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April 17, 1968

Mr. Kenneth B. Nash
Pesticide Regulation Division
Agricultural Research Service
U. S. Department of Agriculture
Washington, D. C. 20250

Reg. Nos. 241-RR, 241-51
Referral Data - 3/22/68

Dear Mr. Nash:

The toxicological data on Dodecylguanidine Acetate has been reviewed in connection with the above listed Reg. Nos.

We do not object to the registration of this chemical for use as a fungicide on crops. However, we do feel that an acute rodent inhalation study should be made available for review.

Sincerely,

Robert D. Coberly
Biologist
Registration Section
Pesticides Program

RDCoberly:mw

cc: Toxicity folder

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RDCoberly:deg
April 19, 1968

Chemical Name	:	Dodecylguanidine acetate
Chemical Structure	:	$C_{12}H_{25}NHC(=NH)NH_2 \cdot CH_3\ COOH$
Molecular Formula	:	$C_{13}H_{29}N_3 \cdot C_2H_4O_2$
Physical Form	:	White crystalline, slightly-waxy solid.
Purity	:	96.6%
Melting Point	:	132.5-133.5°C
Use	:	Fungicide (crops)
Reason	:	First review by PHS
Company	:	American Cyanamid

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Ninety Dat Rat Feeding	:	The only level tested, 3,200 ppm caused body weight loss. No effect level = <3,200 ppm.
Two Year Rat Feeding	:	Levels tested were 50, 200, and 800 ppm. Body weight depression at 800 ppm. No effect level = ~200 ppm.
One Year Dog Feeding	:	Levels tested were 50, 200, and 800 ppm. Thyroid stimulation at 800 ppm. No effect level is approximately 200 ppm.
Rat Reproduction	:	The only level tested i.e. 800 ppm did not produce effects during the two generation study.
Acute Rat Oral	:	Male LD_{50} = 750 mg/Kg (fasted) Male LD_{50} = 870 mg/Kg (unfasted) Female LD_{50} = 660 mg/Kg (unfasted)
Acute Mice Oral	:	LD_{50} = 1,720 mg/Kg (1,190-2,480)
Acute Dog Oral	:	Levels of 2 and 4 gm/Kg caused the animals to vomite. No mortality.
Acute Rabbit Dermal	:	Severe irritation noted.
Study No. 1	:	LD_{50} = >10 gm/Kg
Study No. 2	:	LD_{50} = 2.1 gm/Kg
Study No. 3	:	A dilution of 0.12% caused no appreciable irritation.
Eye Irritation	:	10 mg of dry product produced severe irritation.
Study No. 2	:	0.1 ml of a 0.12% caused a very slight degree of irritation.

RDCoberly:deg
April 19, 1968

Dodecylguanidine Acetate

Acute Rat Oral

Male and female rats in groups of ten were tested over a dosage range of from 250 to 4,000 mg/Kg. Depending on the study the animals were either fasted or unfasted. The test material was given as a 10% aqueous suspension. The vehicle was a solution of 0.2% Agar plus 0.1% Tween 80.

Results

Fasted Male LD_{50} = 750 mg/Kg (660-870). Unfasted Male LD_{50} = 870 mg/Kg (705-1,080). Unfasted Female LD_{50} = 660 mg/Kg (525-830). Another study using an 8% suspension gave an LD_{50} of 1,230 mg/Kg. Still another study using a 5% suspension gave an LD_{50} of 1,540 mg/Kg.

Dosages which were equal to two or three times the LD_{50} produced death only after several days. Postmortem examination generally revealed a minor degree of gastrointestinal tract irritation. There was a tendency for adhesions to be established between the stomach and the liver and spleen.

Acute Mice Oral

Ten mice were tested per dosage level of 500, 1,000, 2,000, and 4,000 mg/Kg. The test material was given as a suspension in aqueous Agar.

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Results

LD_{50} = 1,720 mg/Kg (1,190-2,480).

Acute Dog Oral

One dog was tested per dosage level of 2.0 and 4.0 gm/Kg.

Results

Both animals vomited profusely within the first half an hour.

No mortality was noted.

Acute Rabbit Dermal

Four animals were tested per dosage level of 1.25, 2.5, 5.0, and 10 gm/Kg. The test material was moistened with sufficient water to form a paste, and was retained in contact with the skin for 24 hours.

Results

At 24 hours erythema and edema of the skin were of the most severe degree in all cases. A maximum rating was assigned to both erythema and edema readings. The edema persisted with only slight reduction throughout the seven day observation period. During this time the skin of the effected area assumed a black leathery appearance. One animal at 5 gm/Kg died on the fourth day and two animals at 10 gm/Kg died on the fourth and fifth days respectively.

At autopsy the following observations were noted: diffuse subcutaneous hemorrhage, enlargement of the mesenteric lymph nodes, and hyperemia of the stomach together with thickening of the pyloric area. In one

case, at 5 gm/Kg, there was adhesion between the stomach and the liver.

Body weight loss was noted in all animals but one with the degree of weight loss increasing as the dosage level increased.

Study No. 2

Four rabbits were tested per dosage level of 1.25, 2.5, 5.0, and 10 gm/Kg.

LD_{50} = 2.1 gm/Kg.

Study No. 3

In order to explore the potential skin irritation hazzard in field applications an aqueous dispersion of 0.12%, equivalent to a use concentration of one pound per 100 gallons of water, was prepared. Doses of 10 ml/Kg of this dispersion were held in contact for 24 hours with a closely clipped abdomens of each of five male albino rabbits.

Results

No appreciable irritation resulted from application of the product in this dilution.

Rabbit Eye Irritation

Ten mg of the dry product was placed into the conjunctival sac of the right eye of each of five rabbits. The eyelids were held closed for approximately 30 seconds.

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Results

There was evidence of immediate discomfort followed by the development of a severe conjunctivitis. Within 24 hours a degree of injury developed which was assigned the maximum score of 110 (Draize et al). This degree of injury persisted for several days and was complicated in all cases by the onset of secondary infection. In some cases by the end of the study recovery was complete but in others improvement was only negligible.

Study No. 2

A 0.1 ml quantity of a 0.12% test material was introduced into the left eye of five albino rabbits.

Results

A very slight reddening and swelling of the conjunctivae together with moderate discharge was noted at 24 hours. No signs of irritation remained by 24 hours after the application.

Ninety Day Rat Feeding

Eighteen females and twenty males were tested at a dosage level of 3,200 ppm. Histological examination was conducted on the thyroid, trachea, thymus, stomach, pancreas, small intestines, large intestines, mesenteric lymph node, skeletal muscle, sternum, femur and prostate and seminal vesicles, or uterus and vagina.

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Results

All animals survived the study. The growth of both males and females on this level was immediately and markedly inhibited. A large measure of this failure to grow appears to be related to the reduced food consumption. These rats also appeared more irritable upon handling and exhibited more activity in their cages.

When expressed as a organ to body weight ratio, the brain, heart, lung, spleen, kidney, adrenal, and testes weights were considerably higher for the males than for the corresponding control. For the female rats only the brain weights differed markedly. Both of these findings may be due to the markedly reduced body weight loss. Microscopic study of the tissues did not disclose any pathology which could be related to the test material.

Two Year Rat Feeding (78 Week Progress Report)

Forty males and forty females were tested per dosage level of 50, 200, and 800 ppm.

Results

Survival of the test groups was comparable to the control group. Food intake of the males receiving 800 ppm was significantly depressed. Significant enhancement of growth was noted in the males on the 50 and 200 ppm whereas significant depression at 800 ppm was noted. Females of this same dosage level also showed significant depression.

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No effect was noted on hemoglobin, hematocrit, or leucocyte count at any level.

Slightly but significantly lower pituitary and spleen weights were noted for the 800 ppm males at 53 weeks, and a slightly higher lung weight for the 50 ppm females at 78 weeks.

Microscopic Pathology - Results of this review show the tissues to be variable but within a close enough range to be considered normal.

Comments

These data indicate that an effect is demonstrated by the test material at 800 ppm and consist of a decrease in growth rate, reduced food intake, and a slight decrease in efficiency of food utilization.

One Year Dog Feeding

Two males and two females were tested per dosage level of 50, 200, and 800 ppm.

Results

The test material appear to have no effect on the food intake or body weight gain at any level. No significant alterations in hemoglobin, hematocrit, total and differential leucocyte count, blood sugar, nor any significant increases in blood urea and bromsulphalein retention were noted.

Thyroid changes in one dog at the 200 ppm level consisted of a shift of the follicular epithelium from a squamous to a predominately cuboidal variety. Most follicles were filled with colloid, and the latter

stained with an intensity equal to that of the controls. There was also a suggestion of increased vascularity. The two cases in the females at 800 ppm showed a similar picture. The thyroid glands of the males at 800 ppm, however, showed definite evidence of stimulation. Although some squamous follicular epithelium remained, the cell type was predominately cuboidal with a transition to low columnar, and the increase in vascularity was marked. About one-half of the total number of follicles were filled with colloid, and the remainder were partly filled. The colloid did not stain as intensly with eosin as did that of the thyroids of animals at lower dosage levels.

Summary

It appears that the effects of the test material at the dietary level of 800 ppm were limited to stimulation of the thyroid gland. The threshold of this effect appears to extend down to 200 ppm.

Rat Reproduction Study

During the two year rat feeding study the animals which received the dietary level of 800 ppm were mated. These animals produced an F_1 generation which was allowed to obtain sexual maturity and in turn were mated to produce an F_2 generation. All descendants were continued on the 800 ppm dietary level.

The test material did not cause any discernible disturbance of any phase of reproduction.

U. S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
PESTICIDES REGULATION DIVISION
WASHINGTON, D. C. 20250

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INTERDEPARTMENTAL COORDINATION OF ACTIVITIES RELATING TO PESTICIDES

Referral of Application for Registration under the Federal Insecticide, Fungicide, and Rodenticide Act

American Cyanamid Company
Agricultural Division
P. O. Box 400
Princeton, New Jerseyy

CYPREX 65-W	241-51	
FRUIT FUNGICIDE	Petition #8F0655	3-15 WA OF 3-22-65

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