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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF PREVENTION,
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Secondary Scientific Review of Product Chemistry and Toxicity Studies of Registration Application for **AG3 LIQUID** Containing 10.30% Mono and Dipotassium Salts of Phosphorous Acid and 0.15% Copper Sulfate (EPA Reg. Symbol 8622-AI)

FROM: Tetrahedron, Inc.

THROUGH: Carol E. Frazer, Ph.D., Toxicologist *Carve*
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511C)

TO: Todd Peterson, Ph.D., RAL
Biochemical Pesticides Branch
Biochemical and Pollution Prevention Branch (7511C)

CONTENTS:

Cover letter, label, product chemistry, toxicity studies and waiver requests (MRID Nos. 460409-01 through -11; DP Barcode D296864).

ACTION REQUESTED:

On July 17, 2003, J. Michael Kelly, Ph.D. of toXcel, Authorized Representative for Ameribrom, Inc., submitted registration of this biochemical fungicide, containing 10.3% mono and dipotassium salts of phosphorous acid and 0.15% copper. To support the registration, the registrant sent in product chemistry comprised of 880.1100-1300; acute oral (870.1100), dermal (870.1200) and inhalation (870.1300) toxicity studies, primary eye (870.2400) and dermal (870.2500) irritation studies and a dermal sensitization (870-2600) study. Also, a Request for a waiver for the non-target organisms (§154-6 through -11). Tetrahedron Inc. reviewed product chemistry and toxicity studies on **AG3 Liquid**, a new agricultural use fungicide for the control of *Pythium* and *Phytophthora* of agronomic crops.

CONCLUSIONS:

The toxicology studies are all ACCEPTABLE and the waivers for the product chemistry physical and chemical characteristics studies, the residue chemistry and the long-term, Tier II and III toxicity studies are granted. The only problems with this submission are listed below and easily correctable.

1. Product chemistry is for the most part acceptable, with only a few corrections needed.
 - a. On the CSF, one of the inerts is not approved for OPP. The registrant must either limit the inert used for that purpose to the alternative proposed, or request approval through the Registration Division. The source of the diluent needs to be more specifically provided, i.e., an address. More details are in the Confidential attachment.
 - b. The physical/chemical characteristics have not been completed. The results of the long-term storage stability study, corrosion characteristics and the dielectric breakdown voltage will be finished at a later date (not provided).
2. The ecotoxicity waiver requests are considered SUPPLEMENTAL as only the mono and dipotassium salts of phosphorous acid were addressed, and in addition, the discussion only dealt with the human/mammalian toxicity, not the other possible toxic effects of those compounds. The copper component of the product was not dealt with at all.

1a. Revised/amended CSF dated
2/3/04 drops (not yet
approved by Agency)

1b. Storage stability → OK
Corrosion characteristics → OK
dielectric breakdown voltage → OK

TOXICITY PROFILE

Acute oral toxicity	IV	MRID 460409-05
Acute dermal toxicity	IV	MRID 460409-06
Acute inhalation toxicity	IV	MRID 460409-07
Primary eye irritation	III	MRID 460409-08
Primary dermal irritation	IV	MRID 460409-09
Dermal sensitization	No	MRID 460409-10

LABELING: The Signal word is Caution from the Toxicity Rating of III for primary eye irritation.

Study Summaries:

PRODUCT CHEMISTRY OF AG3 LIQUID

Guideline 880.1100: Product identity and disclosure of ingredients (MRID 450319-01, CSF)

AG3 LIQUID contains 3.4% mono- and 6.9% dipotassium salts and 0.15% copper sulfate and 89.55% other ingredients. This product is to be used as a systemic fungicide for the control of *Pythium* Damping-Off and Root Rot, *Phytophthora* Root Rot and Downy Mildew diseases of agronomic crops.

The following table summarizes information submitted by the registrant regarding the active ingredients.

Chemical Names:	phosphonic acid, monopotassium salt phosphonic acid, dipotassium salt copper sulfate
Synonyms:	monopotassium salt of phosphorous acid, potassium dihydrogen phosphite, monopotassium phosphite, monopotassium phosphonate dipotassium salt of phosphorous acid, dipotassium hydrogen phosphite, dipotassium phosphite, dipotassium phosphonate
CAS Registry Nos.:	13977-65-6 13492-26-7
Molecular Formulae:	KH_2PO_3 K_2HPO_3 $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$
Chemical Family:	metallic salts
Source of Biochemical:	manufactured
Mode of Action:	fungicide

The confidential statement of formula needs correction.

BPB's Comment Regarding §880.1100: Data submitted on the product identity of AG3-LIQUID satisfies the requirements of 40 CFR 158.155, guideline §151B-10, 880.1100.

Guideline §880.1200: Manufacturing process (MRID 460409-01)

BPB's Comment Regarding §151B-11: Data submitted on the manufacturing process of AG3-LIQUID satisfy the requirements of 40 CFR 158.160 and 40 CFR.165, guideline §151B-11, 880.1200. No additional data required.

Guideline §880.1400: Discussion on the formation of unintentional ingredients (MRID 460409-01)

BPB's Comment Regarding §880.1400: Data submitted on the formation of unintentional ingredients of AG3-LIQUID satisfy the requirements of 40 CFR 158.167, guideline §151B-12, 880.1400. No additional data required.

Guideline §880.1700: Preliminary Analysis (MRID 460409-01)

BPB's Comment Regarding §880.1700: Data submitted on the preliminary analysis of AG3-LIQUID satisfy requirements of 40 CFR 158.170, guideline §151B-13, 880.1700. No additional data required.

Guideline §880.1750: Certification of ingredient limits (MRID 460409-01)

BPB's Comment Regarding §880.1750: Data submitted on the certification of ingredient limits of AG3-LIQUID do not totally satisfy the requirements of 40 CFR 158.175, guideline §151B-15, 880.1750. The CSF needs correction with one of the other ingredients and an address. See Confidential Attachment.

Guideline §880.1800: Enforcement analytical methods (MRID 460409-01)

BPB's Comment Regarding §880.1800: Data submitted on the enforcement analytical methods for certified limits of AG3-LIQUID satisfy the requirements of 40 CFR 158.180, guideline §151B-16, 880.1800. No additional data required.

Guideline §151B-17: Physical and Chemical Characteristics (MRID 460409-02)

The registrant submitted information on the physical and chemical characteristics of AG3-LIQUID which are summarized below:

STUDY TYPE	CHARACTERISTIC	GUIDELINE NUMBER
Color	Aqua blue @ 20°C	830.6302
Physical state	Transparent liquid @ 20°C	830.6303
Odor	Odorless @ 20°C	830.6304

Oxidation/reduction, chemical incompatibility	<p>Compatible with:</p> <ul style="list-style-type: none"> • water • 10% monoammonium phosphate solution • zinc granules and kerosene <p>Incompatible with:</p> <ul style="list-style-type: none"> • 10% potassium permanganate solution 	830.6314
Flammability/Flame extension	Waiver request	830.6315
Explosibility	Waiver request	830.6316
Storage stability	<p>Two-year storage stability study to be conducted @ 25 ± 2°C:</p> <p>6-mo. interim results: % PO₃ went from 5.86 to 5.87%, color went from light blue transparent liquid with some suspended particles to aqua blue transparent liquid with some suspended particles, Munsell Color maintained at 10BG 8/4, odor maintained as odorless, and 0.126% weight loss</p>	830.6317
Miscibility	Not applicable	830.6319
Corrosion characteristics	<p>To be conducted in conjunction with 2-yr storage stability study @ 25 ± 2°C:</p> <p>6-mo. interim results: no signs of corrosion or degradation</p>	830.6320
Dielectric breakdown voltage	To be conducted in conjunction with 2-yr storage stability study	830.6321
pH	6.56 @ 25°C	830.7000

Viscosity	1.36 mm ² /s @ 20°C 0.884 mm ² /s @ 40°C	830.7100
Melting point	Not required	830.7200
Boiling point	Not required	830.7220
Specific gravity Pounds/gal or Bulk density	1.11 @ 20°C	830.7300
Dissociation constant	Not required	830.7370
Water solubility	Not required	830.7840
Vapor pressure	Not required	830.7950
Persistent foaming	Foam disappeared at the maximum (0.2% active ingredient) or minimum (0.025% active ingredient) field application concentrations within 3 minutes (CIPAC method MT 47.2)	
Low temperature stability	Physically stable to storage at 0 ± 1.0°C for 48 hours (length of trial, CIPAC method MT 39.2)	
Surface tension	72.2 mN/m (1.02 g/l solution) @ 21.0 ± 0.5°C (ISO 304, method A5 of 92/69/EEC). Not considered to be a surface-active material.	

BPB's Comment: Information submitted on chemical and physical characteristics is incomplete. Results of long-term storage stability study the corrosion characteristics and the dielectric breakdown voltage will not be complete until later. The submission thus does not meet the requirements of 40 CFR 158.690.

PRODUCT TOXICOLOGY FOR AG3 LIQUID

Guideline 870.1100: Acute oral toxicity study in the female rat (MRID 460409-05)

The LD₅₀ of AG3 LIQUID is >5,000 in an up-and-down study in nine female rats. One death at the highest dose within 2 hours. Piloerection, hunched posture, lethargy and decreased respiratory rate were seen in that animal. Two other females demonstrated the abnormal posture, and one of those also had piloerection, but they didn't start demonstrating that until the time the first one died, and they recovered. The dead animal was the only one with abnormal necropsy findings, hemorrhaging in the lungs and dark kidneys and liver. Weight gain and necropsy findings normal in the surviving animals. Classification: Acceptable; Toxicity Category IV.

Guideline 870.1200: Acute dermal toxicity (limit test) study in the rat (MRID 460409-06)

A single limit dose of AG3 LIQUID tested in male and female rats (5/sex). The LD₅₀ > 5,000 mg/kg. No deaths, overt toxicity or dermal irritation observed. Weight gain and all animal necropsies normal. Classification: Acceptable; Toxicity Category IV.

Guideline 870.1300: Acute inhalation toxicity study (nose only) in the rat (MRID 460409-07)

No deaths observed at the maximum achievable LC₅₀ of this product for rats (5/sex) of >6.00 mg/L, MMAD 3.29 μM, GSD of 2.04, and 60.8 % of particles were below 4 μM. Minor clinical signs, altered respiratory rate in all animals, piloerection, hunched posture – cleared by day 1. Necropsy and weight gain in animals normal. Classification: Acceptable; Toxicity Category IV

Guideline 870.2400: Acute eye irritation study in the male rabbit (MRID 460409-08)

Single (0.1 ml) dose of AG3 LIQUID applied to 3 male rabbits' eyes. This substance is a minor irritant to rabbit eyes, causing grade 1 conjunctivitis in all animals at the first reading, and, continuing on in 1 animal until 24 hours. All eyes clear by 48 hours. Classification: Acceptable; Toxicity Category III.

Guideline 870.2500: Acute dermal irritation study in the male rabbit (MRID 460409-09)

Single (0.5 ml) dose of AG3 LIQUID applied to skin of 3 male rabbits. This substance is not irritating, demonstrating no erythema or edema. Classification: Acceptable; Toxicity Category IV.

Guideline 870.2600: Magnusson & Kligman maximization study in the guinea pig (MRID 460409-10)

Ten treated (5% injected, undiluted topical) and five naive control males tested for sensitization with AG3 LIQUID and, six months previously, an equal number tested with a

positive control (mercaptobenzothiazole). No response to challenge (75%) in the tested animals, but positive control acceptable. Classification: Acceptable; Toxicity Category Non-sensitizer.

BPB's Comment: Data submitted on the product toxicology of **AG3 LIQUID** satisfies the requirements of 40 CFR 158.690.