Shaughnessy No.:018101

Date Out of EAB: 17 JUL 1984

To: Robert Taylor
Product Manager 25
Registration Division (TS-767)

From: Samuel Creeger, Chief
Review Section #1
Exposure Assessment Branch
Hazard Evaluation Division (TS-769)

Attached, please find the EAB review of...

Reg./File # : 241-EUP-RNG

Chemical Name: Chlormequat Chloride

Type Product : Growth Regulator

Product Name : CYCOCEL

Company Name : American Cyanamid

Purpose : EUP: Use on Wheat

ZBB Code : other

EAB #(s) : 4332

Action Code(s): 710

TAIS Code: 53

Date Received: 5/1/84

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Date Completed: 7/16/84

Deferrals to:

____ Ecological Effects Branch

____ Residue Chemistry Branch

____ Toxicology Branch

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1.0 INTRODUCTION

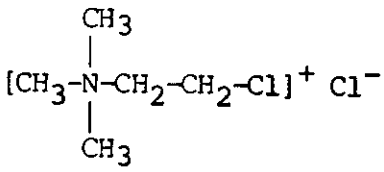
American Cyanamid has submitted data (accession number's 072386, 072387, 072396 and 072397) to support a proposed EUP use of CYCOCEL (Chlormequat Chloride) on Wheat.

According to EAB files, data have previously been submitted by this registrant (review of 5/10/76) to support the use of Cycocel 4L Plant Growth Regulator on sugar cane in Hawaii only. At that time, a number of studies were found to be deficient, including those on field dissipation and Greenhouse (Hawaiian) soil.

A number of additional studies reviewed then, may have been re-submitted with the current data.

2.0 STRUCTURE

Chlormequat Chloride
Chlorocholine Chloride
Cycocel
AC 38,555
BAS 062-W
Chlormequat
CCC



CAS: 2-chloroethyl trimethylammonium chloride (#999-81-5)

3.0 DIRECTIONS FOR USE

A copy of the proposed label is appended to this review.

In brief, the product is applied either aerially (preferred) or by ground equipment at a rate of 17 and 26 fl. oz/A (0.8 - 1.2 lb ai/A) to spring and winter wheat, respectively. Application to each type of crop is once per season at a point in the growth when plants are 6 to 12 inches high (as defined by the presence of a specified growth node or joint).

Label proscriptions:

- Avoid discharge into lakes, streams, ponds or public waters (NPDES).
- Do not apply if rain in imminent.
- Do not graze treated wheat or feed straw to livestock.

The registrant has requested a temporary tolerance for residues of chlormequat chloride in or on wheat grain, at the 5.0 ppm level.

4.0 EXPERIMENTAL PROGRAM

A copy of the proposed experimental program is appended to this review.

In brief, the registrant proposes to conduct the program for two years, applying a total of 3000 lb ai to 2400 acres in 4 states (CA, ID, OR, WA) in 1984 and 6000 lb ai to 4800 acres in 11 states (CA, ID, OR, WA, AZ, IL, IN, KY, AR, GA, MS) in 1985. Maximum test block size will be 100 acres, consisting of 4 - 25 acre plots to be treated as follows:

1. CYCOCEL and normal fertilization.
2. CYCOCEL and additional nitrogen.
3. No CYCOCEL but normal fertilization.
4. No CYCOCEL but additional nitrogen.

5.0 SUBMITTED DATA

Since the current submission is for purposes of an EUP, only those studies which relate to these data requirements will be reviewed in depth. The remaining studies should be resubmitted for EAB evaluation as conventional (Sec.3) data.

5.1 Haugwitz, M.I. and S.K. Eisner. 1975. CYCOCEL® Plant Growth Regulant: A Study of Its Behavior in an Hydrolytic and in a Photolytic Environment. Project #2566. Agricultural Division, American Cyanamid Company, Princeton, NJ. (Company Confidential) 20 pages, 2 tables, 2 figures, 1 appendix, 11 references November 7, 1975.

Introduction

This study has been previously submitted and reviewed (5/10/76). From that review... "Cycocel hydrolyses to form choline chloride as the only major product. Half-life of parent compund is greater than 4 weeks. Hydrolysis rate is somewhat greater at higher temperature, and lower pH levels. Hydrolysis is very rapid initially, followed by a much slower rate at 4 weeks."

"Cycocel converted rapidly to choline chloride in exposed as well as 'dark' control samples on glass surfaces and in aqueous solution."

Discussion

Due to the apparent contradictory results noted above (i.e. hydrolytic half-life >4 weeks, but rapid conversion to choline chloride in dark controls), the submitted data were reevaluated.

Radiolabled chlorocholine-1,2-^{14}C chloride was used in these studies, and found to have a radiopurity >95% by TLC. Specific Activity was not reported. A stock solution in methanol was prepared at a concentration of 0.363 mg/ml.

Hydrolysis: Buffers of pH 3, 6, and 9 were prepared with "sterile" water according to Clark and Lubs. It was not reported whether or not these solutions were sterilized.

Appropriate volumes of stock solution were pipetted into 6 volumetric flasks, evaporated to dryness under nitrogen, then made q.s. with the appropriate buffer, to give final concentrations of either 5 ppm or 50 ppm, at each pH. Aliquots of each stock solution were transferred to parafilm-capped test tubes, which were then stored in "temperature-controlled" areas in the dark.

Samples were taken at 0.5, 1, 2 and 4 weeks, with radiocounting (LSC) of each solution (apparently none were taken at time 0). Solutions were subsequently "freeze-dried" (procedure not specified), residues dissolved in methanol, then spotted on TLC plates for component quantification.

TLC was two dimensional using the same solvent system in each direction. Spots were visualized with Dragendorff's reagent, as well as with radioautography (Kodak SB-54 film). Neither sample chromatograms nor radioautographs were included with the report.

Report table 1 containing the reported hydrolysis data is appended to this review, and is summarized below:

Hydrolysis Data
Cycocel % Remaining for 5 ppm Solutions at 25°C

	Weeks			
	0.5	1	2	3
pH 3	58.4	----	----	----
pH 6	----	----	----	----
pH 9	----	----	----	----

It is obvious that virtually no data were reported which could be evaluated statistically.

Photolysis: Five hundred mls of a 5.1 ppm solution was prepared in distilled water, transferred to 10-125 ml Vycor flasks, and sealed with parafilm. Half were wrapped with foil to exclude sunlight. All tubes were then placed in direct sunlight in an area with "a white background." It was not specified whether the tubes were indoors or outdoors, although the inclusion of meteorological data suggest the latter.

Samples were taken after 1, 3, 6, 9 and 12 days (apparently none were taken at time 0), and were apparently processed as with the hydrolysis samples.

Report table 2 containing the reported photolytic data is appended to this review. Statistical analysis of the reported sample data yielded a half-life of 5.7 days (r^2=0.69), while the data for the "blank" (foil-wrapped samples) samples yielded a half-life of 2.0 days (r^2=.74, assuming the data at day 12 was an outlier, a 76% probability). Thus, paradoxically, the data seem to suggest that degradation of Cycocel appears to be inhibited by sunlight!

Conclusion

It is apparent that neither the hydrolysis nor the photolysis studies contain sufficient valid data to support their respective data requirements.

5.2 Marei, A.H. 1973. CYCOCEL® Plant Growth Regulant: Fate of Carbon-14 Chlorocholine Chloride in Soil. Project #2-524. Agricultural Division, American Cyanamid Company, Princeton, NJ. (Company Confidential) 47 pages, 5 tables, 6 figures, 1 appendix, 6 references. July 25, 1973.

Introduction

This study has previously been reviewed (5/10/76) and found to contain sufficient deficiencies to render the study invalid. Based on current data requirements, this study would still be unacceptable.

Conclusion

This study cannot be used to support the aerobic soil metabolism data requirement.

6.0 CONCLUSIONS

The Experimental program was clearly defined, and is acceptable to EAB.

Submitted hydrolytic and aerobic metabolism test are inadequate to support the proposed EUP. No data have been submitted to support either the accumulation in fish, or accumulation in rotated crops data requirements.

7.0 RECOMMENDATION

EAB cannot concur with the proposed EUP at this time, due to the lack of requisite EF data.

Since no data have yet been submitted to support the accumulation in rotated crops data requirement, the label must bear a 2-year restriction against the planting of any other crops in rotation with the target crops, or, alternatively, should bear a crop destruct warning for such crops.

The registrant should be referred to the Subpart N guidelines in designing and conduction future studies to satisfy EF data requirements. EAB would be willing to review test protocols prior to initiation of any particular study.

Emil Regelman
Chemist
EAB/HED
July 16, 1984

SECTION B

PROPOSED LABEL

AC 38,555

Plant Growth Regulator

For Experimental Use Only —
In Spring and Winter Wheat

NOT FOR SALE TO ANY PERSON OTHER THAN A PARTICIPANT OR COOPERATOR IN THE EPA APPROVED EXPERIMENTAL PROGRAM

Active Ingredient:

Chlormequat (2-Chloroëthyl)trimethyl) ammonium chloride	63.7%
Inert Ingredients	36.3%
	100.0%

(1 gallon contains 6.0 lbs. active ingredient)

EPA Experimental Use Permit No. 241-EUP- EPA Est. No. 7969-WG-1

KEEP OUT OF REACH OF CHILDREN

WARNING!

See Back Panel for Other Warnings

AVISO!

AL USUARIO: Si usted no lee ingles, no use este producto hasta que la etiqueta le haya sido explicada ampliamente.

English Translation

(TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.)

In case of an emergency endangering life or property involving this product, call collect, day or night, 201-835-3100.

American Cyanamid Company
Agricultural Research Division
Princeton, NJ 08540

Net Contents: 6.6 gallons
25 liters

Exp-1

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PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

WARNING

MAY BE FATAL IF SWALLOWED OR ABSORBED THROUGH THE SKIN. Do not get in eyes, on skin, or on clothing. Wash thoroughly after handling. Wash clothing before reuse.

FIRST AID

If swallowed: Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person. Get medical attention.

In case of contact: Immediately flush eyes or skin with plenty of water. Remove contaminated clothing and shoes. Get medical attention.

NOTE TO PHYSICIANS: (2-chloroethyl)trimethyl ammonium chloride is a weak ganglionic stimulant with an action similar to that of nicotine. An effective antidote has not been established.

ENVIRONMENTAL HAZARDS

This product is toxic to wildlife. Do not discharge into lakes, streams, ponds, or public waters unless in accordance with an NPDES permit. For guidance contact your Regional Office of the EPA.

STORAGE AND DISPOSAL

DO NOT STORE BELOW 32°F (0°C)

PROHIBITIONS: Do not contaminate water, food, or feed by storage or disposal.

STORAGE: Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

AC 38,555 is for use as a plant growth regulator on wheat. It causes shorter, thicker, stronger stems and improves resistance to lodging. It can improve root system development and increase the number of tillers surviving to bear heads, which will often result in increased yields.

AC 38,555 is beneficial as part of an intensive management program involving the application of increased levels of nitrogen. Follow local recommendations for fertilization and disease control.

Single Application: Apply the rates recommended below as a spray during good growing conditions in the spring and at the end of tillering but not later than when the first node or joint can be felt at the base of the majority of main stems. At this time most of the plants will be 6 to 12 inces tall.

Correct timing of applications is essential.

Ground Application: Apply in sufficient volume to adequately cover the crop.

Aerial Application: Apply 2.5-5.0 gallons of finished spray per acre. Results may not be as uniform as for ground applications.

DO NOT apply wheat under stress from cold weather, poor fertility, or other factors. DO NOT apply if the crop is wet or if rain is imminent. DO NOT apply if a frost is expected. DO NOT graze treated wheat or feed straw to livestock.

Crop	Suggested Rate (fl. oz. formulation/A)	Growth Stage Timing
Spring Wheat	17	Apply at the end of tillering, but not later than when the first node or joint can be felt at the base of the majorit of main stems. At this time most of the plants will be 6 to 12 inches tall.
Winter Wheat	26	

DISCLAIMER

American Cyanamid Company warrants only that the material contained herein conforms to the chemical description on the label and is reasonably fit for the use therein described when used in accordance with the directions for use.

Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damage such as loss of profits or values, etc.

American Cyanamid Company makes no other express or implied warranty, including any other express or implied warranty of FITNESS or MERCHANTABILITY.

User assumes the risk of any use contrary to label instructions or under abnormal conditions, or under conditions not reasonably foreseeable by American Cyanamid Company.

Manufactured for American Cyanamid Company
by
BASF Aktiengesellschaft
D-6700 Ludwigshafen
Federal Republic of Germany

AC 38,555 has been referred to by various designations in the reports included in this Application.

Technical Material has been referred to by:

AC 38,555
BAS 062-W
Chlormequat
Chlormequat Chlorid(e)
2-chloroethyltrimethylammonium chloride
Chlorocholine chloride
CCC

Formulated Material has been referred to by:

750 BASF
5C — a mixture of chlorocholine chloride and choline chloride
CCC + CC
CYCOCEL 4L

All of these designations refer to either technical AC 38,555 or formulations thereof.

SECTION G

Proposed Testing Program

Participant and Cooperators

This Experimental Use Permit will be coordinated by Dr. Cyril A. Kust, Senior Research Biologist, American Cyanamid Co., P. O. Box 400, Princeton, NJ 08540, 609-799-0400, Ext. 2540. Dr. Kust will have overall responsibility for the program, including final material accounting and data evaluation. He will work closely with the following American Cyanamid Co. field personnel. These field personnel will be instructed to permit authorized EPA or state enforcement personnel to observe the trials.

WESTERN REGION

Mr. A. O. Jensen, Regional Coordinator
106 Las Vegas
Orinda, California 94563
415-254-3103

Mr. C. R. Amen
1445 N.W. Fourteenth Place
Corvallis, Oregon 97330
503-753-5048

Mr. D. R. Colbert
2133 Jackson Street
Lodi, California 95240
209-369-1102

SOUTH CENTRAL REGION

Mr. P. J. Ogg, Regional Coordinator
3619 Mountain View Avenue
Longmont, Colorado 80501
303-772-0843

Mr. Kenneth Carlson
312 N. Evergreen
Wichita, KS 67212
316-722-4181

Ms. R. L. Rasmussen
617 West 6th Street
York, Nebraska 68467
402-362-7128

SOUTHEAST REGION

Mr. J. B. O'Neil, Regional Coordinator
2997 Gant Place
Marietta, Georgia 30067
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Mr. H. M. Hackworth
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Pocahontas, Arkansas 72455
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Dr. Franklin Congleton
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912-386-8413

NORTHEAST REGION

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Mr. T. O. Ballard
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Fowler, Indiana 47944
317-884-1369

Mr. F. Arnold
2010 Clover Lane
Champaign, Illinois 61821
217-398-6140

The above individuals will be responsible for the distribution of the test material. A record of the amount shipped, destination, test location, amount used, and amount returned will be maintained for each state involved in the EUP. Note that only some of these individuals will be involved in the proposed EUP program, depending on the year in question.

The names, addresses, and telephone numbers of the grower cooperators will be provided to the EPA and state officials as appropriate.

States and Acreages

TABLE 1

Proposed 1984 Program for Evaluation of CYCOCEL

State	Base Acres	Lbs. Active Ingredient
California	600	750
Idaho	600	750
Oregon	600	750
Washington	600	750
Totals	2,400	3,000

A 1985 program is being proposed, assuming that satisfactory results and additional residue samples are obtained in 1984.

TABLE 2

Proposed 1985 Program for Evaluation of CYCOCEL

State	Base Acres	Lbs. Active Ingredient
California	600	750
Idaho	600	750
Oregon	600	750
Washington	600	750
Arizona	300	375
Illinois	300	375
Indiana	300	375
Kentucky	300	375
Arkansas	600	750
Georgia	300	375
Mississippi	300	375
Totals	4,800	6,000

Program Details

Under proper moisture and edaphic conditions cereal crops respond to nitrogen fertilization by producing higher yields. However, optimum nitrogen levels cannot always be used in typical farm practice because vigorously growing cereals may lodge, precluding mechanical harvesting. CYCOCEL strengthens and shortens culms of wheat, thereby providing resistance to lodging. The product has been sold for many years in Europe and Asia on wheat and other crops for just this anti-lodging purpose.

All the tests in this program will be conducted under typical grower conditions on large blocks that typically yield uniformly. Each block will be divided into four similar plots. The following four treatments will be assigned, at random, to the four plots.

1. CYCOCEL and normal fertilization (based on soil analysis and typical local practice)

2. CYCOCEL and additional nitrogen (up to 80 units/A)

3. No CYCOCEL, normal fertilization (as in 1. above)

4. No CYCOCEL, additional nitrogen (as in 2. above)

The rate of CYCOCEL will depend on the crop.

The following data will be taken from each test: yield and lodging (observed 3 weeks before harvest). In certain tests, harvest samples of grain and straw will be taken for residue analyses.

The maximum plot size will be 25 acres, resulting in a maximum block size of 100 acres per test. Thus the entire program, if executed, will result in 9,000 lbs. active ingredient being applied to 7,200 base acres.

This testing program will allow us to accomplish the following objectives:

1. To determine the usefulness of CYCOCEL as an anti-lodging agent under normal fertilization regimes.

2. To determine whether CYCOCEL will permit growers to apply increased amounts of nitrogen.

3. To determine if phytotoxicity or other adverse effects alter the crop and the grower's management of it.

4. To obtain residue and efficacy data necessary for registration.

Disposal

All unused material will be disposed of acording to label directions or collected and returned to Cyanamid for disposal.

TABLE I

Hydrolysis of ^{14}C-CYCOCEL in Various pH Buffers at Several Temperatures
(% on Thin-Layer Chromatogram)

	0.5 Weeks						1 Week					
	25° pH 3		37° pH 6		45° pH 9		37° pH 3		45° pH 6		25° pH 9	
Fragment	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm
1. Unknown	2.3	3.7		1.2				1.0		2.0		1.8
2. CYCOCEL	58.4	56.4	65.8	57.3	71.9	54.1	75.3	59.9		62.6		64.3
3. Choline Chloride	39.3	39.9	32.8	41.1	28.1	45.9	23.8	38.5	22.3	35.4	26.3	26.3
4. Origin			1.3	0.4			0.9					

	2 Weeks						4 Weeks					
	45° pH 3		25° pH 6		37° pH 9		25° pH 3		37° pH 6		45° pH 9	
Fragment	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm	5 ppm	50 ppm
1. Unknown	5.1	1.5		1.6		0.8		2.3		2.0		
2. CYCOCEL		58.9		69.2		62.0		62.2		54.1		51.8
3. Choline Chloride	23.9	39.6	21.4	29.3	20.4	36.5	24.5	35.5	18.3	43.2	21.8	48.2
4. Origin					0.8	0.7			1.4	0.7		

TABLE II

Distribution of ^{14}C-CYCOCEL Degradation Products After Exposure to Sunlight
(% on Thin-Layer Chromatogram)

Thin-Film on Glass

	1 Day		3 Days		6 Days		9 Days		12 Days	
	Sample	Blank	Sample	Blank	Sample	Blank	Sample	Blank	Sample	Blank
Unknown	2.1	2.1	5.5	10.4	0.7	1.6	1.9	1.8	14.6	1.3
CYCOCEL	24.6	26.3	17.6	5.5	18.3	2.7	11.5	8.6	14.3	19.6
Choline Chloride	72.6	71.0	75.1	82.1	79.9	94.7	85.0	88.5	67.9	77.3
Origin	0.7	0.6	1.8	2.0	1.1	1.1	1.6	1.1	1.4	1.7

In Distilled Water

	1 Day		3 Days		6 Days		9 Days		12 Days	
	Sample	Blank	Sample	Blank	Sample	Blank	Sample	Blank	Sample	Blank
Unknown	3.0	4.3	10.0	9.5	1.3	-	3.0	8.0	1.8	1.5
CYCOCEL	29.6	23.6	12.1	3.9	9.9	7.2	13.7	0.8	4.8	30.3
Choline Chloride	66.8	71.3	76.9	85.4	88.0	91.9	82.7	90.2	92.9	67.6
Origin	0.6	0.8	1.0	1.2	0.8	0.9	0.6	1.0	0.6	0.5