Mr. Coberly

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: 1,2-dimethyl-3,5-diphenyl pyrazolium methyl sulfate (Avenge)

DATE: February 27, 1974

FROM:

TOXR 001266

TO: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Pesticide Petition No. 4G1453

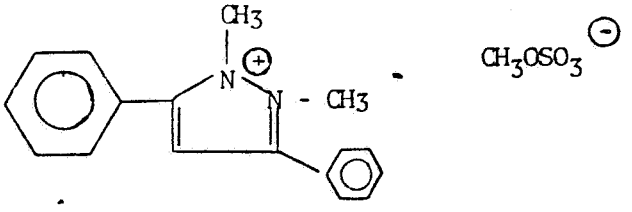
Action Requested: Temporary Tolerances

0.5 ppm in or on barley straw
0.05 ppm (negligible) barley grain
0.02 ppm (negligible) in meat, fat and meat by-products of cattle, goats, hogs, horses and sheep

American Cyanamid Company
P.O. Box 400
Princeton, NJ 08540

Related Petitions: None

Chemical Structure:



Vapor Pressure: None

Stability: 76.2% in water at 23° C

Use: Herbicide on barley (postemergence)

Formulation: Avenge 2A-S

Active Ingredient

31.8% 1,2-dimethyl-3,5-diphenylpyrazolium methyl sulfate

1/7/12

EPA Form 1320-6 (Rev. 6-72)

Inert Ingredient [redacted]

Application Frequency: At the 3 to 5 leaf stage of growth only.

Application Rate: 2.5 to 4 pints

Application Method: Spray application

TOXICITY DATA

Acute Toxicity

Rat Oral LD_{50} - American Cyanamid Co. - 6/28/73

The material used in this study was identified as Technical No. 84,777, Sample 73-16. Ten fasted male RH Wistar rats were administered the test material (a 20% w/v aqueous dispersion) in a dosage range of from 157 - 1250 mg/kg.

Results

LD_{50} = 270 (220 - 340 mg/kg). Signs of intoxication included dyspnea, prostration, mild convulsions.

Rabbit Dermal LD_{50} - American Cyanamid Co. - 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. An aqueous paste of the test material was applied to each of five rabbits per level. A range of from 625 to 10,000 mg/kg was tested. Exposure was 24 hours under an impervious cuff.

Results

LD_{50} = 3540 (1510 - 8260 mg/kg). Signs of intoxication included lethargy. No edema and slight erythema were noted.

Mice Oral LD_{50} - American Cyanamid Co. - 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. An aqueous dispersion of the test material was administered orally to each of ten male CF1 strain mice per level. A range of from 15.7 to 125 mg/kg was tested.

Results

LD_{50} = 31 (25 - 40 mg/kg)

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Rabbit Oral LD_{50} - American Cyanamid Co. - 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. A 20% w/v aqueous dispersion of the test material was administered orally to each of five male rabbits per level. A range of from 250 to 1000 mg/kg was tested.

Results

LD_{50} = 470 (330 - 660 mg/kg)

Mice Oral LD_{50} - American Cyanamid Co. - 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. A aqueous dispersion of the test material was administered orally to each of ten female mice per level. A range of from 15.7 to 125 mg/kg was tested.

Results

LD_{50} = 44 (34 - 58 mg/kg)

Signs of intoxication included convulsions, prostration and dyspnea.

Rabbit Dermal Irritation - American Cyanamid Co. 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. An aqueous paste (0.5 gm/rabbit) of the test material was applied to six rabbits under an impervious patch for 24 hours. Half the test sites were abraded. Observations were made at 24 and 72 hours.

Results

The intact test sites completely recovered from the very slight to moderate erythema and negative to slight edema by 72 hours; the abraded test sites did not show a meaningful recovery from the severe edema and erythema by the 72 hour observation period.

Rabbit Eye Irritation - American Cyanamid Co. - 6/28/73

The test material was identified as Technical No. 84,777, Sample 73-16. One-tenth milliliter was instilled in the eye of each of six rabbits. Observations were made at 24, 48 and 72 hours.

Results

No cornea or iris reactions were noted. Moderate irritation of the conjunctivae was recorded.

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Rat Inhalation LC_{50} (95-S) - Affiliated Medical Research Inc. - 9/13/73

The test material was identified as Avenge 95-S, 2282-33 which is 96.4% technical and [redacted] This formulation was diluted in water to make a 25% w/v suspension. Six young adult male rats were exposed to a nominal concentration of 298.2 mg/L in a dynamic chamber. Length of exposure was one hour.

Observations and tests included daily physical observation, mortality, and gross autopsy.

Results

LC_{50} = greater than 298.2 mg/L

No mortality occurred. Transient irritation and mild depression were noted.

Rat Oral LD_{50} (AC2233-63-2 formulation) - Affiliated Medical Research 9/13/73

The test material has the following composition:

36.14% w/v CL 84,777

[redacted]

The test material was diluted with distilled water and orally administered to six fasted male rats per level in a dosage range of from 100 to 1000 mg/kg. Length of observation was seven days. Gross autopsy was conducted at termination of study.

Results

LD_{50} = 422 (+ 41.2) mg/kg

Rabbit Oral LD_{50} (AC2233-63-2 formulation) Affiliated Medical Research 9/13/73

The test material has the following formulation:

36.14% w/v CL 84,777 - tech

[redacted]

The test material was diluted with distilled water and administered orally to four male rabbits per level of 500, 1000 and 2000 mg/kg. Length of study was seven days.

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

Results

LD_{50} = 723.6 (410.9 - 1274.3) mg/kg

Pupil dilation, exophthalmia, nystagmus, gasping for breath and tremors were noted. Gross autopsy findings were negative.

4 Rabbit Dermal Irritation (AC2233-63-2 formulation) Affiliated Medical Research 2/13/73

The test material has the following formulation:

36.14% w/v CL 84,777 tech

[redacted]

Five-tenths milliliter of the formulation was applied to the prepared test sites on six male rabbits. Half the test sites were abraded. Exposure was for 24 hours under a patch (1" X 1" gauze pad). Observations were made at 24 and 72 hours.

Results

A PII of 0.50 (Draize) was recorded. Formulation is not a skin irritant.

X Rat Inhalation LC_{50} (AC2233-63-2 formulation) Affiliated Medical Research 9/13/73

The test material was identified as CL 84,777-250A, AC2233-63-2. This material was diluted in water to make a 50% w/v suspension. Six rats were exposed to this suspension in a dynamic chamber at a nominal concentration equal to 292.9 ml/L of the undiluted formula CL 84,777-250A, AC2233-63-2. Length of study was 14 days.

Results

LC_{50} = greater than 292.9 mg/L

Mild depression was noted. The gross autopsy findings were normal.

X Rabbit Dermal LD_{50} - (AC2233-63-2 formulation) Affiliated Medical Research 9/11/73

The test material was applied undiluted to four male rabbits at the level of 10,000 mg/kg. Length of study was seven days.

Results

LD_{50} = > 10,000 mg/kg

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Rabbit Eye Irritation (AC2233-63-2 formulation) Affiliated Medical-Research 9/11/73

One-tenth milliliter of the test formulation was instilled into the left eye of nine male rabbits. Three eyes were washed immediately. Three ten seconds after treatment and three were unwashed.

Results

Moderate to severe eye irritation was evident. The group mean scores at 24, 48, and 72 hours and 7 days were 16.5, 27.9, 17.6 and 14.1.

Rat Oral LD_{50} (AC2233-84-1 formulation) American Cyanamid 12/5/73

The test material contained the following 32.5% - 1,2-dimethyl-3,5-diphenyl pyrazolium methyl sulfate; [redacted]

A 10% v/v aqueous dispersion of the test material was administered ten male RH Wistar rats per level of 340, 680, 1360, and 2720 mg/kg.

Results

LD_{50} = 730 (560-960) mg/kg. Signs of intoxication included prostration and convulsions. No mortality occurred at 340 mg/kg.

Rabbit Dermal LD_{50} (AC2233-84-1) American Cyanamid 12/5/73

The test material contained the following 32.5% - 1,2-dimethyl-3,5-diphenyl pyrazolium methyl sulfate; [redacted]

The undiluted test material was applied under an impervious cuff for 24 hours. Five male rabbits were used per level of 1359, 2718, 5435, and 10870 mg/kg.

Results

LD_{50} = 4980 (2540-9760) mg/kg. Well defined erythema was recorded.

Rabbit Dermal Irritation (AC2233-84-1) American Cyanamid 12/5/73

Six rabbits were treated with 0.5 ml of the test material for 24 hours under an impervious patch. Half the test sites were abraded. The Draize scoring was used.

Results

A primary irritation score of 3.2 was reported indicating a moderate degree of irritation.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Rabbit Eye Irritation (AC2233-84-1) American Cyanamid 12/5/73

One-tenth milliliter of the test formulation was instilled into the left eye of six rabbits. Observations were at 24, 48 and 72 hours.

Results

The moderate degree of ocular irritation observed at 24 hrs was unchanged at 72 hours.

Rabbit Dermal LD_{50} (AC2233-84-3) American Cyanamid 12/5/73

The test material contained the following: 32.5% 1,2-dimethyl-3,5-diphenyl pyrazolium methyl sulfate; [redacted]

This undiluted material was applied undiluted to test sites on five male rabbits for 24 hours.

Results

LD_{50} = 3530 (2010-6200) mg/kg. Well defined erythema was recorded.

Rabbit Dermal Irritation (AC2233-84-3) American Cyanamid - 12/5/73

Six rabbits were treated with 0.5 ml of the undiluted test material for 24 hours. Half the test sites were abraded. All test sites were covered with an impervious patch.

Results

A primary irritation score of 4.6 was reported.

Rabbit Eye Irritation (AC2233-84-3) American Cyanamid 12/5/73

One-tenth milliliter of the undiluted test material was instilled into the eye of each of six rabbits. Observations were made at 24, 48, and 72 hours. The Draize scoring method was used.

Results

The 24, 48 and 72 hour readings were 32, 32, and 30 respectively. Corneal involvement was evident.

Rabbit Dermal LD_{50} (AC2233-84-2) American Cyanamid 12/5/573

The test material contained the following: 32.5% 1,2-dimethyl 3,5-diphenyl pyrazolium methyl sulfate; [redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

[redacted]

This test material was applied undiluted to test sites on each of five male rabbits.

Exposure was for 24 hours under an impervious cuff. Dosage range tested was from 680 to 5440 mg/kg.

Results

LD_{50} = 1760 (1030 - 3020) mg/kg. All deaths occurred within 24 hours. Well defined erythema followed by desiccation and cracking of the skin was reported. Lethargy was also reported.

✓ Rabbit Dermal Irritation (AC2233-84-2) American Cyanamid - 12/5/73

Five-tenths milliliter of undiluted test material was applied to test sites on each of six rabbits for 24 hours. Half the test sites were abraded. Length of study was three days. Draize scoring method was used.

Results

Primary irritation score equals 3.2 moderate to severe erythema and no edema were observed among the intact skin animals; very slight to severe edema was noted among the abraded skin sites.

✓ Rabbit Eye Irritation (AC2233-84-2) American Cyanamid 12/5/573

One-tenth milliliter of the undiluted test material was instilled into one eye of each of six rabbits. Eyes were scored by the Draize system. Length of study was three days.

Results

The scores at 24, 48, and 72 hours were 31, 33 and 35 respectively. The corneal involvement increased between the 24 and 72 hour observation periods.

21 Day Rabbit Dermal - American Cynamid 9/4/73

The two test materials used were identified as Final Formulation AC84,777 and Technical Grade AC84,777. The Final Formulation was tested at 2.0, and 0.5 ml/kg. The Technical Grade was tested at 1.0, 0.5 and 0.25 gm/kg. Four rabbits of each sex were used per dosage level. The test material was applied for six hours a day five days a week for three weeks. Half the test sites were abraded.

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Observations and tests for effects included mortality, weekly body weights, hematology, urinalysis, gross necropsy, and histological examination of the brain, liver, stomach, bladder, eye, spleen, pancreas, gonad, lung, kidney, small intestine, skin, heart, adrenal, large intestine, bone marrow, kidney, bile duct, and skin.

Results

No effect level is greater than 2.0 ml/kg for the "Final Formulation" and greater than 1.0 gm/kg for Technical Grade.

All of the aforelisted parameters revealed no significant differences between the test and control animals.

Two Year Rat Feeding (13 week interim report) (Tech AC84,777) Food & Drug Research - September 12, 1973

Sixty young FDRL/Wistar rats of each sex were used per dosage level of 100, 500, and 2500 ppm. A 90 day sacrifice and complete report at three months were scheduled.

Observations and tests for effects included daily observations for appearance and behavior, ophthalmoscopic examination, food consumption, body weight; hematology - hematocrit, hemoglobin, RBC, leukocyte count, and differential leukocyte count at 3, 6, 12, 18, 24 month intervals; biochemistry-glucose, BUN, SGPT, and SAP at 3 and 24 months; and urine analyses.

The following tissues were examined from ten rats of each sex from the control and 2500 ppm animals at the 90day interval sacrifice;

brain (3 sections)	small intestine
pituitary	large intestine
eye	mesenteric lymph node
thyroids	urinary bladder
heart	mammary gland
lung	testes/epididymis
liver	ovary/uterus
spleen	bone marrow
kidneys	spinal cord
adrenals	rib junction
stomach	sciatic nerve
pancreas	unusual lesions

The following tissues were taken from 10 male and 10 female rats from each of the remaining test groups sacrificed at the 90 day interval.

lung	adrenals
heart	testes/epididymis
liver	ovary/uterus
mammary tissue	unusual lesions
kidneys	

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Results

All observations and tests conducted up to this point in time reveals no significant toxicological differences between the test and control values.

90 Day Dog Feeding (Technical AC84,777) Food & Drug Research Lab 9/28/73

Four young purebred beagle dogs of each sex were used per level of 100, 500, and 2500 ppm. The test material was offered in the regular diet on a six day a week basis.

Observations and tests for effects included ophthalmological examination, body weights, hematology at 1, 2, 4 and 12 weeks (RBC & WBC, differential count, hemoglobin, hematocrit, erythrocyte sedimentation rate and reticulocytes), clinical test at 1, 2, 4 and 12 weeks (SGOT, SGPT, SAP, coagulation time, BUN and glucose), and urinalysis. Terminal observations included the absolute and ratio weights of the kidney, heart, testes, adrenals and ovaries; microscopic examination of the following:

adrenals
aorta
bone (rib junction)
bone marrow
brain
cholecyst
epididymis
eye
gonad
heart (with coronary vessels)
intestine
colon
duodenum
ileum
jejunum
kidney
lens
liver
lungs
all gross lesions
lymph node mesenteric
mammary glands
nerve (with muscle)
pancreas
pituitary
prostate
salivary gland
skeletal muscle (with nerve)
spinal cord
spleen
stomach
pyloric
fundus
thymus
thyroid
urocyst
uterus

Results

A slight reduction in body weight gains for the 2500 ppm level animals was evident. All other parameters were within normal biological variations. NEL is 2500 ppm.

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Three Generation Rat Reproduction (14 week interim report) Hazleton Lab
12/5/73

Ten male and twenty female rats of the Charles River strain were used per level of 0, 500, 2500 ppm. The P_1 generation was raised to an age of 100 days before being placed in the breeding phase of the experiment. During the breeding phase one male was rotated between groups of two females of his same level every fourteen days. From the offspring of this mating (F_{1A}) ten males and twenty females were chosen to become the P_2 generation. At 100 days of age these F_{1A} animals were mated. This procedure was followed for three generations.

Observations and tests for effects included body weights, food consumption, conceptions, live births, stillbirths, litter size, mortality, gross abnormalities in pups and gross necropsies on approximately one-third of the pups in each group (F_{1A} through F_{3A}) at weaning. Histopathological examination of tissue will not be done unless the results of the study so dictate.

Results

This interim report covering the period up to the weaning of F_{1A} pups reveals no significant differences between the test and control findings.

18 Month Mouse Carcinogenic Study (6 Month interim report) Pharmacopathics Research Lab - 11/30/73

Sixty weanling ICR strain mice were used per level of 100, 500, and 2500 ppm. The test material was added to the basal diet which was available to the mice at all times. Observations and tests included body weights, mortality, daily clinical signs, interim sacrifices at six and twelve months. Tissues taken at the sixth month sacrifice for microscopic examination from ten mice per level included:

brain	sub-maxillary gland
pituitary	thyroid
spinal cord	thymus
eye	heart
liver	lungs
kidneys	adrenals
spleen	pancreas
skin	stomach
bone	intestine
bone marrow	lymph node
nerve & muscle	bladder
unusual lesions	gonads

These same tissues are scheduled to be taken from 20 animals of the control and high level at the termination of this study for microscopic examination. Mice were housed ten per cage.

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Results

The histopathology report was not available for review at this time. The mortality and body weights reveal no significant differences between test and control values at six months.

RECOMMENDATION

These toxicity data will support the request for the temporary tolerances.

Robert D. Coberly, Biologist
Toxicology Branch
Registration Division

cc: CB
EEB
Division File
Branch File
PP No. 4G1453

Init: GEWhitmore
CHWilliams

RDCoberly/km 02-27-74

3/4/74