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10-17-75 (4)

EEE BRANCH REVIEW

DATE: IN 10/3/75 OUT 10/17/75 IN _____ OUT _____ IN _____ OUT _____

FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. _____

PETITION OR EXP. PERMIT NO. 241-EUP-64G

DATE DIV. RECEIVED September 19, 1975

DATE OF SUBMISSION September 18, 1975

DATE SUBMISSION ACCEPTED _____

TYPE PRODUCT(S): I, D,(H) F, N, R, S _____

PRODUCT MGR. NO. _____

PRODUCT NAME(S) Avenge 2A-S Wild Oat Herbicide

COMPANY NAME American Cyanamid Co.

SUBMISSION PURPOSE Extension of Permit - BARLEY

CHEMICAL & FORMULATION Difenzoquat methyl sulfate (spray)

100.0 Pesticidal Use

Herbicide for postemergence control of wild oats in barley.

100.1 Application Methods/Directions and Rates

DIRECTIONS FOR USE ON BARLEY GROWN ONLY IN ARIZONA, CALIFORNIA AND OREGON

AVENGE 2A-S Wild Oat Herbicide is a selective herbicide for the postemergence control of wild oats in barley. AVENGE 2A-S is a liquid formulation that contains 2 pounds active ingredient per gallon.

When to Spray

Applications of AVENGE 2A-S should be made when the majority of wild oat plants are in the 3-5 leaf stage of growth. Under optimum growing conditions, the 3-leaf growth stage of wild oats occur approximately 9 days following plant emergence. However, this timing may be delayed under adverse conditions such as cold weather, drought, or low soil fertility. Barley plants will usually be in the 2 to 7 leaf stage of growth when AVENGE 2A-S is applied. Examine the field daily to determine the optimum timing for application of AVENGE 2A-S.

DO NOT apply AVENGE when plants are wet with heavy dew or rain.

DO NOT apply AVENGE if rain is predicted within a minimum of six hours.

DO NOT apply AVENGE in winds over 15 mph.

Most effective control of wild oats is obtained when AVENGE 2A-S applications are made to the barley crop grown under conditions of optimum moisture, fertility, and cultural practices.

Spray Application

The amount of AVENGE 2A-S required to provide optimum wild oat control in barley is dependent on the degree of wild oat infestation of the crop as well as crop vigor. For effective control of wild oats in barley under optimum growing conditions, apply AVENGE 2A-S at the dosage level indicated in the following AVENGE 2A-S Recommendations Table based on the noted density of wild oat

plants. For control of low to moderate infestations of wild oats in barley growing under adverse conditions, apply the highest recommended dose of AVENGE 2A-S.

AVENGE 2A-S Recommendation Table

Wild Oat Population	Wild Oat Plants Per Square Foot[1]	AVENGE 2A-S Rate Per Acre[2,3]
Low	1 - 10	2 1/2 pints
Moderate	11 - 25	3 pints
High	more than 25	4 pints

1 Effective wild oat control will be obtained at the indicated dose of AVENGE 2A-S when the crop is showing optimum growth. Under adverse growing conditions apply AVENGE 2A-S at the rate of 4 pints per acre for all levels of wild oat plant density.

2 Apply AVENGE 2A-S in 5 to 20 gallons of water per acre with ground equipment or 3 to 10 gallons of water per acre by aerial application.

3 For spray volumes in excess of 10 gallons of spray per acre (gpa), the addition of surfactant; Triton X-100 or Surfonic N-95 or Tergitol NPX or Colloidal X-77, at 0.6 fluid ounces per gallon of spray in excess of 10 gpa is necessary. Example: For a 15 gpa spray add 3 fluid ounces of surfactant [0.6 ounces for each gallon of water over 10 gpa] to each 15 gallons of water.

Tank Mixes With Broadleaf Herbicides:

In barley fields where both wild oats and broadleaf weeds are present AVENGE 2A-S may be tank-mixed with MCPA, bromoxynil, or MCPA plus bromoxynil for the postemergence control of both wild oats and broadleaf weeds. The broadleaf herbicide should be applied in accordance with the label recommendations for that particular broadleaf herbicide.

101.0 Chemical and Physical Properties

101.1 Chemical Name

Difenzoquat methyl sulfate (1,2-dimethyl-3,5-diphenyl-1H-pyrazolium methyl sulfate).

101.2 Common Name

Difenzoquat methyl sulfate

Other designations - AC 84,777; CL 84,777; Avenge Wild Oat Herbicide

101.3 Structural Formula

Empirical Formula: $C_{18}H_{20}N_2SO_4$

101.4 Molecular Weight

360.4

101.5 Physical State, Color, Odor

Purity:	96.0%
Odor:	Odorless
Melting Point:	155-157°C
Density:	41 lbs./cu. ft. (10 - 50 mesh)
Vapor Pressure:	None

101.6 Solubility:

Water:	Temperature (°C)	Solubility, % (W/W)
	0	26.8
	18	69.3
	23	76.5
	37	78.2
	56	85.6
Xylene:	0.01 g/100 ml at 25°C	
Isopropyl Alcohol:	0.07 g/100 ml at 25°C	
Kerosene:	Insoluble at 25°C	
Chlorobenzene:	0.04 g/100 ml at 25°C	
Ethylene Dichloride:	8 g/100 ml at 25°C	

102.0 Behavior in the Environment

Summary of section H, petition No. 5G1576 exhibits 1-20.

102.1 Soil

In soils, the only component which occurs at all time intervals studies following application of C^{14} avenge is unaltered avenge (CL 84,777). There appears to be a rapid initial loss of radioactivity following treatment under field conditions, followed by a slower rate of loss over a 16 week period. Field rate disappearance studies show a similar pattern of rapid initial loss of CL 84,777 followed by a slow but continual rate of loss. No defectable residues of CL 84,777 (less than 0.10 ppm) were found in soil from four of the five studies samples one year after application; the fifth study did have some residues after one year (Oregon). CL 84,777 does not leach in the soil as demonstrated by both laboratory and field studies. No appreciable runoff of CL 84,777 was found in laboratory studies using the radioactive compound. The herbicide is apparently not taken up by either wheat or barley grown in soils treated the previous year. The metabolic integrity of soil microorganisms growing in soil treated with a rate equivalent to 10 lb/A of CL 84,777 (at 10 times the highest use rate) was unaffected. Under greenhouse conditions, CL 84,777 apparently was biodegraded (shake flask fermentations, anaerobic and aerobic soil incubation studies) only very slowly (could not be readily measured). No binding of the radioactivity to the soil matrix was observed in field studies. In laboratory studies no metabolites were found which would leach down into the soil.

102.2 Water

The herbicide is stable to hydrolysis in both acidic and basic environments over a 4 month period. Photolysis of CL 84,777 in water results in a rapid conversion of the herbicide to N_2, ethane, and polar products which migrade only slightly in thin-layer chromatographic systems. CL 84,777 apparently does not persist in the aquatic environment, the 1/2 life in sunlight water is about 3 days. It appears that the compound degrades in water by photolytic and not hydrolytic processes.

*(It should be noted that in contrast to the results of photodecomposition experiments conducted in the field under natural conditions, exposure to sunlight of soil thin-layer plates containing CL 84,777 did not result in significant decomposition of the herbicide. Reasons are unknown).

102.3 Plant

Wheat and barley sprayed with radioactive CL 84,777 did not metabolize the herbicide. Negligible levels (less than 0.05 ppm) of radioactivity were found in the seeds of these plants at harvest time. Wheat and barley did not uptake CL 84,777 under field conditions from soils treated the previous year (straw and grain residue study).

102.4 Animal

Rats dosed with radioactive CL 84,777 excreted 95% of the administered radioactivity within 96 hours of administration. The residue level in rat tissues 96 hours after administration of the compound were 0.3 ppm or less. Unaltered CL 84,777 was the only product found in the urine, feces, liver, and muscle indicating rats do not metabolize the product. Lactating goats dosed with radioactive CL 84,777 also excreted the product (89-92% of the initial dose) and milk and blood contained no measurable (less than <0.001 ppm) radioactivity. Chickens were fed 0.5 ppm CL 84,777 in their daily diet (equivalent to 10 X the 0.05 residue in wheat grain) for 28 consecutive days. No apparent CL 84,777 residues were found in eggs (0.05 ppm) or tissues (less than 0.10 ppm) of these chickens.

CL 84,777 is non-toxic to honey bees to the extent that no bees were killed when a dose equivalent to 36 lb/4 was administered.

Bluegill fingerlings exposed to water containing 1.0 ppm radioactive CL 84,777 for 28 days, did not accumulate the chemical.

Metabolism Summary

Barley and wheat plants do not metabolize AVENGE. Radioactive tracer studies (labeled at the 3-carbon position of the pyrazolium ring with carbon-14) indicate AVENGE is translocated through plant to the roots and soil complex. Residues in grain were below the validated sensitivity of the method used (0.05 ppm).

Radioactive tracer studies in the rat shows this compound is excreted unchanged in the urine and in the feces of the rat. The tracer was not stored in any tissue since the tracer was found to deplete rapidly and completely from all tissues. When fed to a lactating goat (radioactive AVENGE was poorly absorbed and only 2% was found in the urine. The material was depleted rapidly in the lactating goat and readings in tissue were very low. There were no detectable levels found in blood or in milk. The low radioactivity in the urine and liver was found to be the unchanged parent compound.

AVENGE is not degraded by the microflora in the soil nor does its presence have any apparent affect on soil microorganisms. AVENGE does not leach in the soil. However, this compound does photodegrade and it is this photodecomposition on the soil surface that apparently accounts for the disappearance of the large amounts of parent compound from the soil under field conditions.

103.0 Toxicological Properties*

103.1 Acute Toxicity

103.1.1 Mammal

Acute Toxicology of Technical AC 84,777 to Rats, Mice and Rabbits

Test animals employed in these studies included RH Wistar albino rats, CFI Strain albino mice and albino rabbits.

The acute oral LD_{50} of technical AC 84,777 to male rats is 270 mg/kg; to male mice is 31 mg/kg; to female mice is 44 mg/kg; and to male rabbits is 470 mg/kg.

The acute dermal LD_{50} of technical AC 84,777 to make rabbits is 3540 mg/kg.

Technical AC 84,777 produces slight irritation of the eye of rabbits. Technical AC 84,777 is not expected to produce significant skin or eye irritation.

Acute Inhalation Study of Technical AVENGE 95S (AC 84,777)

AVENGE 95S was diluted in water to make a W/W suspension prior to each run. An aerosol was generated in a dynamic chamber containing a volume of 1000 liters by passing the AVENGE suspension through a Devilbis atomizer, using compressed air at 40 psig and a flow rate of 4.0 l/min. The uniformity of fog inside the chamber was monitored by observation of refracted light. A group of 6 young adult albino rats, weighing from 186 to 201 grams, were exposed to the aerosol for one hour. Animals were observed during and following the exposure; mortalities were recorded, cumulatively for the subsequent 14 days.

The data show that at a nominal concentration of 298.2 mg/l, this product produced transient evidence of irritation and mild depression as the only sign of gross intoxication in the rats. On gross autopsy there were no significant differences noted between control and AVENGE treated rats.

* For information regarding the various formulations consult fish and wildlife files for AVENGE.

Acute Toxicology Studies With Formulation AVENGE 2A-S

Test animals employed in these studies included RH Wistar albino male rats and albino rabbits.

The acute oral LD_{50} of AVENGE 2A-S to male rats is 730 mg/kg.

The acute dermal LD_{50} of AVENGE 2A-S to albino rabbits is 4980 mg/kg.

AVENGE 2A-S does promote irritation when introduced into the eye of rabbits. Caution should be used to prevent introduction of AVENGE 2A-S into the eyes. AVENGE 2A-S formulation, containing Tergitol NPX, and Surfonic N-95 surfactants were toxicologically similar to AVENGE 2A-S formulation containing Triton X-100.

Acute Oral Toxicity in Rats With Formulation (2233-63-2), AMR Biological Research, September, 1973.

AC 84,777 Formulation (2233-63-2) was diluted in distilled water and administered to rats by oral intubation at dosage levels of 100 to 1000 mg/kg to 5 groups of 6 male albino rats. Initial weights of rats ranged from 118 to 267 grams. The acute oral LD_{50} of AC 84,777 Formulation (2233-63-2) is 422 $\pm$ 41.2 mg/kg.

Acute Oral Toxicity of Formulation (2233-63-2) in Rabbits, AMR Biological Research, September 13, 1972.

AC 84,777 Formulation (2233-63-2) was diluted in distilled water at a concentration of 500 mg/ml and administered by oral intubation to 3 groups of 4 male albino rabbits. Initial body weights of the rabbits ranged from 2135 to 3825 grams. Dosage rates administered were 500, 1000 and 2000 mg/kg.

The acute oral LD_{50} of AC 84,777 Formulation (2233-63-2) to male rabbits is 723.6 mg/kg.

Primary Dermal Irritation of AC 84,777 Formulation (2233-63-2) in Rabbits. AMR Biological Research, September 11, 1973.

The skin on the dorsal surface of six male albino rabbits of the New Zealand strain was shaved by use of electric clippers. Twelve dorsal test areas were utilized. Six of the dorsal test areas were abraded down to, but not through, the dermis, using a hypodermic needle. The remaining test areas were left intact. Standard patch test plasters (1" x 1" gauze pad) were saturated

with 0.5 ml of formulation and applied to the dermal test areas. The patch test plasters were left in place for 24 hours. According to the Draize evaluation, AC 84,777 Formulation (AC 2233-63-2) would not be considered an irritant to the skin.

Acute Dermal LD_{50} Test of AC 84,777 Formulation (2233-63-2) in Rabbits. AMR Biological Research, September 11, 1973.

Male albino rabbits, of the New Zealand strain, were clipped free of dorsal hair with an electric clipper. Appropriate doses of the test material were applied under rubber dental daming held in place with adhesive tape for 24 hours. During this time, the animals were housed in cages and observed for signs of systemic toxicity. Observations for mortality and signs of effect were made for 7 days, and the survivors were sacrificed and examined for gross pathology. The acute dermal LD_{50} of AC 84,777 Formulation (2233-63-2) to albino rabbits is greater than 10,000 m/kg.

Acute Inhalation Study of AC 84,777 Formulation (AC 2233-63-2) in Rats. AMR Biological Research, September 13, 1973.

A dynamic chamber containing a volume of 1000 liters, designed with a sliding tray and double sealing ports, was used in this study. Room air, drawn through the chamber at preselected rates, was monitored by means of a differential pressure flow meter and critical orifice, previously calibrated. AC 84,777 diluted in water to a 50% suspension, was generated as an aerosol by passing the suspension through a Devilbis atomiser, using compressed air at 40 psig and a flow of 4.0 l/min.

A group of 6 rats was exposed to the aerosol for one hour. The animals were observed during and following the exposure; mortalities were recorded, cumulatively, for the subsequent 14 days. At termination, the animals were submitted to autopsy. At a nominal concentration of 292.9 mg/l, a mild depression was the only sign of gross intoxication in the rats. On gross autopsy there were no significant differences noted between control and AVENGE treated rats.

103.1.2 Bird

Eight-Day Dietary LC_{50} - Mallard Ducks Technical AC 84,777

Technical AC 84,777 and Dieldrin (used as standard) were dissolved in corn oil and incorporated into a standard game bird starter ration. The diet consisted of two parts corn oil-test material and 98 parts standard ration by weight.

After 14 days of standard ration the birds were randomly assigned to groups (shown below) for 5 days followed by a 3-day observation period. During the observation period the AC 84,777 and Dieldrin groups received basal diet only.

Treatment	Pens	Birds/Pen	Diet Concentration (ppm)
Negative controls	5	10	basal diet only
Dieldrin controls	5	10	100, 159, 251, 389, 631
AC 84,777 groups	5	10	215, 464, 1000, 2150, 4640

The acute LC_{50} of technical AC 84,777 is 10,388 ppm (confidence limits 1177 to 91,712 ppm). The acute LC_{50} for Dieldrin is 158 ppm (confidence limits 88 to 285 ppm).

Eight Day Dietary LC_{50} - Bobwhite Quail Technical AC 84,777.

Technical AC 84,777 and Dieldrin (used as standard) were dissolved in corn oil and incorporated into a standard game bird starter ration. The diet consisted of two parts corn oil-test material and 98 parts standard ration by weight.

After 14 days of standard ration the birds were randomly assigned to groups (shown below) for 5 days followed by a 3-day observation period. During the observation period the AC 84,777 and Dieldrin groups received basal diet only.

Treatment	Pens	Birds/Pen	Diet Concentration (ppm)
Negative controls	5	10	basal diet only
Dieldrin controls	5	10	15.9, 25.1, 39.8, 63.1, 100
AC 84,777 groups	5	10	215, 464, 1000, 2150, 4640

The acute LC_{50} of Technical AC 84,777 is estimated to be greater than than 4640 ppm, whereas the LC_{50} of Dieldrin is 39.9 ppm (confidence levels 30.1 to 53.0 ppm).

103.1.3 Fish

Acute Toxicity of AC 84,777 to Bluegill (Lepomis macrochirus) and Rainbow Trout (Salmo gairdneri).

TL_{50} Milligram active ingredient/liter

Species	24 hours	96 hours	No Effect Level (mg/L)
Bluegill[a]	>1000	696 (413 - 1170)[c]	280
Rainbow trout[b]	>1000	694 (470 - 1020)	490

a - Bioassays conducted at 21°C(± 1.0), mean weight of bluegill 1.2 gm.
b - Bioassays conducted at 11°C(± 1.0), mean weight of rainbow trout 0.7 gm.
c - 95% confidence interval

Reviewers Please Note: EPA lab Results are significantly different! DJL

Acute Toxicity of PROWL 3E, PROWL 4E and AVENGE 2A-S to Bluegill (Lepomis macrochirus) and rainbow trout (Salmo gairdneri).

TL_{50} Milligram product/liter
(Using AVENGE 2A-S Formulation)

Species	24 hours		96 hours		No Effect Level (mg/L)
bluegill[a]	111.0 (69.8-178.0)[c]		90.4 (68.7-119.0)		56.0
rainbow trout[b]	>140.0	<210.0	>75.0	<100.0	5.0

a - bioassay conducted at 20°C (±1.0) mean weight of bluegill 0.9 g.
b - bioassay conducted at 10°C (±1.0) mean weight of rainbow trout 1.3G.
c - 95% confidence interval.

103.1.4 Aquatic invertebrate: no data available

103.2 Subacute toxicity

Subacute (21 Day) Dermal Toxicity Study in Rabbits With Herbicide AC 84,777. Food and Drug Research Laboratories, Inc. July 26, 1974.

In this study, the commercial formulation of AC 84,777 (AVENGE 2A-S) which contains 2 pounds of active ingredient per gallon (32.1 percent AC 84,777 by weight) and surfactant (Triton X-100) was applied to the shaved backs of rabbits for six hours per day, five days a week for three weeks. The application was made to intact skin of two males and two females, and the abraded skin of the remaining two males and 2 females per group. One group served as a control and was treated with 1.45 ml of vehicle which was the commercial formulation lacking the technical AC 84,777. The other three groups received the following dosages of test material: 0.5, 1.0, and 2.0 ml/kg/day.

The application area of each animal was observed throughout the study. Initial and terminal body weights were recorded for all animals and blood and urine analyses were conducted on all animals from the control and two animals per sex from the test groups. Sacrifice and gross examination of all organs was performed at the conclusion of the series of applications. For microscopic examination, routine hematoxylin and eosin stained slides were prepared from liver, spleen, both kidneys, bone marrow, and four sections of skin of all control animals and two animals per sex per group from the test groups (abraded and intact).

The application of this formulation of AC 84,777 to the intact and abraded skin of albino rabbits was well tolerated through 15 applications (5 days per week) at dosages of 0.5 and 1.0 ml/kg body weight per day. No evidence of systemic absorption or toxicity was seen at these levels, with the inflammatory skin responses being only slightly more severe than those produced by the vehicle control. All parameters remained within normal limits for this species and showed no changes correlated with treatment at the lower dosages.

At the dosage of 2.0 ml/kg, the formulation was lethal to 6 of 8 rabbits. It is probable that the sub-acute lethal dermal dose under these conditions lies between 1.0 and 2.0 ml per kilo.

Sub-Acute Oral Toxicity Studies - AC 84,777 and AC 92,390 - Rats.

This is a 3-month (13 week) interim report of a 24 month toxicology and carcinogenicity feeding study with rats (RH Wistar) currently in progress with technical AC 84,777. Although this long-term study includes toxicology evaluation of two chemicals, the current report deals only with AC 84,777 herbicide. AC 84,777 was applied in the feed ration to individual groups of rats at rates of 100, 500, and 2500 ppm. After 13 weeks, the general appearance and behavior, appetite, and elimination pattern of rats in the AC 84,777 treatment groups were within normal limits and were comparable to those of test animals in the control group. Body weight gains and food consumption were within normal limits and no adverse effects were observed due to compound administration during the 13 weeks of study.

Blood chemistry values were without significant alterations and generally were comparable between control and test animals.

At conclusion of the 13 weeks feeding, gross necropsy was conducted on representative animals from control and each test group. No significant differences in gross necropsy findings or microscopic examination have been found among control or test animals.

90-Day Feeding Study in Dogs With AC 84,777

Observations recorded in this study indicate that AC 84,777 herbicide is not toxic to dogs when administered at dose levels up to 2500 ppm in the diet for 13 weeks. Appearance, behavior, body weight, hematological, biochemical, pathological and urinary findings, for all animals were within normal ranges throughout the study with no dose or treatment-correlated response in any parameter.

AVENGE* Wild Oat Herbicide: Residues in Chicken Tissues (Muscle, Fat, Liver, Kidney, and Skin) and Eggs. American Cyanamid Report C-447.

Chickens were dosed at the rate of 0.5 ppm (equivalent to 10 times the 0.05 negligible residue in wheat grain) in daily diet for 28 consecutive days. Eggs from these chickens were taken every 7 days for analysis throughout the study and chickens were sacrificed for tissue collection 2 to 3 hours after the last treatment. Chicken tissues (muscle, fat, liver, kidney, and skin) and eggs were analyzed for CL 84,777 residue using an analytical method (Method M-504) with a sensitivity of 0.05 ppm in eggs and 0.10 ppm in tissues. Apparent CL 84,777 residues were less than 0.10 ppm in all tissues and less than 0.05 ppm in the eggs at each sampling interval.

Distribution and Persistence of CL 84,777 (Active Ingredient in AVENGE* Wild Oat Herbicide) in Bluegill Fish.

Bluegill fingerlings were exposed to CL 84,777 (labelled with C-14 in the 3-position of the pyrazolium ring) at rates of 1.0 and 0.01 ppm. Throughout the exposure period of 28 days, 25% of the water was removed daily and replaced with fresh water containing an amount of radiolabelled CL 84,777 appropriate to maintaining constant levels of 0.01 and 1.0 ppm. Fish were sampled periodically throughout the exposure period and the edible (eviscerated) portion of each fish combusted and analyzed radiometrically. There was no significant accumulation of CL 84,777 in the edible fish throughout the exposure period at either level. In view of the finding in edible tissue, analyses were conducted on the viscera. There was a maximum accumulation of 5.5 ppm in the viscera after 7 days exposure at 1.0 ppm and 0.21 ppm after 14 days of exposure at 0.01 ppm. When the fish were placed in clean water more than 80% of the residue in viscera was dissipated within 7 days.

103.3 Chronic Toxicity

Interim Report: Eighteen-Month Mouse Carcinogenesis Study With AC 84,777. Pharmacopathics Research Laboratories, Inc. September 13, 1974.

This study was initiated to determine the potential carcinogenicity of AC 84,777 for albino mice by feeding the compound at concentrations of 100, 500, and 2,500 ppm in the diet for 18 months. This interim report summarizes the findings of the first 14 1/2 months of the study. At 6 months and 12 months, 5 males and 5 females of each group were sacrificed and subjected to extensive gross and microscopic examination. Similar examinations were performed on all animals that have died or were sacrificed in a moribund condition.

There were no significant differences in the mean body weights of the test groups and their corresponding controls.

Such gross and microscopic pathology as has been observed to date is only that ordinarily occurring in this species under normal laboratory conditions. None has been observed that can be considered related to administration of AC 84,777.

Second Interim Report: Sub-Acute Oral Toxicity Study in Rats With AC 84,777. Food and Drug Research Laboratories, Inc. September 3, 1974.

The purpose of this study is to evaluate the potential carcinogenicity and systemic toxicity of AC 84,777 by dietary administration to albino rats during a two-year period. This interim report describes the first 70 weeks of the 104-week program. Three groups of 60 males and 60 females were fed a basal diet which contained 100, 500, or 2,500 ppm

of AC 84,777. A fourth group of 100 males and 100 females served as the control. After the 30th week of feeding, the 2,500 ppm concentration was increased to 5,000 ppm. Animals were observed daily for survival and evidence of any toxic and/or pharmacological reaction to the test material. Body weights were recorded weekly and food consumption was recorded weekly for the first 12 weeks, and monthly thereafter.

General appearance and behavior, appetite and elimination were within normal limits and were comparable between the control and test animals. Survival for all groups was similar. Body weight gain and food consumption were not affected by administration of the compound during the first 70 weeks of the study.

Gross opthalmoscopic examination of all animals revealed unilateral changes consistent with those generally observed in large rodent colonies and were not associated with administration of the test material.

The means of various hematological determinations carried out at 3, 6, and 12 months were generally comparable between control and test animals. Random differences consisted of occasional eosinophilia and fluctuations in the differential leukocyte counts for polymorphonuclear cells and lymphocytes.

Mean blood chemistry values were within ranges commonly accepted as normal and generally were comparable between control and test animals.

No significant differences attributable to administration of AC 84,777 were observed in the mean values for certain urinalyses for control or test animals performed during the first 70 weeks of the study.

In the data generated to date from this study, no significant differences have been found in numerical indices between control and test groups and no dose-related effect has been observed by the end of the 70th week of the test period.

Three-Generation Reproduction Study in Rats, AC 84,777 Final Report. Hazleton Laboratories, Inc.

This study was conducted to evaluate and characterize the potential effects of long-term ingestion of AC 84,777 on the reproductive performance of albino rats. AC 84,777 was administered in the diet concentrations of 0, 500, and 2,500 ppm through three successive generations. Criteria for evaluation of compound effect were the survival, body weight, food consumption, appearance, and behavior of the parental generation; indices of fertility and gestation, litter size, appearance, behavior, body weight, and growth of offspring; and results of the gross necropsy of a representative number of weanlings of each group of each generation.

No signs of systemic toxicity were observed at levels of 500 or 2500 ppm throughout feeding of the compound for three successive generations. Body weights of the high-dose rats of all three parental generations were somewhat lower than those of their respective controls. This observations was more evident among the females than the males.

The indices of fertility (no. pregnant/no. mated) and gestation (no. delivered/no. pregnant) were unaffected through three generations at both the 500 and 2500 ppm levels. No affect on litter survival was noted.

Gross necropsy of a representative number of weanlings of each group of each generation failed to reveal any treatment-related gross visceral changes.

Teratology Study in Rats - AC 84,777, Final Report, Hazleton Laboratories, Inc. July 22, 1974.

This study was conducted to evaluate the potential of AC 84,777 for embryotoxic and/or teratogenic effects in albino rats. The test material was administered in the diet of pregnant females at levels of 0, 500, and 2,500 ppm from Day 6 through Day 15 of gestation. All females were sacrificed for Cesarean delivery on Day 19 of gestation and the following observations recorded: number and placement of implantation sites (sum of living and dead fetuses and resorption sites), number of corpora lutea, number of living and dead fetuses, and sex distribution, weight and length of individual fetuses.

All females maintained normal appearance and behavior, and survived to Day 19 of gestation. Test and control groups gained weight equally well.

There were no meaningful or compound-related differences in the mean number of implantation sites, resorption sites, and corpora lutea or in the number, weight, or length of live fetuses of the test groups as compared to controls. Incidental statistically significant differences included an elevation of the mean number of live fetuses and a corresponding elevation of the mean number of implantation sites among the animals at the highest dosage.

Dominant Lethal Study in Rats with AC 84,777. Food and Drug Research Laboratories, Inc. September 3, 1974.

The purpose of this study was to determine the potential mutagenic effects of orally administered AC 84,777 to maturing albino rats. Three groups of 15 male weanling albino rats were selected. One group served as the control and received only the basal laboratory diet, the second group received AC 84,777 incorporated in the diet at a level of 500 ppm and the third group received AC 84,777 incorporated in the diet at a level of 2,500 ppm.

Following exposure to control or test diets, for 60 days, male rats were mated 1:1 with untreated virgin females. Impregnation of the female rat was determined by the presence of a vaginal plug, and the day on which a plug was observed was considered to be Day 0 of gestation. On Day 13 of gestation, Cesarean sections were conducted on all females so mated, and individual data recorded. This mating schedule was repeated with additional untreated virgin female rats mated 1:1 with the control or treated males for eight consecutive weeks.

A "mutagenic index" (the ratio of resorption sites to total implants on a percentage basis) was calculated for each female. Inasmuch as there were no significant differences between the means of the mutagenic indices of the control and test groups, AC 84,777 is considered to have exhibited no mutagenic activity in this test.

104.0 Hazard Assessment

104.1 Discussion

This chemical does not appear to pose a hazard to the environment based upon the data submitted. Its apparent mobility, persistence and toxicity profile do not raise concern from the environmental safety review staff. Under proposed uses, accumulation in fish and/or aquatic food chains does not appear to be a problem. Sufficient data has been provided to address the majority of concerns regarding chronic hazard, and the review staff finds no objection at present to the proposed uses; however, additional 70-15 data may indicate unforseen problems (such as with persistence).

104.1.1 Adequacy of toxicity data: sufficient at present

104.1.2 Additional data required: none at present

104.1.3 Likelihood of exposure to non-target organism: ground and aerial applications to barley fields represent potential for exposure to many diversified life forms, both aquatic and terrestrial.

105.0 Conclusions

The Environmental safety review staff finds no objections to the extension of the temporary permit as proposed.

The following precautionary statements should be added to the label in a separate paragraph, apart from the other precautions and directions:

> Keep out of lakes, streams, and ponds. Do not contaminate water by cleaning of equipment or disposal of wastes. Apply this product only as specified on this label.

SF

Scott Fredericks
Environmental Safety Review
B

10/17/75