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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 06, 2011

SUBJECT: Registration of AXXE (EPA Reg. #: 70299-EN) Containing 61.1% of Pelargonic Acid as Active Ingredient; Review of Product Chemistry, CSFs, and Waiver Requests for Toxicology and Non-Target Organism

Decision Number: 443903
DP Number: 385722
EPA Reg. #: 70299-EN
Chemical Class: Biochemical
PC Code: 217500
Active Ingredient Tolerance Exemption: 40 CFR 180.
MRID Number: 48342301 through 48342302

FROM: Manying Xue, Chemist
BPB/BPPD (7511P)

TO: John Fournier, Regulatory Action Leader
BPB/BPPD (7511P)

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

Action Requested:

BioSafe Systems LLC has submitted an application for a new product registration for AXXE (EPA Reg. #: 70299-EN) containing 61.1% of pelargonic acid as active ingredient. The technical grade active ingredient (TGAI) Pelargonic acid for this EP product is unregistered. AXXE is similar to the registered product — Scythe (EPA Reg. No. 62719-529).

In support of this registration, the registrant has submitted the label, basic Confidential Statements of Formula (CSF), dated 01/03/2011, product chemistry for the TGAI of pelargonic acid and the EP, AXXE (MRIDs: 48342201 and 48342302). In addition, the registrant has also submitted waiver requests for toxicity and non-target organism.

BPPD has reviewed and evaluated the submissions for this registration. The decisions are made to reflect the current OPP policies.

RECOMMENDATIONS AND CONCLUSIONS:

1. The submitted product chemistry studies for the TGAI, pelargonic acid and the EP, AXXE are **ACCEPTABLE.**

2. The submitted waiver requests for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, primary dermal irritation, dermal sensitization, 90-day oral toxicity, 90-day dermal toxicity, 90-day inhalation toxicity, teratogenicity, genotoxicity, biochemical pesticide test guidelines, immunotoxicity, and hypersensitivity incidents are **ACCEPTALE** for the EP, AXXE (EPA Reg. #: 70299-EN).

3. The submitted waiver requests for ecological effects test guidelines, avian acute oral toxicity, avian dietary toxicity, fish acute toxicity, aquatic invertebrate toxicity, terrestrial plant toxicity, seedling emergence, terrestrial plant toxicity, vegetative vigor and non-target insect testing are **ACCEPTALE** for the EP, AXXE (EPA Reg. #: 70299-EN).

STUDY SUMMARIES

Directions for Use (OPPTS 860.1200)

Product Properties (OPPTS 830 Series GLNs)

The registrant has submitted the label, basic Confidential Statements of Formula (CSFs), dated 01/14/2011 (Table 1) for the EP, AXXE (EPA Reg. #: 70299-EN) and product chemistry (MRIDs: 48337301 and 48337302).

Table 1 lists the nominal concentrations and certified limits for the ingredients in the technical product, AXXE (EPA Reg. #: 70299-EN), respectively.

TABLE 1. Nominal CSF concentrations and limits for the EP, AXXE [a]

Ingredients (CAS number)	PC Code/ 40CFR	Purpose	Concentration (% by weight)		
			Nominal	Upper	lower
Active Ingredient					
Pelargonic Acid (94% technical grade) CAS 112-05-0 [redacted] Contains: Pelargonic acid; CAS 112-05-0	217500	AI	65.00 (61.10) 94.00	66.9 (66.95) 96.82	63.05 (63.05) 91.18
[redacted]					
[redacted]					
Total:			100		

[a] Data from CSF, dated 01/03/11.

Physical and Chemical Characteristics

The product chemistry data base for the TGAI of pelargonic acid and the EP, AXXE (EPA Reg. #: 70299-EN) are essentially complete (MRID 48342301). There are no reported impurities of toxicological concern. The Series 830 physical and chemical properties are given in Table 2.

TABLE 2. Physical and Chemical Properties for the TGAI, Pelargonic Acid & the EP, AXXE

Guideline Reference No.	Property	Description of Result	Methods
830.6302	Color	TGAI: Light yellow EP: Not required	
830.6303	Physical State	TGAI: Liquid EP: Liquid	
830.6304	Odor	TGAI: Pronounced individual odor EP: Not required	Merck Index 11 Edition, 1998
830.6313	Stability	TGAI: Stable at normal condition. Avoid heating. Keep away from source of ignition and naked flames EP: Not required	
830.6314	Oxidation/Reduction: Chemical Incompatibility	NA[1]	
830.6315	Flammability	TGAI: Not required for TGAI EP: NA	
830.6316	Explodability	NA	
830.6317	Storage Stability	TGAI: Not required for TGAI EP: Stable for up to 1year when stored in commercial packing at room temperature.	
830.6319	Miscibility	TGAI: Not required for TGAI EP: NA	
830.6320	Corrosion Characteristics	TGAI: Not required for TGAI EP: Not corrosive to packaging for up to one year when stored in commercial packaging at room temperature.	
830.7000	pH	TGAI: 3.8 in water EP: 2.0-3.0	
830.7050	UV/Visible	TGAI: NA EP: Not required	
830.7100	Viscosity	TGAI: Not required EP:50 cps @4°C	ASTM D 445
830.7200	Melting Range	TGAI: 11°C EP: Not required	
830.7220	Boiling Range	TGAI: 230-237°C EP: Not required	Merck Index 11 Edition, 1998
830.7300	Bulk Density	TGAI: 0.904 g/rn3 EP: 7.756 lbs/gal	ASTM D 4052
830.7520	Particle Size	TGAI: NA EP: Not required	

830.7550	Partition Coefficient	TGAI: EP: Not required	
830.7840	Water Solubility	TGAI: Slight insoluble in water EP: Not required	
830.7950	Vapor Pressure	TGAI: $1.6x10^{-3}$ mmHg EP: Not required	

[1] NA: Not applicable.

Preliminary analysis

Five separate batches for the analysis of pelargonic acid in AXXE were conducted using GCMS. The percentage recoveries were 66%, 92%, 13%, 18% and 12%, respectively. The average recovery was 40.2%.

Description of manufacturing process

Description of manufacturing process for the TGAI, pelargonic acid was not provided. However, MSDSs are provided for the starting materials.

Discussion of formation of impurities

Formation of major impurities was discussed (MRID 48343201). The technical grade active ingredient pelargonic acid contains the impurities [redacted] and [redacted] [redacted] [redacted] used in the manufacturing process of the technical.

Manufacturing Process (AI)

Manufactory process has described in this study (MRID 48342301). Pelargonic Acid is linear nonanoic acid. [redacted]

Production and Formulation Process

[redacted]

[redacted]

Waiver Requests for Studies of Toxicity

The registrant has submitted waiver requests for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, primary dermal irritation, dermal sensitization, 90-day oral toxicity, 90-day dermal toxicity, 90-day inhalation toxicity, teratogenicity, genotoxicity, biochemical pesticide test guidelines, immunotoxicity, and hypersensitivity incidents. The rationales are as follows:

Rationale:

The acute toxicity of pelargonic acid has been characterized, and EPA has classified it as a category IV for acute oral toxicity (FR 62, 1997; MRID #43843501 Shutoh, 1993). The reported LD_{50} for oral toxicity is greater than 5,000 mg/kg body weight. The fact that AXXE contains approximately 60% a.i. suggests that the product will be of lower acute oral toxicity than the technical a.i. and the appropriate category **for oral toxicity is category IV.**

The acute toxicity of pelargonic acid has been characterized, and EPA has classified it as **a category III for acute inhalation toxicity** (FR 62, 1997; MRID #43843503 Holbert, 1993). The pelargonic acid LC_{50} in rats is reported to be between 0.46 and 3.8 mg/L (mean gravimetric exposure concentration). Eight of ten rats died from a four-hour exposure to 3.8 mg/L and there were no mortalities at 0.46 mg/L (summarized in NLM, HSDB, accessed 2/2010).

The acute toxicity of pelargonic acid has been characterized, and EPA hasclassified it as a category III for acute dermal toxicity (FR 62, 1997; MRID #43843502 Shutoh, 1993). The reported LD_{50} for dermal exposure is greaterthan 2,000 mg/kg body weight. The fact that AXXE contains approximately 60%a.i. suggests that the product will be of equal or lower acute oral toxicity than the technical a.i. and the appropriate category supported by data **for dermal toxicity** is **category III**.

The primary eye irritation potential of pelargonic acid has been characterized, and EPA has classified it as **a category II for eye irritation** (FR 62, 1997; MRID 43843504,

Glaza, 1993). The approval of all inert ingredients in AXXE for use on food indicates the inert ingredients are of low irritation potential. The inert ingredients in AXXE are: [redacted], and [redacted]. None of these inert ingredients is expected to alter the irritation potential of pelargonic acid following ocular exposure.

The primary dermal irritation potential of pelargonic acid has been characterized, and EPA has classified it as a **category II for dermal irritation** (FR 62, 1997; MRID# 43843505, Glaza, 1993). The approval of all inert ingredients in AXXE for use on food indicates the inert ingredients are of low irritation potential. The inert ingredients in AXXE are: [redacted] and [redacted]. None of these inert ingredients is expected to alter the irritation potential of pelargonic acid following dermal exposure.

The dermal Sensitization potential of pelargonic acid has been characterized, and EPA has determined that **pelargonic acid is not a sensitizer** (FR 62, 1997; MRID# 43843506, Glaza, 1993). The approval of all inert ingredients in AXXE for use on food indicates the inert ingredients are not sensitizing agents. The inert ingredients in AXXE are: [redacted] and [redacted]. None of these inert ingredients is expected to alter the Sensitization potential of pelargonic acid.

Sufficient data are available to fulfill the requirement of a 90-day oral toxicity study. A 14-day range-finding oral toxicity study in rats (MRID No. 43843507Kulin, 1995) showed no systemic toxicity in either sex at the highest dose tested, 20,000 ppm (1,834 mg/kg/day). There were no adverse effects of exposure on survival, clinical signs, body weight gain, food consumption, hematology, clinical chemistry or gross pathology.

A chronic dermal toxicity study was performed in mice (MRID No. 43961801, Barkley, 1985). This chronic toxicity/carcinogenicity study evaluated the effects of repeated dermal application of 50 mg pelargonic acid per mouse twice a week for 80 weeks. No treatment-related clinical signs of toxicity were observed. Average body weights of treated and untreated control mice were similar. Histopathology revealed no treatment-related lesions either of the skin or the internal organs.

There is a low likelihood of significant levels of repeated inhalation exposure to pelargonic acid as a gas, vapor, or aerosol based on the proposed uses of AXXE. In accordance with 40 CFR 2050, footnote 8, the lack of potential for repeated inhalation exposure indicates that a 90-day inhalation study is not necessary.

Data are available that demonstrate that pelargonic acid is not a developmental toxicant (FR 62, 1997; MRID # 43843508 Wakefield, 1994). Pregnant female rats (22/group) were dosed by gavage with pelargonic acid at 0 or 1500 mg/kg/day during days 6 to 15 of gestation. On gestation day 20, dams were sacrificed and one-third of the fetuses were examined for visceral abnormalities and two-thirds were subjected to skeletal examination. There were no effects on mortality, clinical signs, body weight, food consumption, or gross pathology. No effects were seen on mean litter size, pregnancy rates, corpora lutae, implantation sites, fetal viability, fetal weight, sex, gross pathology or visceral and skeletal examination. The NOAEL for maternal and developmental toxicity =1500 mg/kg/day, and the LOAEL > 1500 mg/kg/day.

Data are available to show that pelargonic acid is not mutagenic in the Ames assay (FR 62, 1997, MRID # 43603703 Lawlor). There was no evidence that pelargonic acid was mutagenic in Salmonella typhimurium with or without metabolic activation. In a mouse lymphoma forward mutation assay, pelargonic acid induced an apparent weak mutagenic response at levels greater than or equal to 50 g/ml in mouse TK +/- lymphoma cells in the presence of S9 metabolic activation (MRID # 43603701 Cifone, 1993). This event occurred in the presence of increasing toxicity and is thought to indicate gross chromosomal changes or damage rather than mutational changes within the TK gene locus.

According to 40 CFR 2050, footnote 13, the micronucleus rodent bone marrow assay is acceptable as an immumotoxicity assay. An in-vivo mousemicronucleus assay was conducted using pelargonic acid (MRID # 43603702 Murli, 1993). In this study, groups of ICR mice (15/sex/dose) received single oral doses of 1,250, 2,500, or 5,000 mg/kg pelargonic acid. The bone marrow cells were harvested 24, 48, and 72 hours after dosing. No significant increases in the frequency of micronucleated polychromatic erythrocytes were observed in either sex at any dose; thus, pelargonic acid was negative in the micronucleus assay.

Conclusions:

The submitted waiver requests for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, primary dermal irritation, dermal sensitization, 90-day oral toxicity, 90-day dermal toxicity, 90-day inhalation toxicity, teratogenicity, genotoxicity, biochemical pesticide test guidelines, immunotoxicity, and hypersensitivity incidents are **ACCEPTALE** for the EP, AXXE.

Waiver Requests for Toxicity and Non-Target Organisms

Rationales:

The registrant has also submitted waiver requests for ecological effects test guidelines, avian acute oral toxicity, avian dietary toxicity, fish acute toxicity, aquatic invertebrate toxicity, terrestrial plant toxicity, seedling emergence, terrestrial plant toxicity, vegetative vigor and non-target insect testing. The rationales are as follows:

An avian acute toxicity study was performed on the Northern Bobwhite Quail (US EPA ECOTOX, accessed 2/2010). According to the ECOTOX summary that referenced an EPA OPP database, birds were observed for fourteen days after exposure to pelargonic acid via gavage. The resulting LD_{50} was greater than2250 mg/kg body weight.

Avian dietary toxicity studies were performed on the Northern Bobwhite Quail and the Mallard duck (US EPA ECOTOX, accessed 2/2010). According to the ECOTOX summary that referenced an EPA OPP database, birds were exposed to pelargonic acid in the diet for 8-days. The dietary LC_{50} concentration of pelargonic acid was greater than 5620 ppm for both species of birds.

Data are available to describe the potential effects of pelargonic acid on freshwater fish (NLM, HSDB, accessed 2/2010). According to the summary that referenced an EPA OPP

database, an LC_{50} study on bluegill sunfish was conducted that exposed the fish for 96 hours to static concentrations of 99.7% pure pelargonic acid. The LC50 appears to be 105 mg/L.

A second study is available to evaluate the LC_{50} of pelargonic acid in Rainbow trout. Rainbow trout (Oncorhynchus mykiss) were exposed to static pelargonic acid (99.7% purity) in freshwater under static conditions for 96 hours. The LC_{50} concentration appears to have been 91000 ug/L (68000-121000 ug/L).

Data are available to describe the potential effects of pelargonic acid on freshwater aquatic invertebrates (NLM HSDB, accessed 2/2010). Daphnia magna less than 24 hours old were evaluated for adverse effects in a laboratory study. The study was a static design using a concentration of 96000 ug/L for 48 hours. The EC_{50} for immobilization was reported at this concentration.

The active ingredient (a.i.) in AXXE is pelargonic acid. AXXE works on contact to control weeds and may be used as a harvest aid to remove leaves of crops prior to harvest. The product label language is intended enable applicators to minimize exposure to nontarget plants.

Data are available to describe the potential effects of pelargonic acid on Honey bees (NLM HSDB, accessed 2/2010). Honey bees were exposed to pelargonic acid topically for 2 days and an LD_{50} was determined. The Honey bee contact LD_{50} of pelargonic acid was > 25 pig/bee.

Conclusions:

The submitted waiver requests for ecological effects test guidelines, avian acute oral toxicity, avian dietary toxicity, fish acute toxicity, aquatic invertebrate toxicity, terrestrial plant toxicity, seedling emergence, terrestrial plant toxicity, vegetative vigor and non-target insect testing are **ACCEPTALE** for the EP, AXXE.

Cc: J. Fournier; BPPD Chron File; OHAD/ARS
M. Xue, BPPD, 09/06/11