by humans under normal working conditions. The multi-dermal exposure level which caused toxic effects appear to be within the reach of man working long hours with the material. In order to abate this possibility, dermal contact should be limited as much as possible.