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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Difenzoquat methy sulfate (1-3-dimethyl-3,5-diphenyl-1H-pyrazolium methyl sulfate)

DATE: JAN 30 1976

001268

FROM: Toxicology Branch

TO: Product Manager

Pesticide Petition No.: 6F1703

Petitioner: American Cyanamid Company

Tolerances Requested: 20 ppm in or on barley straw and wheat straw
0.2 ppm in or on barley grain
0.05 ppm in or on wheat grain
0.05 ppm in the meat, fat and meat by-products of cattle, goats, hogs, horses, sheep and poultry

Recommendation: Do not establish tolerances until Chemistry Branch determines that azoalkanes are not plant metabolites.

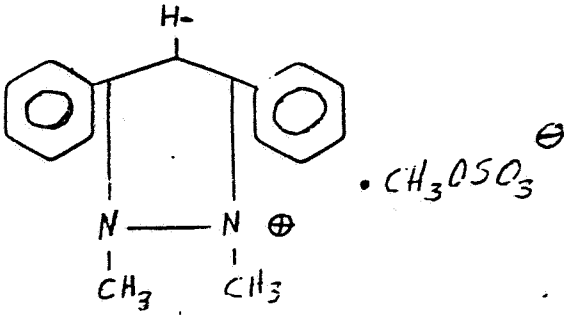
Related Petitions: 4G1453, 5G1576

Existing Tolerances: none

Other Names: Avenge, CL 84777, AC 84777, and 1,3-dimethyl-3,5-diphenylpyrazolium methyl sulfate

Common Name: Difenzoquat methyl sulfate

Structural Formula:



Molecular Weight: 360.4

Vapor Pressure: none

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

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CO 1268

Formulation: Avenge Wild Oat Herbicide

Active Ingredient

31.8% Difenzoquat methyl sulfate

Inert Ingredient

[redacted]

*cleared under 40 CFR Section 180.1001 (c).

Use: Herbicide

Formulations Tested:

#AC 2233-63-2

36.14% CL 84777

[redacted]

#AC 2233-84-1

32.5% CL84777

[redacted]

#AC 2233-84-2

32.5% CL 84777

[redacted]

#AC 2233-84-3

32.5% CL 84777

[redacted]

Avenge 95S

96.6% CL 84777

[redacted]

Avenge 2A-S

32.1% CL 84777

[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

001268

Background Information

PP# 4G1453 - reviewed by R. Coberly on 2/27/74 for the tolerances of 0.5 ppm in or on barley straw; 0.05 ppm in or on barley grain; and 0.02 in meat, fat and meat by-products of cattle, goats, hogs, horses and sheep. The following toxicity data was judged adequate to support the temporary tolerances:

Acute Rat Oral LD_{50} - Tech	270 mg/kg
Acute Mice Oral LD_{50} - Tech	44 mg/kg
Acute Mice Oral LD_{50} - Tech	31 mg/kg
Acute Rabbit Oral LD_{50} - Tech	470 mg/kg
Acute Rat Inhalation LC_{50} - Tech	293.2 mg/L
Acute Rabbit Dermal LD_{50} - Tech	3540 mg/kg
Acute Rabbit Dermal Irritation -Tech.	-severe edema and erythema at 72 hrs. on abraded skin
Acute Rabbit Eye Irritation - Tech	moderate irritation
Acute Rat Oral LD_{50} - 36.14% formulation*	422 mg/kg
Acute Rabbit Oral LD_{50} - 36.14% formulation*	723.6 mg/kg
Acute Rabbit Dermal Irritation - 36.14% formulation*	PIS of 0.50
Acute Rat Inhalation LC_{50} - 36.14% formulation*	greater than 292.9 mg/L
Acute Rabbit Dermal LD_{50} - 36.14% formulation*	greater than 10,000 mg/L

*Formulation No. AC 2233-63-2

Acute Rabbit Eye Irritation	36.14% formulation*	PII of 14.1 at day 7. Corneal opacity at day 7.
Acute Rat Oral LD_{50}	32.5% formulation**	730 mg/kg,
Acute Rabbit Dermal LD_{50}	32.5% formulation**	4980 mg/kg
Acute Rabbit Irritation	32.5% formulation**	PII = 3.2 (moderate irritation)
Acute Rabbit Eye Irritation	32.5% formulation**	moderate irritation at 72 hours
Acute Rabbit Dermal LD_{50}	32.5% formulation***	3530 mg/kg
Acute Rabbit Dermal Irritation	32.5% formulation***	PII = 4.6
Acute Rabbit Eye Irritation	32.5% formulation***	PII = 30 at 72 hrs. corneal involvement was evident.
Acute Rabbit Dermal LD_{50}	32.5% formulation****	1760 mg/kg
Acute Rabbit Dermal Irritation	32.5% formulation****	PII = 3.2 (moderate irritation)
Acute Rabbit Eye Irritation	32.5% formulation****	PII = 35 at 72 hrs corneal involvement at 72 hrs.

*Formulation No. AC 2233-63-2
**Formulation No. AC 2233-84-1
***Formulation No. AC 2233-84-3
****Formulation No. AC 2233-84-2

21 Day Rabbit Dermal	Tech	NEL = greater than 1.0 gm/kg
	Final Formulation*	NEL = greater than 2.0 ml/kg
90 Day Dog Feeding	Tech	NEL = 2500 ppm
2 Year Rat Feeding	(13 week interim report)	no adverse findings
3 Generation Rat Reproduction	(14 week interim report	no adverse findings
18 Month Mouse Carcinogenic	(6 month interim report)	no adverse findings

*Average 2A

An amended Section F requesting the proposed tolerance in meat, fat and meat by-products be increased from 0.02 ppm to 0.05 ppm was reviewed and accepted by the Toxicology Branch on May 1, 1974.

On November 21, 1974, Mr. Robert Jaeger, reviewed PP# 4G1453 with regards to increasing the temporary tolerances in or on barley straw from 0.5 ppm to 20 ppm, and grain from 0.05 ppm to 0.2 ppm, and grain from 0.05 ppm to 0.2 ppm. An extension of the EPA temporary permit No. 241-EXP-64G was also requested. Both requests were granted.. However, TB deferred to CB for its metabolism and residue levels in meat, milk, eggs and meat by-products. The following toxidity data were also reviewed:

21 Day Rabbit Dermal - 31.8% formulation - NEL $\geq$ 1000 < 2000mg/kg

Rat Teratology — not a teratogen at 2500 ppm (highest level)

Rat Dominant Lethal — not a mutagen at 2500 ppm (highest level)

3 Generation Rat Reproduction — NEL = 2500 ppm

18 Month Mice Oral - (14.5 month interim report)- no adverse effects at highest level of 2500 ppm.

2 Year Rat Oral - (70 week interim report)- no adverse effects at highest level of 2500 ppm.

During the January 9, 1975 conference with American Cyanamid, information was requested by TB as to whether or not azomethane was a metabolite of Avenge. A recent chemical abstract publication indicated that azomethane was a carcinogen.

An extension of both the temporary tolerance and the temporary permit were granted by TB on 11/3/75.

Present Action

The following toxicity data were submitted in support of the requested tolerances:

Acute Rabbit Dermal LD_{50} - 32.1% formulation* - LD_{50} = >5432 mg/kg

Acute Rabbit Dermal Irritation - 32.1% formulation* - PIS = 2.5

Acute Rabbit Eye Irritation - 32.1 formulation* - severe corneal involvement evident at 72 hrs.

Acute Rabbit Dermal LD_{50} - mixture** - LD_{50} = >5085 mg/kg

Acute Rabbit Dermal Irritation - mixture** - PIS = 1.7

Acute Rabbit Eye Irritation - mixture** - no corneal involvement
PIS = 1.7 at 72 hrs.

Acute Rabbit Dermal LD_{50} - mixture** - LD_{50} = 5044 mg/kg

Acute Rabbit Dermal Irritation - mixture*** - PIS = 1.0

Acute Rabbit Eye Irritation - mixture*** - no corneal involvement
PIS = 0.0 at 72 hrs.

Acute Rabbit Dermal LD_{50} - mixture**** - LD_{50} = >5059 mg/kg

Acute Rabbit Dermal Irritation - mixture**** - PIS = 1.4

Acute Rabbit Dermal Irritation - mixture**** - PIS = 0.0 at 72 hrs.
no corneal involvement

*32.1% Active, [redacted]
**16.7% Avenge 2A-S, 4.2% MCPA Amine
***16.7% Avenge 2A-S, 4.2% MCPA Ester
****16.7 Avenge 2A-S, 8.3% Bromoxymil, [redacted]

Acute Rabbit Dermal LD_{50} - mixture(1) - LD_{50} = >5083 mg/kg

Acute Rabbit Dermal Irritation - mixture(1) - PIS = 1.5

Acute Rabbit Eye Irritation - mixture(1) - PIS = 0.0 at 72 hrs.

Acute Rat Inhalation LC_{50} - Avenge 2A-S - LC_{50} = >410.5 mg/L

21 Day Rabbit Dermal - Avenge 2A-S - NEL $\leq$ 0.5 ml/kg

2 Year Rat Feeding - Food and Drug Research Lab - 9/19/75

The material tested was identified as AC 84777 (Tech), Lot No. AC-1786-158; (98.1%). This material was fed to 60 rats of each sex per level of 100, 500, or 2500/5000 ppm. The 2500 ppm level was changed to 5000 ppm after the 30th week.

(1) 16.7% Avenge 2A-S, 4.2 MCPA Ester, 8.3% Bromoxynil, [redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Observations and tests for effects included body weights, food consumption, opthalmoscopic examination, interim sacrice at day 90, and the following laboratory test:

hematocrit	glucose
hemoglobin	BUN
RBC	SGPT
WBC	SAP
differential count	urinalysis

Terminal studies included a histopathological examination of the following tissues from all rats of the control and high levels:

Brain	Large Intestine
Pituitary	Mesenteric Lymph Node
Eye	Urinary Bladder
Thyroids	Mammary Gland
Heart	Testes/Epididymis
Lung	Prostate
Liver	Ovary/Uterus
Spleen	Bone Marrow
Kidneys	Spinal Cord
Adrenals	Skeletal Muscle
Stomach	Rib Junction
Pancreas	Sciatic Nerve
Aorta	Tissue Masses
Small Intestine	All Lesions

The following tissues were also examined from 10 rats of each sex from each level:

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

Terminal studies also included organ weights of the following organs from all animals:

Thyroids	adrenals
Heart	Testes/epididymis
Liver	Ovary
Spleen	Uterus
Kidneys	

Results: 2500/5000 ppm level - body weight gain was depressed for both sexes at the 52, 78 and 104 week periods.

500 ppm level - normal biological variations.

100 ppm level - normal biological variations.

Conclusion: The no effect has to be established at 500 ppm for this study due to the depressed body weight gain at the high level. This effect is not considered to be of a severe nature but rather a consistance one during a significant part of the study.

18 Month Mice Carcinogenic - Pharmacopathics Research Lab - 2/26/75

The material tested was identified as AC 84777. This material was fed to 120 CD-1 outbred albino mice of each sex per level of 0, 100, 500 and 2500 ppm.

Observations and tests for effects included body weights, interim sacrifice at six months and twelve months and mortality.

Terminal studies included a histopathological examination of all tumors and a complete examination of tissues from ten mice of each sex of the high dose group and control group.

Results: As is evident from the following chart, no carcinogenic activity was detected in this study:

Diagnosis	Male				Female			
	0 PPM	100 PPM	500 PPM	2500 PPM	0 PPM	100 PPM	500 PPM	2500 PPM
VASCULITIS	3							
TUMORS, BENIGN								
ADENOMA								
PULMONARY	6		1					
THYROID								1
CYSTADENOMA, OVARY							1	
FIBROMA	1							
HEMANGIOMA, CAVERNOUS, UTERINE							1	
LUTEOMA OF OVARY						1		
TUMORS, MALIGNANT								
CARCINOMA								
ADENOCARCINOMA								
HEPATOMA	3	1					1	
MAMMARY GLANDS						1	1	1
PANCREAS	1							

DIAGNOSIS	Male 0 PPM	Male 100 PPM	Male 500 PPM	Male 2500 PPM	Female 0 PPM	Female 100 PPM	Female 500 PPM	Female 2500 PPM
SARCOMA								
FIBROSARCOMA, UTERUS								1
LYMPHOSARCOMA, TESTIS			1					
RETICULUM CELL	1				1			
LEUKEMIA								
LYMPHOCYTIC, CHRONIC	4		2		6	2		
MYELOGENOUS, ACUTE					1			
THYMOMA			1					
METASTASIS								
LUNG					1			

The other test parameters did not indicate a significant difference between the test and control findings.

The NEL = 2500 ppm

Three Generation Rat Reproduction - Hazleton Lab - 10/14/74

~~The material tested was identified~~ as AC 84,777. The project No. for this study was 362-147. This test material was tested in ten males and twenty females per level of 0, 500 and 2500 ppm.

Observations and tests for effects included survival, body weight, food consumption, appearance and behavior of the parental generation; indices of fertility and gestation, litter size, appearance, behavior, body weights, and growth of offspring; and results of the gross necropsy of a representative number of weanlings of each group of each generation.

Results - The only consistent finding is the reduced pup body weight at weaning. This is not considered a reproduction effect.

The no effect level is 2500 ppm.

Antidote Testing - Cyanamid - 10/31/75

The following is a chart supplied by the Petitioner as a summary of the antidote studies in either mice or rats:

Prospective Antidote	Result	Comment
Physostigmine sulfate	Inconclusive	Increased survival time with no decrease in mortality.
Physostigmine sulfate/ Norepinephrine	Inconclusive	Increased survival time with no decrease in mortality.
Physostigmine sulfate/ Picrotoxin	Negative	Decreased survival time and increased mortality.
Neostigmine methylsulfate	Negative	Not different from control.
Neostigmine methylsulfate/ Amphetamine sulfate	Negative	Not different from control.
Amphetamine sulfate	Negative	Not different from control.
Atropine sulfate	Negative	Decreased survival time and increased mortality.
Caffeine	Negative	Not different from control.
Picrotoxin	Negative	Decreased survival time and increased mortality.
Hydralizine HCl	Negative	Decreased survival time.
Propranolol HCl	Negative	Not different from control.
Diazepam	Negative	Decreased survival time and increased mortality.
Pentylenetetrazol	Negative	Decreased survival time and increased mortality.
Norepinephrine	Inconclusive	Increased survival time with no decrease in mortality.

Neuromuscular Screen In Cats - Bio-Test Lab - 10/21/75

Avenge was found to reduce neuromuscular activity 8.9% with an initial injection of 0.3 mg/kg. There also appeared to be some augmentation with repeated doses. Epinephrine was also shown to prevent the fatal decrease in blood pressure caused by the injections of Avenge.

Cardiovascular Study In Dogs - Bio-Test - 10/21/75

An injection of 0.1 mg/kg produced an increase then a 25% depression of arterial blood pressure, an increase in respiration, no change in ECG and a blockage of vagus nerve. Higher injections of 0.5 mg/kg and 1.0 mg/kg produced a temporary reduction in amplitude of the R wave in additional to the effects produced at the lower level.

Summary: These toxicity data show the material tested to displayed no adverse teratogenic, reproductive or mutagenic effects at the highest tested level of 2500 ppm and chronic no effects levels of 500 ppm and 2500 ppm in the rat and mouse respectively. The ADI for a 60 kg man is 15 mg/day based on the rat NEL of 500 ppm.

Conclusion: The one outstanding point in this petition is the question concerning whether or not one or more of the azoalkanes are plant metabolites of Avenge. This point must be settled prior to establishing the requested tolerance. If the azoalkanes are not plant metabolites the tolerance request are considered safe.

Robert Coberly
Biologist, Toxicology Branch

OEP 11/30/76