Case No. _____

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

MIGRANT CLINICIANS NETWORK, BEYOND PESTICIDES, CENTER FOR BIOLOGICAL DIVERSITY, ENVIRONMENTAL CONFEDERATION OF SOUTHWEST FLORIDA, FARMWORKER ASSOCIATION OF FLORIDA, FARMWORKER JUSTICE, NATURAL RESOURCES DEFENSE COUNCIL, INC., AND UNITED STATES PUBLIC INTEREST RESEARCH GROUP

Petitioners,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AND MICHAEL S. REGAN, in his official capacity as Administrator of the United States Environmental Protection Agency,

Respondents.

PETITION FOR REVIEW
of a final order of the U.S. Environmental Protection Agency

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Counsel for Petitioner U.S. Public Interest Research Group

Dated: March 25, 2021

PETITION FOR REVIEW

Pursuant to Rule 15(a) of the Federal Rules of Appellate Procedure and section 16(b) of the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. § 136n(b), Petitioners Migrant Clinicians Network, Beyond Pesticides, Center for Biological Diversity, Environmental Confederation of Southwest Florida, Farmworker Association of Florida, Farmworker Justice, Natural Resources Defense Council, and United States Public Interest Research Group petition this Court to review and set aside the final order of the U.S. Environmental Protection Agency (EPA) granting unconditional registration of the new use of the active ingredient streptomycin sulfate on citrus crop group 10-10 for a period of seven years.

Petitioners respectfully petition this Court to find that EPA's approval of streptomycin as a pesticide on citrus violated the Federal Insecticide, Fungicide, and Rodenticide Act because the Agency failed to ensure that the use of streptomycin would not cause unreasonable harm to human health or the environment. 7 U.S.C. §§ 136a(c)(5)(C), (D), 136(bb). Petitioners further request that this Court find that EPA violated the

Endangered Species Act by failing to consult with the U.S. Fish and Wildlife Service or the National Marine Fisheries Service to insure EPA's action will not jeopardize any listed species or destroy or adversely modify any of their critical habitats. 16 U.S.C. § 1536(a)(2); 50 C.F.R. § 402.14(a).

The challenged order was finalized in two regulatory decision documents signed on January 12, 2021, and entered on EPA docket EPA-HQ-OPP-2016-0067, after public notice and comment. Pursuant to 40 C.F.R. § 23.6, the order became final for the purpose of this Court's jurisdiction on January 26, 2021, at 1:00 p.m. eastern time. The final regulatory decision documents are attached as Exhibit A to this petition; the accompanying document announcing EPA's decision is also attached as Exhibit B.

Dated: March 25, 2021

Respectfully submitted,

s/ Hannah Connor
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Counsel for Petitioner U.S. Public Interest Research Group

CERTIFICATE OF SERVICE

I hereby certify that I caused the foregoing Petition for Review, the exhibits thereto, and the accompanying Corporate Disclosure Statement to be served by certified mail on respondents at the following addresses:

Michael S. Regan, Administrator
Office of the Administrator, Mail Code 1101A
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Correspondence Control Unit
Office of General Counsel, Mail Code 2311
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

I also certify that I caused the listed documents to be served by certified mail on counsel for respondents at the address below:

Merrick Garland, U.S. Attorney General
Office of the U.S. Attorney General
U.S. Department of Justice
950 Pennsylvania Avenue NW
Washington, DC 20530

Dated: March 25, 2021

s/ Margaret T. Hsieh
Margaret T. Hsieh

Exhibit A

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

January 12, 2021

Rob Jones
Agent for Agrosource, Inc.
c/o Delta Analytical Corporation
12510 Prosperity Drive, Suite 160
Silver Spring, MD 20904

Subject: PRIA Label Amendment – Streptomycin Sulfate – New Time-Limited Use on Citrus Crop Group 10-10 expiring January 12, 2028; supplemental label for citrus
Product Name: AGRI-SEED™ 50 WP
EPA Registration Number: 80990-3
Application Date: 11/30/2015
Decision Number: 512076

Dear Rob Jones:

The application referred to above, submitted under the Federal Insecticide, Fungicide and Rodenticide Act, as amended is acceptable under FIFRA sec 3(c)(5) for a limited period of time. The new uses being granted in this amendment will automatically expire 01/12/2028. The following terms apply:

1) Resistance Management Plan implementation (education/training and stewardship plan). A yearly summary report describing the Resistance Management Plan implementation details must be submitted to the Registration Division by December 31st of each year for confirmatory purposes.
2) Annual sales reports listed by state, submitted by Agrosource, Inc. to the Registration Division by December 31st of each year
3) Monitoring requirement
   a. You must submit protocol submissions describing how you plan to monitor both soil and citrus foliage for incidences of antibiotic resistance on a yearly basis for 3 years of this new use amendment on Citrus Crop Group 10-10. The protocol submission to the Registration Division must be made 3 months prior to each use season to allow for Agency review prior to start of monitoring. The first protocol submission will be made by January 31, 2021, which due to the timing of the registration is less than three months prior to the use season.

   b. Annual monitoring report submissions by December 31st of each year starting in 2021.

4) One year prior to expiration, if you choose to seek an extension or remove the time limitation for the Citrus Crop Group 10-10 use, you are required to submit an application for amendment along with a revised assessment on the development of streptomycin sulfate resistance in human pathogens addressing release, exposure, consequence assessments and overall risk estimation regarding public health effects resulting from cumulative usage of streptomycin sulfate on all citrus crops in all states where it is registered and used. The Agency will consult with the federal partners to reevaluate the current risk picture for streptomycin sulfate prior to extending or removing the time limitation on citrus or allowing the use to expire.

5) If the Agency determines it will not be able to grant an extension or remove the time limitation, the Agency will notify you by 2 months prior to the use expiring. Upon notification, you must submit revised labeling with the Citrus Crop Group 10-10 use removed by 1 month prior to expiration.

6) You must submit and/or cite all data required for registration/reregistration/registration review of your product when the Agency requires all registrants of similar products to submit such data.

A stamped copy of your labeling is enclosed for your records. This labeling supersedes all previously accepted labeling. You must submit one (1) copy of the final printed labeling before you release the product for shipment with the new labeling. In accordance with 40 CFR 152.130(c), you may distribute or sell this product under the previously approved labeling for 18 months from the date of this letter. After 18 months, you may only distribute or sell this product if it bears this new revised labeling or subsequently approved labeling. "To distribute or sell" is defined under FIFRA section 2(gg) and its implementing regulation at 40 CFR 152.3.

Should you wish to add/retain a reference to the company's website on your label, then please be aware that the website becomes labeling under the Federal Insecticide Fungicide and Rodenticide Act and is subject to review by the Agency. If the website is false or misleading, the product would be misbranded and unlawful to sell or distribute under FIFRA section 12(a)(1)(E). 40 CFR 156.10(a)(5) list examples of statements EPA may consider false or misleading. In addition, regardless of whether a website is referenced on your product's label, claims made on the website may not substantially differ from those claims approved through the registration process. Therefore, should the Agency find or if it is brought to our attention that a website contains false or misleading statements or claims substantially differing from the EPA approved registration, the website will be referred to the EPA's Office of Enforcement and Compliance.

Your release for shipment of the product constitutes acceptance of these terms. If you have any questions, please contact Heather A. Garvie by phone at 703-308-0034, or via email at garvie.heather@epa.gov.

Sincerely,

Cynthia Giles-Parker, Chief
Fungicide Branch
Registration Division (7505P)
Office of Pesticide Programs

Enclosure -stamped label

AGRI-SEED™ 50 WP

Fungicide/Bactericide Agricultural Streptomycin

For control or suppression of:

- Fire Blight for apples and pears
- Huanglongbing ("HLB", "citrus greening", "greening") and citrus canker in the citrus crop group
- Other bacterial diseases in beans, celery, pepper, potatoes, tobacco, tomatoes, and selected ornamentals

STREPTOMYCIN	GROUP	25	FUNGICIDE

Note to EPA: This product will also be marketed as FireWall™ 50 WP for use on listed vegetable crops, tree fruit, ornamentals, and row crops.

Active Ingredient:	
Streptomycin Sulfate*	65.80%
Other Ingredients	34.20%
TOTAL	100.00%

*Equivalent to 50% streptomycin

KEEP OUT OF REACH OF CHILDREN

CAUTION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

See Side/Back Panel for Additional Precautionary Statements, First Aid and Directions for Use

EPA Reg. No. 80990-3
EPA Est. No. XXXXX-XX-X

AgroSource, Inc.
P.O. Box 3091
Tequesta, Florida 33469

NOTICE: Read the entire Directions for Use and Conditions for Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product within 90 days, unopened and undamaged, and the purchase price will be refunded.

NET CONTENTS: XXXXXXX

FIRST AID	
If On Skin or Clothing:	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If Inhaled:	• Move person to fresh air • If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for further treatment advice.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact InfoTrac at 1-800-535-5053 for emergency medical treatment information.	

PRECAUTIONARY STATEMENTS

Hazards to Humans & Domestic Animals

CAUTION: Avoid contact with skin, eyes, or clothing. Harmful if absorbed through skin. Causes moderate eye irritation. Do not breathe dust or spray mist. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. This material is not to be used for medical, veterinary, or human purposes.

Personal Protective Equipment (PPE):

All applicators and other handlers must wear a minimum of:

- Protective eyewear (goggles, safety glasses or face shield);
- Coveralls over short-sleeved shirt and short pants;
- Chemical-resistant gloves;
- Socks and shoes; and
- NIOSH approved particulate filtering facepiece respirator with any N, R, P filter (TC-84A);

OR an elastomeric NIOSH approved particulate respirator with any N, R or P filter (TC-84A); OR a NIOSH approved powered air purifying respirator with an HE filter (TC-21C). Higher level respirators that are NIOSH approved for particulates that contain oil may also be used.

Applicators must also wear:

- Chemical-resistant headgear ensuring full coverage of the neck

Applicators do not have to wear the protective eyewear, chemical-resistant gloves, chemical-resistant headgear, or a respirator when using closed cab systems that meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.607(e)].

When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.607(d) and (e)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables are available, use detergent and hot water. Keep and wash PPE separately from other laundry.
Applicators do not have to wear the protective eyewear, chemical-resistant gloves, chemical-resistant headgear, or a respirator when using closed cab systems that meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.607(e)].

When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.607(d) and (e)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables are available, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations:
Users should:
- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS

This product may be hazardous to aquatic plants. Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water by cleaning of equipment or disposal of wastes.

Attention: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

USE PARAMETERS AND APPLICATION RESTRICTIONS

To Reduce Potential for Selection of Bacterial Resistance:
AGRI-SEED™ 50 WP fungicide/bactericide contains a Group 25 fungicide/bactericide. Fungal isolates/bacterial strains with acquired resistance to Group 25 may eventually dominate the fungal/bacterial population if Group 25 fungicides/bactericides are used repeatedly in the same field or in successive years as the primary method of control for targeted species. This may result in partial or total loss of control of those species by **AGRI-SEED ™ 50 WP** fungicide/bactericide or other Group 25 products.
To delay antibiotic/fungicide/bactericide resistance, take one or more of the following steps:
- Use only the specified and full-strength application rates.
- The streptomycin pesticidal mode of action is inhibition of protein synthesis. This product should be used to treat or prevent infection that are proven or strongly suspected to be caused by the indicated target bacteria. To reduce the likelihood of

bacteria developing resistance to streptomycin, follow the crop specific resistance management and use direction information present on this labeling. Use of this product should conform to resistance management practices/strategies established for the crop and use area (for example, the use of IPM, disease forecasting models, resistance crop varieties, etc.) Consult your local extension/crop consultant or State agricultural authority if reduced efficacy is suspected.

- Adopt an integrated disease management program that includes scouting, uses historical information related to pesticide use, and crop rotation, and which considers host plant resistance, impact of environmental conditions on disease development, disease thresholds, as well as cultural, biological and other chemical control practices.
- Where possible, make use of predictive disease models to effectively time applications.
- Avoid the consecutive use of Agri-Seed 50 WP Fungicide/Bactericide Agricultural Streptomycin or other target site of action Group 25 products that have a similar target site of action, on the same pathogens.
- Use tank-mixtures or premixes with products from different target site of action Groups as long as the involved products are all registered for the same use and are both effective at the tank mix or prepack rate on the pathogen(s) of concern. Do not use any 19 product that has a prohibition on tank mixing and follow the more restrictive use directions.
- When feasible, Agri-Seed 50 WP Fungicide/Bactericide Agricultural Streptomycin should be alternated with a comparable bactericide with a different mode of action.
- Base use on a comprehensive IPM program.
- Monitor treated bacterial/fungal populations for loss of field efficacy.
- Contact your local extension specialist, certified crop advisors, and/or manufacturer for fungicide/bactericide resistance management and/or IPM recommendations for specific crops and resistant pathogens.
- For further information or to report suspected resistance contact AgroSource, Inc. at 908-931-9001.
- Do not apply more than two consecutive applications before alternating with another fungicide/bactericide of a different mode of action.
- Do not apply streptomycin in orchards in which the soil has been fertilized with animal waste/manure or human biosolids.
- Animal Grazing in treated areas is prohibited. The public must be notified by posting restriction signs along the perimeter of the treatment area.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other fungicide/bactericide products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria or fungi.
- Not to be used for medical, veterinary, or human purposes.
- Not for residential use.
- Do not apply this product through any type of irrigation system, including chemigation.
- Do not apply this product by aerial application.
- Spray Drift Precaution - ALL uses - to help reduce off-target drift, direct spray into the canopy, and turn off outward pointing nozzles at row ends and when spraying outer rows.

DIRECTIONS FOR USE

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

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

This product contains the antibiotic streptomycin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other antibacterial products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

AGRICULTURAL USE REQUIREMENTS

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE) and restricted entry interval. The requirements in this box apply to uses that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted-entry Interval (REI) of 12 hours. Exception: Once seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface.

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil or water, wear:

- Coveralls over long-sleeved shirt and long pants
- Chemical-resistant gloves made of a waterproof material
- Shoes plus socks
- Protective eyewear

Seed Treatment Use – Control of Halo Blight in Beans *(Pseudomonas syringae pv. phaseolicola)*

MIXING INSTRUCTIONS				
Concentration Desired	**Quantity AGRI-SEED™ 50 WP Per Volume of Water**			
	1 pt.	**1 qt.**	**1 gal.**	**5 gals.**
1%	0.3 oz. (9.5g)	0.6 oz. (19.0 g)	2 2/3 oz.	13 1/3 oz.
2%	0.6 oz. (19.0 g)	1 1/3 oz. (38.0 g)	5 1/3 oz.	26 2/3 oz.
5%	1.5 oz. (47.5 g)	3.0 oz. (90.0 g)	13 1/3 oz.	66 2/3 oz.

The application range of **AGRI-SEED™ 50 WP** for beans is 0.17 to 0.87 oz. / cwt. of seed. For best protection, use the higher specified rate. **AGRI-SEED™ 50 WP** will dissolve in water. Slurry rates will vary with components and treating equipment. Apply using commercial mist, spray, or other application equipment.

Seed Bag Label Requirements: – The Federal Seed Act requires that containers containing treated seeds shall be labeled with the following statements:

-This seed has been treated with a fungicide containing streptomycin sulfate.
-Do not use treated seed for feed, food, or oil purposes.
-Use an EPA-approved dye or colorant that imparts an unnatural color to the seed.

The U.S. Environmental Protection Agency requires the following statements on containers containing streptomycin sulfate treated seed:

-Store treated seed away from food and feedstuffs.
-Do not allow children, pets or livestock to have access to treated seeds.
-Wear long pants, long-sleeved shirt, shoes, socks, chemical resistant gloves, and a NIOSH-approved respirator with an approval prefix TC-84-A when handling treated seed.
-Treated seeds exposed on soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting.
-Dispose of all excess treated seed by burying seed away from bodies of water.
-Do not contaminate bodies of water when disposing of planting equipment wash water.
-Dispose of seed packaging or containers in accordance with local requirements.

After the seeds have been planted, do not enter, or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours. Exception: Once the seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface. Excess treated seed may be used for ethanol production if (1) by-products are not used for livestock feed and (2) no measurable residues of pesticide remain in ethanol by-products that are used in agronomic practice.

Additional information regarding use of **AGRI-SEED™ 50 WP** may be obtained from your local Agricultural Extension Agent or State Experimental Station.

Crop Use Directions (Note to EPA: Uses listed below will be marketed under the Alternate Brand Name of FireWall™ 50 WP).

- **Vegetable Crops**

Crop	Disease (Pathogen)	AGRI-SEED™ 50 WP Application Rate	Use Directions	Restrictions
Celery (Florida area)	Bacterial Blight (*Pseudomonas cichorii*)	1.36 oz. per 25 gal. (0.056 lbs. a.i.) applied to 10,000 ft^2	Seedlings in Greenhouse†: Apply first spray when seedlings are at 2-leaf stage, when first true leaves appear.	Minimum retreatment interval: 4 days. Maximum number of applications per year: 6 Not for Use in California
Peppers	Bacterial Spot (*Xanthomonas campestris* pv *vesicatoria*)	1.36 oz. per 25 gal. (0.056 lbs. a.i.) applied to 10,000 ft^2	Seedlings in Greenhouse†: Apply first spray when seedlings are at 2-leaf stage, when first true leaves appear.	Minimum retreatment interval: 4 days. Maximum number of applications per year: 6 Not for Use in California
Potatoes	• Soft Rot (*Erwinia carotovora* subsp. *atroseptica* Blackleg (*Erwinia carotovora* subsp. *carotovora*)	0.68 oz. per 25 gal. (0.028 lbs. a.i.) drench solution	Pre-Plant: Soak cut seed pieces in solution for several minutes; plant as usual. NOTE: A suitable fungicide (such as Maxim® Potato Seed Protectant or Maxim ® MZ Potato Seed Protectant) should be used as an adjunct to this treatment for the control of fungal diseases associated with potato seed pieces.	Do not retreat seed. Not for Use in California
Tomatoes	• Bacterial Spot (*Xanthomonas campestris* pv *vesicatoria*) • Bacterial speck (*Pseudomonas syringae* pv *tomato*) Bacterial canker (*Clavibacter michiganensis* pv *michiganensis*)	Greenhouse†: 1.36 oz. per 25 gal. (0.056 lbs. a.i.) applied to 10,000 ft^2	Seedlings in Greenhouse†: Apply first spray when seedlings are in the 2-leaf stage, when first true leaves appear.	Minimum retreatment interval: 4 days. Maximum number of applications per year: 6 Not for Use in California

- **Tree Fruit Crops**

Crop	Disease (Pathogen)	AGRI-SEED™ 50 WP Application Rate	Use Directions	Restrictions
Apples	Fire Blight (*Erwinia amylovora*)	8 – 16 oz. (0.34 lbs. – 0.67 lbs. a.i.) per acre per application	Begin spraying trees at 20%-30% bloom, according to risk potential based on fire blight forecasting model and advice from extension and/or professional crop advisor. For control of fire blight after hail/wind damage ("trauma blight"), spray within 24 hours after injury event.	Do not apply within 50 days of harvest. Minimum retreatment interval: 3 days. Maximum number of applications per year: 9 Not for Use in California
Apples (California)	Fire Blight *(Erwinia amylovora*)	9.6 oz. (0.40 lbs. a.i.) per acre per application	Spray trees at full bloom. Apply at petal fall and late secondary bloom according to risk potential based on fire blight forecasting model and advice from extension and/or professional crop advisor. For control of fire blight after hail/wind damage ("trauma blight"), spray within 24 hours after injury event.	Do not apply within 50 days of harvest. Minimum retreatment interval: 5 days. Maximum number of applications per year: 9
Pears	Fire Blight (*Erwinia amylovora*)	8 – 16 oz. (0.34 lbs. – 0.67 lbs. a.i.) per acre per application	Begin spraying trees at 20%-30% bloom according to risk potential based on fire blight forecasting model and advice from extension and/or professional crop advisor. For control of fire blight after hail/wind damage ("trauma blight"), spray within 24 hours after injury event.	Do not apply within 30 days of harvest. Minimum retreatment interval: 3 days. Maximum number of applications per year: 9 Not for Use in California
Pears (California)	Fire Blight (*Erwinia amylovora*)	9.6 oz. (0.40 lbs. a.i.) per acre per application	Spray trees at 10% bloom until all late bloom is over according to risk potential based on fire blight forecasting model and advice from extension and/or professional crop advisor. For control of fire blight after hail/wind damage ("trauma blight"), spray within 24 hours after injury event.	Do not apply within 30 days of harvest. Minimum retreatment interval: 5 days. Maximum number of applications per year: 9

- **Tree Fruit Crops, Continued**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Citrus Fruit (all types and varieties) Australian desert lime; Australian finger-lime; Australian round lime; Brown River finger lime; calamondin; citron; citrus hybrids; grapefruit; Japanese summer grapefruit; kumquat; lemon; lime; Mediterranean mandarin; mount white lime; New Guinea wild lime; orange, sour; orange, sweet; pummelo; Russell River lime; satsuma mandarin; sweet lime; tachibana orange; Tahiti lime; tangelo; tangerine (mandarin); tangor; trifoliate orange; uniq fruit; cultivars, varieties, and/or hybrids of these	Huanglongbing also known as "HLB", "Greening" or "Citrus Greening" disease	11 oz. (0.45 lbs. a.i.) per acre per application	Apply as a foliar spray using sufficient carrier volume to ensure complete coverage. Contact your local AgroSource representative for guidance on the use of adjuvants Make **first** application at initiation of spring flush to suppress HLB titer and disease symptoms. Make a **second** application mid-summer (not less than 21 days after first application). Make a **third** application in late summer to reduce the incidence of HLB-induced fruit drop and to further suppress HLB titer and disease symptoms (not less than 21 days after second application). Young trees: spray to near runoff.	Do not apply within 60 days of harvest. Minimum retreatment interval: 21 days. Maximum number of applications per year: 3 Maximum annual amount that may be applied per acre: 33 oz. (0.45 lbs. a.i)

- **Tree Fruit Crops, Continued**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Citrus Fruit (all types and varieties) Australian desert lime; Australian finger-lime; Australian round lime; Brown River finger lime; calamondin; citron; citrus hybrids; grapefruit; Japanese summer grapefruit; kumquat; lemon; lime; Mediterranean mandarin; mount white lime; New Guinea wild lime; orange, sour; orange, sweet; pummelo; Russell River lime; satsuma mandarin; sweet lime; tachibana orange; Tahiti lime; tangelo; tangerine (mandarin); tangor; trifoliate orange; uniq fruit; cultivars, varieties, and/or hybrids of these	Citrus Canker (*Xanthomonas citri* pv. *citri*)	11 oz. (0.45 lbs. a.i.) per acre per application	Apply as a foliar spray using sufficient carrier volume to ensure complete coverage. Contact your local AgroSource representative for guidance on the use of adjuvants Make **first** application when spring flush is approximately 75% expanded to protect new growth from canker infection. Make a **second** application in summer when weather conditions warrant during periods of high citrus canker risk (not less than 21 days after first application). Make a **third** application in late summer to reduce the incidence of canker-induced fruit drop (not less than 21 days after second application). Young trees: spray to near runoff.	Do not apply within 60 days of harvest. Minimum retreatment interval: 21 days. Maximum number of applications per year: 3 Maximum annual amount that may be applied per acre: 33 oz. (0.45 lbs. a.i)

- **Ornamentals**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Berberis, Carnation, Forsythina, Geranium, Hederea (Ivy), Impatiens, Lonicera (Honeysuckle), Philadelphus, Poinsetta, Rudbeckia (Black-eyed Susan), Salvia, Syringa, Virburnum	Bacterial Leaf Spot, Bacterial Leaf Rot, Bacterial Blight (*Pseudomonas* and *Xanthomonas* spp.)	1.36 oz. per 25 gal. (0.056 lbs. a.i.) in drench solution	Apply at first signs of water-soaked areas on leaf. For curative action, remove all rotted leaves from plant and then spray.	Minimum retreatment interval 4 days. Maximum number of applications per year: 6. Not for Use in California
Chrysanthemums	Bacterial Wilt (*Erwinia chrysanthemi*), Bacterial Blight (*Pseudomonas solanacearum*)	0.34 oz. per 25 gal. (0.014 lbs. a.i.) in drench solution	Soak plant cuttings in solution for 4 hours; plant as usual.	Do not retreat. Not for Use in California
Hydrangea	Bacterial Blight (*Pseudomonas solanacearum*) Bacterial Leaf Spot *(Pseudomonas cichorii*)	0.34 oz. per 25 gal. (0.014 lbs. a.i.) in drench solution	Soak plant cuttings in solution for 4 hours; plant as usual.	Do not retreat. Not for Use in California
Dieffenbachia Cutting	Bacterial Stem Rot (*Erwinia chrysanthemi*, *Erwinia carotovora* pv *carotovora*)	1.36 oz. per 25 gal. (0.056 lbs. a.i.) in drench solution	Soak cuttings in solution for 20 minutes. Plant cuttings in sterilized rooting medium.	Do not retreat. Not for Use in California
		0.68 oz. per 25 gal. (0.028 lbs. a.i.) applied to 5,000 ft^2	Apply as foliar application to check spread of stem rot in stock plants.	Minimum retreatment interval 5 days. Maximum number of applications per year: 6. Not for Use in California
Philodendron	Bacterial Leaf Spot, Bacterial Leaf Rot (*Xanthomonas campestris*), Bacterial Blight (*Pseudomonas* and *Xanthomonas* spp.)	1.36 oz. per 25 gal. (0.056 lbs. a.i.) applied to 10,000 ft^2	Apply as foliar application at first signs of water-soaked areas on leaf. If disease has spread, remove all rotted leaves from plant before spraying.	Minimum retreatment interval: 4 days. Maximum number of applications per year: 6 Not for Use in California
Roses	Crown Gall (*Agrobacterium spp.)*	1.36 oz. per 25 gal. (0.056 lbs. a.i.) in drench solution	Remove infected plant. Cut out gall tissue. Soak the plant root system and cut surfaces of the infected area in solution for 15 minutes. Replant in soil free of the crown gall organism.	Do not retreat. Not for Use in California
		0.34 oz. per 25 gal. (0.014 lbs. a.i.) applied to 3,000 ft^2	Use once as watering solution. Follow with foliar sprays.	Minimum retreatment interval: 7 days. Not for Use in California Maximum number of applications per year: 6.

- **Row Crops**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Tobacco	Wildfire and Blue Mold (*Peronospora tabacina*)	Before plants are set in the field: • For preventative action: 0.68 oz./25 gal. (0.028 lbs. a.i.) applied to 5,000 ft.^{2}	Apply first spray when plants are in the 2-leaf stage or about the size of a dime or when blue mold first appears in the area. Repeat application until plants are set in the field. Additional protection may be obtained by spraying field plants.	Minimum retreatment interval: 5 days. Maximum number of applications per year: 4. Not for Use in California
		• For curative action: 1.36 oz. /25 gal. (0.056 lbs. a.i.) applied to 5,000 ft.^{2}		Minimum retreatment interval: 7 days. Maximum number of applications per year: 6 Not for Use in California
		After plants are set in field: 5.4 oz. (0.22 lbs. a.i.)/A	In locations where wild fire mold has been a problem in recent years or where applications have been delayed until the disease appears, a foliar spray of FireWall™ 50 WP at the rate of 5.4 oz. per 100 gallons is recommended.	Minimum retreatment interval: 7 days. Maximum number of applications per year: 6 Not for Use in California

† Or similar type structure

Additional information regarding use of **AGRI-SEED™ 50 WP** fungicide/bactericide may be obtained from your local Agricultural Extension Agent or State Experimental Station.

Use of **AGRI-SEED™ 50 WP** fungicide/bactericide may cause phytotoxicity to the fruit and/or foliage of sensitive varieties of pears and apples.

STORAGE AND DISPOSAL

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

Storage: Keep tightly closed and sealed. Product is moisture, temperature and light sensitive. Product is hygroscopic so protect from moisture. Store in a cool (<77°F, 25°C), dry place away from heat and open flames with minimum exposure to the atmosphere. Avoid extremes in temperature.

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

Container Handling: Non-refillable Container. Do not reuse or refill this container. Completely empty bag into application equipment. Then offer bag for recycling if available or dispose of in a sanitary landfill, or by incineration, or if allowed by State and local authorities, by burning. If burned, stay out of smoke.

CONDITION OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

The Directions for Use of this product must be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials, resistant strains or other influencing factors in the use of the product, which are beyond the control of AGROSOURCE, INC. or Seller. To the extent consistent with applicable law, all such risks shall be assumed by Buyer and User, and Buyer and User agree to hold AGROSOURCE, INC. and Seller harmless for any claims relating to such factors. AGROSOURCE, INC. warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions.

This warranty does not extend to the use of the product contrary to label instructions, or under conditions not reasonably foreseeable to or beyond the control of Seller or AGROSOURCE, INC., and Buyer and User assume the risk of any such use. AGROSOURCE, INC. MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE. In no event shall AGROSOURCE, INC. or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product.

TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF AGROSOURCE, INC. AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF AGROSOURCE, INC. OR SELLER, THE REPLACEMENT OF THE PRODUCT. AGROSOURCE, INC. and Seller offer this product, and Buyer and User accept it, subject to the foregoing conditions of sale and limitations of warranty and of

liability, which may not be modified except by written agreement signed by a duly authorized representative of AGROSOURCE, INC.

AGRI-SEED and FIREWALL are trademarks of AgroSource, Inc.
Manufactured in the U.S.A. by AgroSource, Inc.

FireWall™ 50 WP Alternate Brand Names (ABN): TITER™ 50 WP

AGRI-SEED™ 50 WP

Fungicide/Bactericide Agricultural Streptomycin

Supplemental Label to add Directions for Use on Citrus Crop Group 10-10
This supplemental label expires on 1/12/2024 and must not be used or distributed after this date.

For control or suppression of:

- Huanglongbing ("HLB", "citrus greening", "greening") and citrus canker in the citrus crop group 10-10

STREPTOMYCIN	GROUP	25	FUNGICIDE

Note to EPA: This product will also be marketed as FireWall™ 50 WP for use on listed vegetable crops, tree fruit, ornamentals, and row crops.

Active Ingredient:	
Streptomycin Sulfate*	65.80%
Other Ingredients	34.20%
TOTAL	100.00%

*Equivalent to 50% streptomycin

KEEP OUT OF REACH OF CHILDREN

CAUTION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

See Side/Back Panel for Additional Precautionary Statements, First Aid and Directions for Use

EPA Reg. No. 80990-3
EPA Est. No. XXXXX-XX-X

AgroSource, Inc.
P.O. Box 3091
Tequesta, Florida 33469

NOTICE: Read the entire Directions for Use and Conditions for Sale and Limitation of Warranty and Liability before buying or using this product. If the terms are not acceptable, return the product within 90 days, unopened and undamaged, and the purchase price will be refunded.

NET CONTENTS: XXXXXXX

FIRST AID	
If On Skin or Clothing:	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.
If In Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If Inhaled:	• Move person to fresh air • If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. • Call a poison control center or doctor for further treatment advice.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact InfoTrac at 1-800-535-5053 for emergency medical treatment information.	

PRECAUTIONARY STATEMENTS

Hazards to Humans & Domestic Animals

CAUTION: Avoid contact with skin, eyes, or clothing. Harmful if absorbed through skin. Causes moderate eye irritation. Do not breathe dust or spray mist. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. This material is not to be used for medical, veterinary, or human purposes.

Personal Protective Equipment (PPE):
All applicators and other handlers must wear a minimum of:
· Protective eyewear (goggles, safety glasses or face shield);
· Coveralls over short-sleeved shirt and short pants;
· Chemical-resistant gloves;
· Socks and shoes; and
· NIOSH approved particulate filtering facepiece respirator with any N, R, P filter (TC-84A); OR an elastomeric NIOSH approved particulate respirator with any N, R or P filter (TC-84A); OR a NIOSH approved powered air purifying respirator with an HE filter (TC-21C). Higher level respirators that are NIOSH approved for particulates that contain oil may also be used.

Applicators must also wear:
● Chemical-resistant headgear ensuring full coverage of the neck

Applicators do not have to wear the protective eyewear, chemical-resistant gloves, chemical-resistant headgear, or a respirator when using closed cab systems that meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.607(e)].

When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.607(d) and (e)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables are available, use detergent and hot water. Keep and wash PPE separately from other laundry.
Applicators do not have to wear the protective eyewear, chemical-resistant gloves, chemical-resistant headgear, or a respirator when using closed cab systems that meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.607(e)].

When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.607(d) and (e)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables are available, use detergent and hot water. Keep and wash PPE separately from other laundry.

User Safety Recommendations:
Users should:
- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS

This product may be hazardous to aquatic plants. Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high-water mark. Do not contaminate water by cleaning of equipment or disposal of wastes.

Attention: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

USE PARAMETERS AND APPLICATION RESTRICTIONS

To Reduce Potential for Selection of Bacterial Resistance:
AGRI-SEED™ 50 WP fungicide/bactericide contains a Group 25 fungicide/bactericide. Fungal isolates/bacterial strains with acquired resistance to Group 25 may eventually dominate the fungal/bacterial population if Group 25 fungicides/bactericides are used repeatedly in the same field or in successive years as the primary method of control for targeted species. This may

result in partial or total loss of control of those species by **AGRI-SEED ™ 50 WP** fungicide/bactericide or other Group 25 products.

To delay antibiotic/fungicide/bactericide resistance, take one or more of the following steps:

- Use only the specified and full-strength application rates.
- The streptomycin pesticidal mode of action is inhibition of protein synthesis. This product should be used to treat or prevent infection that are proven or strongly suspected to be caused by the indicated target bacteria. To reduce the likelihood of bacteria developing resistance to streptomycin, follow the crop specific resistance management and use direction information present on this labeling. Use of this product should conform to resistance management practices/strategies established for the crop and use area (for example, the use of IPM, disease forecasting models, resistance crop varieties, etc.) Consult your local extension/crop consultant or State agricultural authority if reduced efficacy is suspected.
- Adopt an integrated disease management program that includes scouting, uses historical information related to pesticide use, and crop rotation, and which considers host plant resistance, impact of environmental conditions on disease development, disease thresholds, as well as cultural, biological and other chemical control practices.
- Where possible, make use of predictive disease models to effectively time applications.
- Avoid the consecutive use of Agri-Seed 50 WP Fungicide/Bactericide Agricultural Streptomycin or other target site of action Group 25 products that have a similar target site of action, on the same pathogens.
- Use tank-mixtures or premixes with products from different target site of action Groups as long as the involved products are all registered for the same use and are both effective at the tank mix or prepack rate on the pathogen(s) of concern. Do not use any 19 product that has a prohibition on tank mixing and follow the more restrictive use directions.
- When feasible, Agri-Seed 50 WP Fungicide/Bactericide Agricultural Streptomycin should be alternated with a comparable bactericide with a different mode of action.
- Base use on a comprehensive IPM program.
- Monitor treated bacterial/fungal populations for loss of field efficacy.
- Contact your local extension specialist, certified crop advisors, and/or manufacturer for fungicide/bactericide resistance management and/or IPM recommendations for specific crops and resistant pathogens.
- For further information or to report suspected resistance contact AgroSource, Inc. at 908-931-9001.
- Do not apply more than two consecutive applications before alternating with another fungicide/bactericide of a different mode of action.
- Do not apply streptomycin in orchards in which the soil has been fertilized with animal waste/manure or human biosolids.
- Animal Grazing in treated areas is prohibited. The public must be notified by posting restriction signs along the perimeter of the treatment area.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other fungicide/bactericide products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria or fungi.
- Not to be used for medical, veterinary, or human purposes.
- Not for residential use.
- Do not apply this product through any type of irrigation system, including chemigation.

- Do not apply this product by aerial application.
- Spray Drift Precaution - ALL uses - to help reduce off-target drift, direct spray into the canopy, and turn off outward pointing nozzles at row ends and when spraying outer rows.

DIRECTIONS FOR USE

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

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

This product contains the antibiotic streptomycin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other antibacterial products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

AGRICULTURAL USE REQUIREMENTS

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This Standard contains requirements for the protection of agricultural workers on farms, forests, nurseries and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE) and restricted entry interval. The requirements in this box apply to uses that are covered by the Worker Protection Standard.

Do not enter or allow worker entry into treated areas during the restricted-entry Interval (REI) of 12 hours. Exception: Once seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface.

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil or water, wear:

- Coveralls over long-sleeved shirt and long pants
- Chemical-resistant gloves made of a waterproof material
- Shoes plus socks
- Protective eyewear

Crop Use Directions (Note to EPA: Uses listed below will be marketed under the Alternate Brand Name of FireWall™ 50 WP).

- **Tree Fruit Crops**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Citrus Fruit (all types and varieties) Australian desert lime; Australian finger-lime; Australian round lime; Brown River finger lime; calamondin; citron; citrus hybrids; grapefruit; Japanese summer grapefruit; kumquat; lemon; lime; Mediterranean mandarin; mount white lime; New Guinea wild lime; orange, sour; orange, sweet; pummelo; Russell River lime; satsuma mandarin; sweet lime; tachibana orange; Tahiti lime; tangelo; tangerine (mandarin); tangor; trifoliate orange; uniq fruit; cultivars, varieties, and/or hybrids of these	Huanglongbing also known as "HLB", "Greening" or "Citrus Greening" disease	11 oz. (0.45 lbs. a.i.) per acre per application	Apply as a foliar spray using sufficient carrier volume to ensure complete coverage. Contact your local AgroSource representative for guidance on the use of adjuvants Make **first** application at initiation of spring flush to suppress HLB titer and disease symptoms. Make a **second** application mid-summer (not less than 21 days after first application). Make a **third** application in late summer to reduce the incidence of HLB-induced fruit drop and to further suppress HLB titer and disease symptoms (not less than 21 days after second application). Young trees: spray to near runoff.	Do not apply within 60 days of harvest. Minimum retreatment interval: 21 days. Maximum number of applications per year: 3 Maximum annual amount that may be applied per acre: 33 oz. (0.45 lbs. a.i)

- **Tree Fruit Crops, Continued**

Crop	Disease (*Pathogen*)	Agri-Seed™ 50 WP Application Rate	Use Directions	Restrictions
Citrus Fruit (all types and varieties) Australian desert lime; Australian finger-lime; Australian round lime; Brown River finger lime; calamondin; citron; citrus hybrids; grapefruit; Japanese summer grapefruit; kumquat; lemon; lime; Mediterranean mandarin; mount white lime; New Guinea wild lime; orange, sour; orange, sweet; pummelo; Russell River lime; satsuma mandarin; sweet lime; tachibana orange; Tahiti lime; tangelo; tangerine (mandarin); tangor; trifoliate orange; uniq fruit; cultivars, varieties, and/or hybrids of these	Citrus Canker (*Xanthomonas citri* pv. *citri*)	11 oz. (0.45 lbs. a.i.) per acre per application	Apply as a foliar spray using sufficient carrier volume to ensure complete coverage. Contact your local AgroSource representative for guidance on the use of adjuvants Make **first** application when spring flush is approximately 75% expanded to protect new growth from canker infection. Make a **second** application in summer when weather conditions warrant during periods of high citrus canker risk (not less than 21 days after first application). Make a **third** application in late summer to reduce the incidence of canker-induced fruit drop (not less than 21 days after second application). Young trees: spray to near runoff.	Do not apply within 60 days of harvest. Minimum retreatment interval: 21 days. Maximum number of applications per year: 3 Maximum annual amount that may be applied per acre: 33 oz. (0.45 lbs. a.i)

STORAGE AND DISPOSAL

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

Storage: Keep tightly closed and sealed. Product is moisture, temperature and light sensitive. Product is hygroscopic so protect from moisture. Store in a cool (<77°F, 25°C), dry place away from heat and open flames with minimum exposure to the atmosphere. Avoid extremes in temperature.

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

Container Handling: Non-refillable Container. Do not reuse or refill this container. Completely empty bag into application equipment. Then offer bag for recycling if available or dispose of in a sanitary landfill, or by incineration, or if allowed by State and local authorities, by burning. If burned, stay out of smoke.

CONDITION OF SALE AND LIMITATION OF WARRANTY AND LIABILITY

The Directions for Use of this product must be followed carefully. It is impossible to eliminate all risks inherently associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as manner of use or application, weather or crop conditions, presence of other materials, resistant strains or other influencing factors in the use of the product, which are beyond the control of AGROSOURCE, INC. or Seller. To the extent consistent with applicable law, all such risks shall be assumed by Buyer and User, and Buyer and User agree to hold AGROSOURCE, INC. and Seller harmless for any claims relating to such factors. AGROSOURCE, INC. warrants that this product conforms to the chemical description on the label and is reasonably fit for the purposes stated in the Directions for Use, subject to the inherent risks referred to above, when used in accordance with directions under normal use conditions.

This warranty does not extend to the use of the product contrary to label instructions, or under conditions not reasonably foreseeable to or beyond the control of Seller or AGROSOURCE, INC., and Buyer and User assume the risk of any such use. AGROSOURCE, INC. MAKES NO WARRANTIES OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE NOR ANY OTHER EXPRESS OR IMPLIED WARRANTY EXCEPT AS STATED ABOVE. In no event shall AGROSOURCE, INC. or Seller be liable for any incidental, consequential or special damages resulting from the use or handling of this product.

TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, THE EXCLUSIVE REMEDY OF THE USER OR BUYER, AND THE EXCLUSIVE LIABILITY OF AGROSOURCE, INC. AND SELLER FOR ANY AND ALL CLAIMS, LOSSES, INJURIES OR DAMAGES (INCLUDING CLAIMS BASED ON BREACH OF WARRANTY, CONTRACT, NEGLIGENCE, TORT, STRICT LIABILITY OR OTHERWISE) RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, SHALL BE THE RETURN OF THE PURCHASE PRICE OF THE PRODUCT OR, AT THE ELECTION OF AGROSOURCE, INC. OR SELLER, THE REPLACEMENT OF THE PRODUCT. AGROSOURCE, INC. and Seller offer this product, and Buyer

and User accept it, subject to the foregoing conditions of sale and limitations of warranty and of liability, which may not be modified except by written agreement signed by a duly authorized representative of AGROSOURCE, INC.

AGRI-SEED and FIREWALL are trademarks of AgroSource, Inc.
Manufactured in the U.S.A. by AgroSource, Inc.

FireWall™ 50 WP Alternate Brand Names (ABN): TITER™ 50 WP

Exhibit B

Final Registration Decision for the New Use of the Active Ingredient Streptomycin Sulfate on Citrus Crop Group 10-10

Approved by: _____

Ed Messina, Esq., Acting Director
Office of Pesticide Programs

Date: January 11, 2021

Introduction

This document announces that the Environmental Protection Agency, referred to in this document as EPA or the Agency, has completed its evaluation of the new use of the active ingredient streptomycin sulfate on citrus crop group 10-10 and has concluded that it meets the regulatory and safety standards under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Streptomycin is an antibiotic of the aminoglycoside class and is derived from the bacteria *Streptomyces griseus*. The aminoglycosides are so named because they consist of several sugars with glycosidic bonds and contain amino groups. Streptomycin is classified by the Fungicide Resistance Action Committee (FRAC) as a Code 25 fungicide and a member of glucopyranosyl antibiotic group. Tolerances are already established for residues of streptomycin on beans, pome fruit crop group 11, seedlings of celery, pepper and greenhouse tomato as well as a seed treatment for potatoes, and for use on gardens and ornamentals including in residential areas. The streptomycin uses for these crops are for control of several bacterial diseases. Emergency exemptions under Section 18 of FIFRA have been authorized to California (2018, 2019 and 2020) and to Florida (2016, 2017, 2018, 2019 and 2020) for streptomycin use on the citrus crop group 10-10 to manage Huanglongbing (HLB), also known as citrus greening.

Streptomycin is also approved by the Food and Drug Administration (FDA) for use as a human and animal drug to treat certain bacterial infections. These uses are often indicated when less toxic alternatives are not effective or are administered as a combination therapy with other antibacterial agents.

Registrations for one technical product, EAC Streptomycin Manufacturing Use Product (EPA Reg. #71185-4) and one end-use product, Agri-Seed 50 WP (EPA Reg. #80990-3), are amended under FIFRA 3(c)(5) to add the citrus crop group 10-10 for management of HLB, and *Xanthomonus citri* subsp. *Citri* (Xcc), the causal agent of citrus canker disease. One additional end-use product amendment (FireWall 17 WP; EPA Reg # 80990-4) was initially requested with the application but was subsequently withdrawn. The uses are registered for up to three foliar ground applications with a maximum single application rate of 0.45 lb streptomycin sulfate/A (0.34 lb streptomycin/A) for a maximum annual rate of 1.35 lbs streptomycin sulfate/A (1.02 lbs streptomycin/A). Applications are made via ground airblast equipment.

Background

On November 30, 2015, the EPA received applications from Geo Logic Corporation and AgroSource Inc. to add new uses of streptomycin (CAS Number 3810-74-0) on citrus crop group 10-10. Geo Logic Corporation petitioned EPA under the Federal Food, Drug and Cosmetic Act (FFDCA) to establish tolerances for the proposed food crops listed above (petition # 5F8427). Currently, there are no Mexican, Canadian or Codex maximum residue limits (MRLs) for streptomycin on citrus or the citrus crop group 10-10. Therefore, there are no issues with respect to harmonization of MRLs.

Evaluation

In evaluating a pesticide registration application, the EPA assesses a wide variety of pesticide specific information including where and how the pesticide is used, environmental fate *(i.e.,* what happens to the pesticide once it's applied), and toxicity studies *(i.e.,* effects on humans and other non-target organisms) to determine the likelihood of adverse effects *(i.e.,* risk) from exposures

associated with the proposed use of the product. Risk assessments are developed to evaluate the environmental fate of the compound as well as how it may affect humans and non-target organisms including terrestrial and aquatic wildlife (plants and animals). In the case of pesticides that are antibiotics, EPA also evaluates, in consultation with public health officials from the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the United States Department of Agriculture (USDA), the potential for development of resistance, or cross-resistance. On the basis of these assessments and guidance, the EPA evaluates each pesticide label to ensure the directions for use and safety measures are appropriate to protect against unreasonable risk. In this way, the pesticide's label helps to communicate essential limitations and mitigations that are necessary for public safety. The use of a pesticide in a manner inconsistent with the label is a violation under FIFRA.

Assessment of Ecological Risk

Environmental Fate Profile

Aerobic soil metabolism data on four soils indicate single first order half-lives of streptomycin to be between 13 and 49 days. The study was performed without a radiolabeled compound, resulting in overall recoveries, extractable and nonextractable residues, and volatilization being unaddressed. Measured concentrations of streptomycin were variable so there is uncertainty associated with the calculated half-lives.

Sampling intervals were too infrequent to accurately assess the rate of degradation in two of the four soils, since a majority of the applied streptomycin dissipated between sampling intervals. However, the data are the best that can be realistically produced considering streptomycin cannot be radiolabeled at this time. Though overall recovery cannot be directly addressed, volatilization is very unlikely due to streptomycin's low vapor pressure. Nonextractable residues are very unlikely due to streptomycin's high solubility and low sorption coefficient.

Environmental Effects

EPA uses a deterministic approach, or the quotient method, to compare toxicity to environmental exposure. In the deterministic approach, a risk quotient (RQ) is calculated by dividing a point estimate of exposure by a point estimate of effects. This ratio is a simple, screening-level estimate that identifies high- or low-risk situations. Calculation of RQs are based upon ecological effects data, pesticide use data, fate and transport data, and estimates of exposure to the pesticide. In this method, the estimated environmental concentration (EEC) is compared to an effect level, such as an LC_{50} (the concentration of a pesticide where 50% of the organisms die).

The risk assessment indicates the new uses result in potential risk to mammals from chronic exposure [RQs are less than 10; level of concern (LOC) = 1.0] and risk to sensitive aquatic nonvascular plants (RQ = 3.4; LOC = 1.0). No other taxa are shown to be at risk from the new uses at this time; however, the pollinator data are incomplete. The risk conclusions are similar to those for other currently registered uses of streptomycin. The assessment for the new use on citrus does not contain effects determinations for any specific listed species or designated critical habitat.

Risk to Terrestrial Organisms

Mammals and Birds

Based on the available data, streptomycin is practically nontoxic to birds on an acute exposure basis with non-definitive toxicity values. The LC_{50} and LD_{50} are greater than the highest dose tested in the three available studies and therefore, RQs are not calculated as risk is presumed low. Two recently submitted studies on potential effects to avian species show that there are effects on eggshell thickness and viable embryos in the bobwhite quail study, but at higher levels than predicted EECs, with a no observed adverse effect concentration (NOAEC) of 486 mg ai/kg-diet. While it is important to know what effects are presented in a given study, it is important to consider that the RQ presented in the assessment is 0.47, half the level of concern. Thus, EECs from the citrus use pattern are unlikely to reach high enough concentrations to result in adverse effects. Mammalian data reported in the 1992 Reregistration Eligibility Decision shows streptomycin is practically nontoxic to mammals on an acute exposure basis with non-definitive toxicity values. No effects were reported in a two-generation rat reproduction study at the highest dose tested. Calculated with the NOAEC, RQ-values exceed the chronic level of concern (LOC) for mammals; the chronic dose-based RQ are less than 9.82. However, if mean rather than peak exposure values are used to estimate risk, then all mammalian RQ values for mammals are below the chronic risk LOC.

Terrestrial Invertebrates

No effects were reported at 100 µg a.i./bee in a honey bee acute contact study; therefore, streptomycin is classified as "practically nontoxic" to honey bees on an acute exposure basis. Additional pollinator data, in accordance with the recent pollinator guidance (https://www.epa.gov/sites/production/files/2016-08/documents/bee_guidance.pdf), are not available for streptomycin at this time. These additional studies examine potential toxicity to larval and adult honey bees from acute and chronic exposure. As part of EPA's registration review program, EPA is currently determining whether additional pollinator data are needed for streptomycin. If the Agency determines that additional pollinator exposure and effects data are necessary to help make a final registration review decision for streptomycin, then EPA will issue a data call-in to obtain these data.

Risk to Terrestrial Plants (Monocots)

Terrestrial plant toxicity studies are required for pesticides that have terrestrial use patterns or may move off of the application site via drift or volatilization. To evaluate the effect of streptomycin on terrestrial plants' vegetative vigor or seedling emergence, available supplemental data from limit tests were used. These data indicate that the inhibition concentrations (IC_{25}s) for both seedling emergence and vegetative vigor are >1.3 lbs a.i./A; however, no-effect values were not defined in either study with effects on biomass and survival. Non-listed species are evaluated with IC_{25}s, which are determined to be greater than 1.3 lbs ai/A (the seasonal rate for this assessment). Therefore, exposures at less than this rate are expected to be of low concern for non-listed species. There is no indication of risk to non-listed terrestrial plants.

Risk to Aquatic Animals

Risk estimates are below the LOC for non-target aquatic animals for the proposed use on citrus.

Fish and Invertebrates

Available data suggest streptomycin is practically nontoxic to fish and aquatic invertebrates on an acute exposure basis. Review of data regarding the potential effect of streptomycin on aquatic animals on a chronic exposure basis show no effects on fathead minnow at the highest concentration tested

(NOAEC =14.4 mg a.i./L). There was 100% mortality in a daphnid study at the highest concentration tested (22.7 mg a.i./L) with a NOAEC = 12.2 mg ai/L; no other effects were observed. Data for chronic exposure to daphnids indicate effects, but at concentrations several orders of magnitude higher than estimated high-end environmental exposures, thus risk of concern is unlikely. There are no data regarding the potential effect of streptomycin on estuarine/marine organisms, but based on the available information these data are thought to be of limited additional value in risk assessment. While there is a lack of data for estuarine/marine species, the paucity of effects shown in freshwater species suggests the potential for risks to these taxa are low. Estuarine/marine data is not required at this time.

Aquatic Plants:
Aquatic plant species have been shown to be sensitive to streptomycin in several microcosm and open literature studies. EPA has data for all five required taxa available. Most of these data are only useful qualitatively and should not be used in risk estimation. A study by Halling-Sorensen (2000) provides quantitative estimates of the sensitivity of green algae and cyanobacteria, two of the four taxa necessary for risk assessment to aquatic plant species. The cyanobacteria *Microcystis aeruginosa* is the most sensitive of the available species, with an IC_{50} of 0.007 mg a.i./L. Other nonvascular plant data were considerably less sensitive. Available data indicate a low potential for risk to aquatic vascular species; however, for aquatic non-vascular plants, the RQ is 3.4 (LOC = 1.0). Generally, at the LOC (1.0), there is expected to be an impact on 50% of the exposed population of a given taxon. Therefore, RQs greater than one implies effects greater than 50% for sensitive species (which are not necessarily limited to the surrogate species tested). There are less sensitive species for which risk is not expected.

Assessment of Risk to Human Health

EPA requires a wide range of studies in order to assess risks of a pesticide. For streptomycin, the database of studies required to support EPA's standard assessment of risk to human health is complete. There are no risks of concern. A human health risk assessment is the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals from current and proposed use patterns, now or in the future. This section, *Assessment of Risk to Human Health*, is a summary of the standard assessment that the Agency conducts; the full Human Health Risk Assessment can be found in docket ID number EPA-HQ-OPP-2016-0067. However, as with all antibiotics, concerns exist regarding the potential for development of human pathogen resistance, or cross-resistance with other antibiotics, that could result from pesticide applications. The Agency has also addressed this issue and it will be presented in the *Concerns for Development of Resistance in Human and Plant Pathogens* section of this document.

EPA has concluded that additional toxicity data are not required because the available laboratory animal toxicity data, in conjunction with the conclusions that can be drawn from the decades of use of streptomycin as a human antibiotic drug without significant incidents, is sufficient to assess the safety of streptomycin; therefore, additional toxicity data have been waived by the Agency. The database provides sufficient information for selection of endpoints when the extensive literature for streptomycin is included.

Streptomycin has a very low acute toxicity for the oral route in both rats and mice (LD_{50} = 9,000 mg/kg). A 2-year rat carcinogenicity study, used by FDA and the World Health Organization (WHO) (to set tolerances for animal drug residues), is available for streptomycin and did not demonstrate evidence of carcinogenicity (although limited histopathology was reported). A literature search for streptomycin toxicity in animals and humans also did not result in data with evidence of carcinogenicity.

The end-use products are currently labeled with a precautionary signal word of "CAUTION."

Injections of streptomycin as a human drug (up to a gram), at doses much higher than expected from dietary or residential routes of exposure to pesticide uses, can cause inner ear toxicity resulting in vestibular problems with loss of balance or equilibrium. Injections also sometimes cause hearing loss and mild, reversible kidney toxicity. Children born to mothers treated with streptomycin injections have sometimes had hearing loss. No teratogenic effects were noted in a non-guideline rabbit developmental study. In a non-guideline 2-year rat feeding study, the only adverse effect noted was reduced body weight in males; an increase in treatment-related tumors was not reported.

Because the oral dose selected for risk assessment is much lower than the injected dose at which toxicity occurs in humans and at the levels of exposure anticipated due to pesticide uses, there is no indication of neurotoxicity or susceptibility (no teratogenic effects have been attributed to streptomycin treatment), and there are no residual exposure concerns, the Food Quality Protection Act (FQPA) safety factor was reduced to 1x.

Based on the toxicity, duration of exposure, and proposed uses of streptomycin, the following toxicity endpoints were selected

> **Acute dietary (all populations):** No appropriate endpoint attributable to a single exposure was identified for the general U.S. population or any population subgroup.
>
> **Chronic dietary (all populations):** The no observed adverse effect level (NOAEL) of 5 mg/kg/day was derived based on the lowest observed adverse effect level (LOAEL) in the 2-year feeding study in rats (LOAEL = 10 mg/kg/day) based on reduced body weight in males.
>
> **Incidental Oral (Short and Intermediate-term), Short-term Oral (adults) and Inhalation (Short and Intermediate-term):** The short- and intermediate-term incidental oral, short-term oral (adults) and short and intermediate-term inhalation endpoints for risk assessment were selected from the same 2-year feeding study in the rat as described above, using the same NOAEL as used for chronic dietary assessment (5 mg/kg/day).
>
> **Dermal:** A dermal endpoint was not selected based on the chemical properties of streptomycin (minimal dermal absorption). No dermal assessment was required.

An unrefined chronic dietary exposure and risk analysis was conducted in support of the new use on citrus. The estimated exposure (food and water) to the U.S. population from the existing and proposed new uses of streptomycin resulted in an estimated risk equivalent to 41% of the chronic population adjusted dose (cPAD). The most highly exposed subpopulation was all infants (<1 year old) with an estimated exposure equivalent to 91% of the cPAD. An analysis of the chronic dietary risk considering exposure to food only results in risks ≤ 9.4% of the cPAD for the general population and 9.1% for all infants (<1 year old); therefore, the risk is mainly associated with drinking water exposure.

There are existing residential uses of streptomycin on ornamentals (gardens and trees). Residential handler exposures are anticipated from the currently registered use on ornamentals. Residential post-application exposures were not assessed since no dermal hazard has been identified for streptomycin. Further, non-dietary ingestion and inhalation post-application exposure is assumed to be negligible following applications to ornamentals. For all handler scenarios considered, estimated inhalation risks

were not of concern [i.e., margins of exposure (MOE) ≥ LOC of 100]: the lowest calculated MOE was 86,000.

For the new use of streptomycin on citrus, occupational handler MOEs are not of concern with label-required personal protective equipment (PPE) (i.e.; use of a dust/mist respirator). MOEs range from 3,400 to 31,000 with the use of a PF5 respirator. As there is no dermal hazard identified for streptomycin, quantification of occupational handler and post-application dermal exposure/risk is not required.

A quantitative assessment of exposure and risk resulting from spray drift has been conducted for streptomycin in a recent exposure and risk assessment (Memo, K. Lowe, 09-FEB-2016, D426601), which resulted in no incidental oral risk estimates of concern for children (1 to <2 year olds) [i.e., all MOEs ≥ 100] at the field edge for the maximum registered agricultural rate of 0.5 lb streptomycin/A for airblast applications.

A short-term aggregate assessment was conducted by combining dietary exposure (food and drinking water) with residential handler inhalation exposure for adults. A dermal assessment was not conducted for non-occupational or occupational handler exposure because of the low dermal absorption of streptomycin. The aggregate MOE is not of concern (i.e., the estimated MOE was greater than the LOC of 100). However, as noted previously, uncertainty exists regarding the potential for development of resistance, or cross-resistance with other antibiotics, that could result from pesticide applications. This issue will be addressed in the *Concerns for Development of Resistance in Human and Plant Pathogens* section of this document.

Streptomycin is used as a pharmaceutical drug treatment by intramuscular injection. Because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA believes that there is a reasonable certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with streptomycin. The Agency sought FDA input on this conclusion. FDA responded to EPA in a letter dated April 6, 2018, available in the public docket (EPA-HQ-OPP-2016-0067) and concluded that the pesticide exposures would be negligible when compared to the potential exposure from pharmaceutical use of streptomycin.

Cumulative Exposure/Risk Characterization

EPA has assessed the potential for streptomycin to share a common mechanism of toxicity with any other substance. Based on its assessment of the available toxicological data, EPA has determined that streptomycin does not share a similar toxicological profile with other pesticides. Thus, no further cumulative evaluation is necessary for streptomycin.

Concerns for Development of Resistance in Human and Plant Pathogens

Background[1]

Antibiotic resistance in human pathogens is a worldwide problem. New forms of antibiotic resistance can cross international boundaries and spread between continents with ease. Many forms of resistance

[1] Antibiotic Resistance Threats in the U.S. (US Department of Health and Human Services, Centers for Disease Control and Prevention, 2013)

spread with remarkable speed. World health leaders have described antibiotic-resistant microorganisms as "nightmare bacteria" that "pose a catastrophic threat" to people in every country in the world. Each year in the U.S., at least 2.8 million people are infected with antibiotic-resistant bacteria or fungi, and more than 35,000 people die as a result. Many more die from other conditions that were complicated by an antibiotic-resistant infection.

In addition, almost 225,000 people required hospital care for infections of antibiotic-resistant *Clostridium difficile (C. difficile)* infections in 2017. More than 12,000 of these patients died from their infections. In most cases, the use of antibiotics was a factor leading to the illness.

Antibiotic-resistant infections add considerable and avoidable costs to the already overburdened U.S. healthcare system. In most cases, antibiotic-resistant infections require prolonged and/or costlier treatments, extend hospital stays, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics. Although the total economic impact of antibiotic resistance is difficult to determine, the CDC estimates that just a subset of resistant infections caused more than $4.8 billion in medical costs in 2017. Antibiotics are responsible for almost one in six emergency department visits for adverse drug events. Antibiotics are involved in more emergency department visits for adverse drug events than any other class of drugs in patients under 50 years of age. In children five or younger, antibiotics cause more than half (56%) of estimated emergency department visits for adverse drug events.

How Bacteria Develop Resistance[2]

There are many types of microbes: bacteria, viruses, fungi, and parasites. While most microbes are harmless and even beneficial to living organisms, some can cause disease among humans, other animals, and plants. These disease-causing microbes are called pathogens. All types of microbes have the ability to develop resistance to the drugs created to destroy them, becoming drug-resistant organisms.

Bacteria will inevitably find ways of resisting the antibiotics developed by humans, which is why aggressive action is needed now to keep new resistance from developing and to prevent the resistance that already exists from spreading. Resistance occurs when bacteria adapt to the antibiotics designed to kill them, making the antibiotics less effective. Some resistant bacteria protect themselves from antibiotics by:

- Restricting access of the antibiotic to the cell by limiting the number or changing the size of the openings in the cell wall, keeping antibiotic drugs from entering the cell.
- Using pumps in their cell walls to remove antibiotic drugs that enter the cell.
- Destroying the antibiotic by using enzymes to break down the antibiotic drug and make it ineffective.
- Changing the antibiotic by using enzymes to alter the antibiotic drug so that it loses its effectiveness.
- Bypassing the effects of the antibiotic by developing different and new processes to get around those disrupted by the antibiotics.
- Changing the look of their targets (parts of a bacterium targeted by the antibiotic) so that the antibiotic does not recognize and destroy them, allowing the bacteria to survive.

[2] https://www.cdc.gov/drugresistance/emerging.html

Bacteria develop the resistance mechanisms described above by using instructions provided by their DNA, or genes. Often, resistance genes are found within plasmids, pieces of DNA that can move between bacterial species in the same family (e.g., between two Enterobacteriaceae like *E. coli*) and sometimes even across bacterial families (e.g., from an *E. coli* to a non-Enterobacteriaceae like *Pseudomonas aeruginosa*). Because of this ability to easily move and share these genetic instructions, plasmids with resistance genes can help bacteria that cause treatable infections to develop new or different resistance mechanisms.

CDC works to prevent the spread of drug resistance by tracking emerging resistance genes and infections caused by resistant bacteria (https://www.cdc.gov/drugresistance/solutions-initiative/index.html). By knowing where and how changes in resistance are occurring, we can inform solutions like outbreak response, drug development, and diagnostic development to prevent spread and slow resistance.

For antibiotic pesticides, resistance can be spread by resistant species in or on food, the skin of workers, or indirectly through the environment or clothing. By minimizing these three routes of exposure, EPA minimizes the growth or spread of resistant microbes on humans or on the crop.

Concerns for Development of Resistance in Human Pathogens

The management of antibiotic resistance development is critical to maintaining and prolonging the effective use of streptomycin and other antibiotics to control bacterial diseases in agriculture. Additionally, proper management will minimize the possibility streptomycin's agricultural use will affect other antibiotics used as both plant pesticides and human clinical drugs. The Agency is considering the development of resistance in the bacteria causing plant disease as well as the potential for these agricultural uses to contribute to the development of antibiotic-resistant diseases in humans. While pathogens rarely share the same hosts, human pathogens and plant pathogens may exist concurrently, allowing for the potential for resistance to develop in human pathogens as a result of antibiotic use on crops.

Other agencies in the federal government (such as CDC, FDA and USDA) are also concerned with the potential for resistance to develop from the use of antibiotics in agriculture and have been working within their areas of expertise to address the problem. CDC is a leader in the fight against this global threat. Through its Antibiotic Resistance Solutions Initiative, CDC works with partners to drive aggressive action and empower the nation to comprehensively respond. For more on CDC's involvement, see https://www.cdc.gov/drugresistance/about.html/ .

FDA is committed to further advancing antimicrobial stewardship by focusing on the following key initiatives: (1) approving new antibiotics to treat resistant bacteria; (2) developing regulations for drugs to address the proper use of antibiotics; (3) partnering with other governmental and private organizations to promote public awareness of resistance; and (4) encouraging the development of new antibiotics. For more on FDA's involvement, see https://www.fda.gov/consumers/consumer-updates/combating-antibiotic-resistance .

The USDA is responsible for protecting American agriculture and the American food supply. One of the many ways USDA does this is by addressing antimicrobial resistance. USDA is funding research where the focus addresses studying the role of agriculture in antimicrobial resistance, reducing potential negative impacts from the use of antibiotics, and identifying alternative strategies for

mitigating antimicrobial resistance (AMR) in the food chain. For more on USDA's involvement, see https://www.usda.gov/topics/animals/one-health/antimicrobial-resistance-overview-amr .

EPA believes that the management of pesticide resistance development is an important part of sustainable pest management and, in conjunction with alternative pest management strategies and Integrated Pest Management (IPM) programs, can make contributions to reducing risks to humans and the environment. In support of these goals, EPA is assessing the potential development of antibiotic resistance as an adverse effect under FIFRA.

As with all antibiotics, concerns exist regarding the potential for development of resistance by human pathogens across a class of antibiotics (e.g., the aminoglycosides) or cross resistance with other classes of antibiotics (e.g., the tetracyclines). Tetracyclines and aminoglycosides act upon the same RNA site within the cell. EPA consulted with antibiotic experts from the FDA, CDC and USDA on potential resistance concerns that might develop from the proposed citrus crop group use.

The Agency has examined the use of streptomycin on citrus to affect the potential resistance of human pathogenic bacteria to streptomycin or other antibiotics used by the health care industry to treat people. This qualitative approach is similar to FDA's regulatory approach for evaluating new requests for antimicrobial agents for veterinary uses. The Agency is focused on the selection of resistant bacteria of human health concern from three areas: the environment, from treated orchards; general public, from residues on food; and, agricultural workers through their daily activities. The Agency's analysis consists of a release assessment, an exposure assessment and a consequence assessment.

The Agency has reviewed information related to the potential of streptomycin's agricultural use on citrus trees to select for bacteria of human health concern. The process for this analysis was adapted from the FDA's Center for Veterinary Medicine's Guidance to Industry #152. This document can also be found on the streptomycin docket (www.regulations.gov; docket # EPA-HQ-OPP-2016-0067). FDA relies on this general process for evaluating the potential effects of new antimicrobial animal drugs on bacteria as part of the new animal drug application process.

EPA's analysis estimates the risk by assessing potential for antibiotic release, exposure to humans, and the consequence of the potential releases and exposures. The Agency assesses the potential release by characterizing the antibiotic's use pattern and considering what is known for target susceptibility, spectrum of activity, resistance mechanisms, and selection pressure. The Agency examines the potential human exposure to bacteria of human health concern from either consumption of a treated commodity or by working in treated fields. Lastly, the Agency addresses the consequences of losing the efficacy of streptomycin and other compounds for human clinical use. The final estimation of overall risk is found by considering the three assessments and developing an estimation of risk (low-medium-high) associated with the proposed conditions of use of streptomycin on crops.

Streptomycin has been used for over 40 years in both animal husbandry and in plant agriculture to control pathogenic bacteria. Streptomycin resistance occurs in fire blight (*Erwinia amylovora*), in *Xanthomonas campestris* pv. *vesicatoria* (Minsavage et al., 1990) as well as some other phytopathogenic bacteria. Selection for resistance to streptomycin in Xcc, HLB and environmental bacteria may occur with its broader adoption as a control measure for citrus crop group 10-10. Streptomycin resistance in environmental bacteria is documented, but the effect of transfer of this resistance to bacteria of human health concern is unknown. Streptomycin's clinical use has become limited due to the presence of resistance in many human pathogenic species and its higher ototoxicity than other aminoglycoside antibiotics. However, it is a useful second line agent in tuberculosis, and is

still efficacious in the treatment of several other human diseases.

Release Assessment

The release assessment rating for the proposed uses of streptomycin for the proposed citrus use is "medium" based on the information available for streptomycin control of Xcc.

AgroSource has not provided any estimate on the total number of acres of citrus with the expectation that all will be treated. The Agency used the figure of 764,000 acres of citrus nationwide from USDA's National Agricultural Statistics Service Census of Agriculture (2014). The rapidly spreading and devastating nature of HLB makes it plausible that the full label-rate will be used on all affected citrus acreage (the acreages are going down as the HLB takes citrus out of production) until more effective and different HLB control measures are discovered. The use for HLB in Florida is not distinguishable from the use for Xcc citrus canker. Since the HLB bacterium cannot be cultured with existing methods, there is no information on selection for streptomycin resistance, however, qualitatively HLB bacterium is less likely than Xcc to interact with environmental isolates since it is carried internally in the citrus plant. HLB does not interact with environmental bacteria so an internal bacterium has less possibility to exchange resistant traits.

There are instances of streptomycin resistance in other related *Xanthomonas* species (Zhang *et al*., 2011) and of these streptomycin resistance traits having similarities to the streptomycin resistance found in clinical strains (Sundin & Bender, 1995).

The incidence of food borne illness is the way that exposure to bacteria of human health concern are identified and given some weight for potential to cause harm in that particular food commodity. There have been several reports of foodborne illness from consumption of citrus products (Krause *et al*., 2001; Jain *et al.* 2009; EFSA, 2013). These reports are associated with non-typhoidal serovars of *Salmonella*. This is especially critical since multiple drug resistant forms of the *Salmonella* microbes of human health concern could be preferentially selected by any streptomycin residues (Scherer *et al*., 2013).

Exposure Assessment

Treated Commodities

The current exposure assessment for citrus crop group 10-10 is based on information collected from three seasons' continuous use of Firewall 50WP in citrus orchards in Florida (Behlau *et al*. 2012a). The new use will allow application to citrus grown in any area for a multitude of uses (both pasteurized and non-pasteurized) including: fresh juice, concentrated juice, fresh fruit, pulp, etc. The streptomycin exposure assessment for the first year would not be expected to be significantly different from that reported in the Behlau *et al*. article and may be much lower based on the rotation with oxytetracycline. Since the new use on citrus expands to all citrus growing areas, the amount of the treated food commodity being consumed is "high." Bacterial contamination or disease in citrus is relatively rare, with the exception of fresh squeezed unpasteurized juice. Citrus is very rarely implicated in food poisoning, primarily because of an increased focus on preventing contamination at the processing level and pasteurizing juice. The low pH of the consumed commodity also makes it an inhospitable environment for most bacteria to grow. Based on these considerations, EPA has determined that the level of food contamination for bacterial disease in citrus merits a rating of "low." The Agency's exposure estimate from consuming treated commodities yields a rating of "medium" based on EPA's adaptation of FDA resistance assessment exposure table.

Worker

FDA's Guideline #152 does not address the potential for resistance in human pathogens to develop from exposure of workers while treating animals with antibiotics. However, EPA is concerned about the new use of streptomycin on citrus and the potential exposure to agricultural workers in treated fields or mixing, loading or applying antibiotics. In addition, there is the potential for sub-therapeutic exposure to human pathogens in or on the treated workers to select for resistance. EPA believes that requiring additional Personal Protective Equipment (PPE) including a respirator, coveralls, protective headgear, and protective eyewear, will reduce the contribution of occupational exposure to the overall risk estimations (see **Final Regulatory Decision** section that follows).

Consequence Assessment

The consequence assessment for streptomycin use on citrus fruit results in a "highly important" rating, which is a moderate risk ranking. This risk rating is due to the indication that streptomycin is a member of the aminoglycosides and is still used in the treatment of tuberculosis and a number of other bacterial diseases (brucellosis, tularemia, plague, urinary tract and endocardial infections). Streptomycin is typically used in combination with other antibacterial agents due to the presence of streptomycin resistance.

This assessment may change to "critical" if it is found that streptomycin resistance, if and when it develops, can affect the clinical efficacy of streptomycin or select for multiple drug resistance. The data to establish or refute this supposition are not available. It is unlikely the clinical streptomycin resistance at the current time is due to streptomycin's use in agriculture, but the movement of streptomycin resistance traits from the streptomycin treated plant agricultural environment to the food chain and subsequently within the hospital has not been established at this time.

Overall Qualitative Risk Estimate

The overall risk estimate represents the potential for human health to be adversely impacted by the selection or emergence of antimicrobial resistant bacteria associated with this use of streptomycin in citrus. The overall qualitative risk estimate integrates the three previous assessments. With a "medium" release, "medium" exposure and "highly important" consequence ratings, the overall qualitative risk estimation for streptomycin use on citrus crop group 10-10 is "medium" for the new uses. In consideration of commercial adoption or additional scientific information, this finding may change over time. EPA proposes to continue to monitor this situation through review of annual sales reports and by revising the streptomycin resistance assessment to incorporate cumulative usage of streptomycin in all states where it is registered and used. Additionally, the Agency will continue consulting with the federal partners to reevaluate the current risk picture for streptomycin prior to extending or removing the time limitation on citrus crop group 10-10.

There are, however, a number of uncertainties relative to the new use patterns for streptomycin and the current ranking. In time and with additional data, the overall qualitative risk estimation may change. For the release assessment, it was noted that information is lacking on streptomycin susceptibility for the range of bacteria associated with food borne incidents in citrus and the movement of traits from the target bacterium and epiphytic bacteria to bacteria of concern for human health. For the exposure assessment, data on the actual level of contamination with bacteria of human concern on citrus and citrus commodities are not available. EPA agrees with AgroSource's assertion that the incorporation of Hazard Analysis and Critical Control Point (HACCP) regulations and orange juice pasteurization should have reduced the incidents of food-borne disease in citrus products.

HACCP is a management system in which food safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution and consumption of the finished product. The juice HACCP regulation requires juice processors to identify food safety hazards that are reasonably likely to occur with the products they process and to develop plans for the control of those hazards.

For the consequence assessment, it is clear that if the citrus use affected clinical uses for streptomycin, the rating could change.

The full *Review of AgroSource's Analysis of Streptomycin's Safety with Regard to Its Microbiological Effect on Bacteria of Human Health Concern (FDA/CVM Guidance to Industry #152) for a Section 3 Registration on Citrus Crop Group 10-10* can be found on www.regulations.gov at EPA-HQ-OPP-2016-0067.

Resistance Management for Plant Pathogens

Given the importance of antibiotics to control bacterial diseases in humans and domestic animals, as well as benefits in crop production, it is essential that procedures be adopted to lessen the likelihood that antibiotic use in agricultural crops will lead to selection for resistance by bacterial populations related to public health. The guidance given in PRN 2017-1 outlines general considerations for prudent agricultural use including the avoidance of single chemistry for control, rotating control measures over the season, employing tank mixes to reduce the selection pressure of the sprays used, and basing control strategies on integrated pest management programs. An important step in any antibiotic resistance control scheme is to monitor for loss of field efficacy, confirm resistance, and determine its source. EPA considers the loss of efficacy due to resistance to be an adverse effect and such developments are reportable under FIFRA section 6(a)(2).

The Agency is concerned about the development of resistance to all pesticides and recognizes that management of the development of pesticide resistance, in conjunction with alternative pest-management strategies and IPM programs, is an important part of sustainable pest management. This concern includes the new use of streptomycin on citrus and the potential for plant pathogens to develop resistance to the pesticide. In general, resistance management strategies can apply across all pest categories (e.g., insects, pathogens, weeds) although specific elements should be designated for each broad category of pest. For HLB and citrus canker management, EPA has identified important resistance management elements [*Review of Label Language and Resistance Management Plan for Streptomycin Sulfate on Citrus Crop Group 10-10 (PC# 006310 and DP# 440091)*] and has included those in this final decision.

The likelihood of development of resistance to streptomycin by pathogens causing HLB or citrus canker over time after use of foliar sprays is not known. Streptomycin has been used to manage bacterial diseases on apple and pear (fire blight), celery (bacterial blight, Florida only), peppers (bacterial spot), potatoes (soft rot and black leg), greenhouse tomatoes (bacterial spot, speck and canker-greenhouse), and ornamentals (bacterial leaf spot, rot, blight and gall). The new use of streptomycin on citrus will expand the number of acres treated with streptomycin. To maintain the effectiveness of streptomycin for use on citrus trees, a resistance management plan should be in place and the registrant should encourage crop consultants and growers to follow the plan.

The Agency identified important resistance management practices [*Review of Label Language and Resistance Management Plan for Streptomycin Sulfate on Citrus Crop Group 10-10 (PC# 006310 and DP# 440091)*] that are intended to provide users and registrants useful strategies that, when implemented, will slow the development of resistance to plant pathogens and prolong the useful life of antibiotic products on agricultural crops. The registrant has provided labeling that addresses the resistance management practices identified by EPA. For example, among other aspects of streptomycin use, the final end-use label includes information for a user to contact state extension specialists for general information on streptomycin use and the recommendation for the user to monitor efficacy in order to identify possible resistance. Research on antibiotic resistance management may change through time and resistance management plans may need to be updated. EPA requires registrants to implement a resistance management plan including education of growers to ensure that their antibiotic resistance plan is effective and that growers follow resistance management plans to ensure the antibiotic pesticides remain effective. The issue of antibiotic resistance in human or animal pathogens or sanitary and phytosanitary measures and food safety was addressed in *Review of AgroSource's Analysis of Streptomycin's Safety with Regard to Its Microbiological Effect on Bacteria of Human Health Concern (FDA/CVM Guidance to Industry #152) for a Section 3 Registration on Citrus Crop Group 10-10*.

Benefits and Alternatives

HLB is caused by the plant bacterial pathogen *Candidatus* Liberibacter asiaticus (*C*Las) and transmitted into the tree phloem by the Asian citrus psyllid, an invasive insect. Citrus canker disease is caused by the bacterium *Xanthomonas citri* subs. *citri,* (*Xcc*). When conditions are favorable it is highly contagious and is spread by means of wind, rain, irrigation, and incidental human and animal activity in citrus groves. In addition, galleries formed by the Asian citrus leafminer damage leaves and cause additional susceptibility to canker. HLB has had a devastating effect on citrus production, especially in Florida. Florida provides the majority of all citrus acreage in the U.S. (~540,000 acres).

Since HLB was first detected in Florida in 2005, the disease has spread, particularly to all commercial citrus growing areas of Florida. Citrus acreage in Florida has dropped from over 750,000 acres in 2000 to 435,000 acres in 2016, a reduction of 42% primarily due to losses from HLB (https://fred.ifas.ufl.edu/pdf/economic-impact-analysis/Economic_Impacts_of_the_Florida_Citrus_Industry_2015_16.pdf).
HLB has been detected on a smaller scale in Georgia, Louisiana, South Carolina, Puerto Rico, Texas, and the U.S. Virgin Islands. An area south of Los Angeles, California has been designated a quarantine area for HLB. In a Florida survey, responses indicated that an average of 90% of citrus acres contained trees with HLB bacteria. Researchers from the University of Florida, Institute of Food and Agricultural Sciences (UF-IFAS) estimated that there are $1.75 billion in cumulative losses in the value of production in Florida citrus that were due to HLB over a 10 year period, growing seasons from 2006/7 to 2015/16, which is an average annual loss of $175 million. Additionally, it should be noted that the annual magnitude of these losses in individual years has been increasing, with over $670 million in losses estimated in 2015/16, a decrease of almost 80% compared to what might have been without HLB (https://fred.ifas.ufl.edu/pdf/economic-impact-analysis/Economic_Impacts_of_the_Florida_Citrus_Industry_2015_16.pdf). The Animal and Plant Health Inspection Service (APHIS) of USDA has issued numerous regulatory updates on managing HLB as it affects, to varying degrees, citrus-growing regions including quarantine areas for psyllid in an attempt to stop the transmission of HLB to new locations (https://www.aphis.usda.gov/aphis/ourfocus/planthealth/plant-pest-and-disease-programs/pests-and-diseases/citrus-health-response-program/ct_regs).

Up until very recently, there were no pesticides currently registered to manage HLB. Only one product containing the recently registered antibiotic oxytetracycline hydrochloride is registered for controlling or suppressing HLB disease caused by *Candidatus* Liberibacter asiaticus (*C*Las) which infects all citrus types. Other pesticides are available to help manage infestations of the psyllid vector, but even so, control of psyllid has not been successful in preventing HLB transmission. Consequently, citrus growers have been unsuccessful in controlling or managing the disease using limited, and primarily non-pesticide measures. Regarding citrus canker, by 2006, after a 10-year effort to eradicate citrus canker from Florida, USDA determined that the disease had spread to such a degree that eradication was not possible (https://www.aphis.usda.gov/aphis/ourfocus/planthealth/plant-pest-and-disease-programs/pests-and-diseases/citrus-health-response-program/ct_citrus_canker). Currently, movement of citrus plant material is restricted by rules published by APHIS-USDA.

Streptomycin treatments likely play a role in resistance management of HLB because it provides a different mode of action than the only registered alternative. Controlling the insect vector can reduce transmission, but it has not been effective in reducing the effects of HLB. As far as citrus canker disease, only copper products have been a standard treatment [*Review of Benefits of a New Use of Streptomycin Sulfate (Fire Wall™ 50WP) on Citrus Crop Group 10-10*]. Streptomycin is also currently registered for foliar use on apples and pears to treat fire blight. Specific emergency exemptions have been granted (effective through the end of 2021 currently) for the use of streptomycin sulfate on Florida citrus trees to suppress HLB. A quarantine emergency exemption has been granted to California on an annual basis since 2018 to prevent the spread of HLB from residential areas where the ACP has been identified in three counties (Los Angeles, Orange, and Riverside) to commercial citrus production areas. The Agency has reviewed documents submitted by the registrant regarding the benefits and efficacy of streptomycin to manage HLB and citrus canker.

EPA has concluded that streptomycin benefits citrus growers in managing HLB (*Review of Benefits of a New Use of Streptomycin Sulfate (Fire Wall™ 50WP) on citrus crop group 10-10*). The submitted efficacy data show that three streptomycin foliar applications to HLB-infected trees substantially reduced bacterial titer in the treated citrus trees, thus improving various parameters of tree health by the second year of treatment, including increased tree height, reduced leaf drop, reduced dieback, reduced fruit drop and increased fruit yields compared to untreated trees. Streptomycin treatments also likely play a role in resistance management of citrus canker because it provides a different mode of action than the registered alternatives, which are primarily copper products, and the recently registered antibiotic oxytetracycline hydrochloride. Treatment of citrus trees with streptomycin plus copper reduced incidence of citrus canker and associated tree defoliation, premature fruit drop and increased fruit yields. The pathogens causing these diseases are not eliminated by the treatment with streptomycin and long-term disease management is necessary. The likelihood of development of resistance to streptomycin by pathogens causing HLB or citrus canker over time after three foliar sprays per year is not known.

The approved end-use labels include citrus use sites that comprise the citrus crop group 10-10. This includes all commercial citrus fruit such as grapefruit, lemon, lime, orange, tangelo, tangerine, citrus citron, kumquat, pummelo, and various citrus hybrids.

Public Comments

On April 04, 2016, the EPA published Notice of Receipts in the Federal Register (docket ID number EPA-HQ-OPP-2016-0067) of applications from Geo Logic Corporation and AgroSource, Inc., and

announced a public comment period of 30 days. No comments were received. On April 25, 2016, the EPA published a Notice of Filing in the Federal Register as well. No comments were received.

Proposed Decision Comments

The EPA announced the proposed decision to grant the amended registrations for the technical product and two end-use products under Section 3(c)(5) of FIFRA for the additional use on the citrus crop group 10-10 with multiple terms of registration (outlined in the "Proposed Regulatory Decision" section) on December 18, 2018. A public comment period was held for 30 days, closing on January 21, 2019. A 30-day extension to the comment period was also announced on February 12, 2019, closing on March 14, 2019. During the comment period, the Agency received over 40,000 comments from stakeholders, non-governmental organizations, academic and medical professionals, USDA, Florida Fruit and Vegetable Association (FFVA) and members of the general public. Most comments came from mass mailer campaigns, and approximately 4,700 unique substantive comments were received from various stakeholders. The Agency has addressed the comments in a separate document titled *Response to Comments Received to the Streptomycin Proposed New Uses on Citrus Group 10-10 Docket*. The comments and submissions received to the public docket did not result in changes to the Agency's risk assessments or the mitigation proposed in the proposed decision document. The suggestions for improving the monitoring aspect of the increased acreage for this new use are a valuable addition and will be taken into consideration when reviewing the monitoring protocols that are submitted. The full comments and the comment response document can be viewed at www.regulations.gov under docket ID: EPA-HQ-OPP-2016-0067.

Final Regulatory Decision

The Agency is granting the amended technical product and end-use products under Section 3(c)(5) of FIFRA with terms of registration for use on the citrus crop group 10-10. The terms of registration include the following;

- Time limited for 7 years on citrus use only
- Resistance Management Plan Implementation (education/training and stewardship plan). A yearly summary report describing the Resistance Management Plan implementation details must be submitted to the Agency by December 31st of each year for confirmatory purposes.
- Annual sales reports by state (from the registrant) submitted to the Agency by December 31st of each year
- Monitoring requirement
    - Required protocol submissions on a yearly basis for the first 3 years describing how the registrant plans to monitor soils and citrus for incidences of antibiotic resistance. Submission of protocol 3 months prior to use season to allow for Agency review prior to start of monitoring.
    - Annual monitoring report submissions
- One year prior to expiration, if the registrant chooses to seek an extension for the citrus use or the removal of the time-limitation, the registrant would be required to submit an application for amendment along with a revised assessment on the development of streptomycin resistance in human pathogens addressing release, exposure, consequence assessments and overall risk estimation with regard to public health effects resulting from cumulative usage of streptomycin

> on all citrus crops in all states where it is registered and used. The Agency expects to consult with the federal partners to reevaluate the current risk picture for streptomycin prior to extending or removing the time limitation on citrus.

Lack of performance and new cases of suspected/confirmed microbial resistance may not be immediately identifiable after application, but rather after multiple seasons of applications. Therefore, a time-limited registration of seven years on the citrus use will allow for a more complete picture of evolving microbial resistance trends than if a shorter time-limitation was allowed. In addition, registration review of existing chemicals already occurs at least every 15 years, and thus a 7-year time-limitation will allow for an additional reevaluation of the resistance risk picture for this antibiotic chemical. By requiring the registrant to implement their Resistance Management Plan which the Agency has reviewed, growers/users will gain knowledge of useful strategies to slow the development of resistance to plant pathogens and prolong the useful life of antibiotic products on agricultural crops. Annual sales reports will show usage trends as they evolve and will provide information on how use may be expanding. Monitoring, including evolving protocols and annual reporting on lack of performance and suspected/confirmed resistance, will feed into this more complete picture of the evolving resistance trends. Also, EPA's consultation with our federal partners prior to the end of the time-limitation period will allow the Agency to incorporate any new medical/veterinary use information and concerns on streptomycin use into a new current risk picture for streptomycin.

The streptomycin database is considered to be complete to assess risk to the environment and human health, when using the Agency's standard processes. While there is potential risk to mammals on a chronic exposure basis and non-vascular plants using conservative assumptions for the proposed use on citrus, the Agency believes there are strong benefits for granting these new uses. In general, EPA's human health risk assessments estimate the nature and probability of harmful health effects in people who may be exposed to pesticides from: consuming food and water; breathing air; working at farms or other locations where the pesticide is used; or as a result of activities that may lead to contact with pesticide residues on treated surfaces. These processes evaluate the toxic risk of a pesticide based on a spectrum of potential toxic effects demonstrated by data. Based on the standard risk assessment process, all human health risk estimates are not of concern (below the LOC.)

For antibiotic pesticides, the potential for the development of antibiotic resistance is an effect that is not considered in the Agency's standard human health risk assessment. However, the management of antibiotic resistance development is critical to maintaining and prolonging the effective use of streptomycin and other antibiotics as both plant pesticides and human drugs. The Agency has assessed the development of resistance in bacteria causing plant disease and also the potential for these uses to contribute to the development of antibiotic-resistant diseases in humans. Only one product of the active ingredient oxytetracycline hydrochloride is registered for controlling or suppressing HLB disease caused by *Candidatus* Liberibacter asiaticus (*C*Las) which infects all citrus types. Oxytetracycline is classified by the FRAC as a Code 41 fungicide and a member of the tetracycline class of antibiotics that exert their activity in bacteria by inhibiting protein synthesis, providing a different mode of action from streptomycin. For citrus canker disease, only copper products have been a standard treatment; thus, streptomycin treatments would likely play a role in resistance management of citrus canker because it has a different mode of action. While streptomycin treatments may inhibit HLB and canker development, pathogens are not killed by the treatment and long-term disease management will be necessary. The Agency concludes that citrus growers will immediately benefit from the availability of streptomycin to help manage HLB and citrus canker.

Because antibiotic pesticides, such as streptomycin, have concerns beyond those of conventional pesticides, the Agency has developed management techniques specifically designed to minimize the likelihood of antibiotic resistance developing from its use in agriculture. Streptomycin is considered highly important in human and veterinary therapy so that these techniques could prolong its effectiveness against bacterial infection in humans and animals. The *National Action Plan for Combatting Antibiotic-Resistant Bacteria* states that, "implementation of the objectives and activities in the *National Action Plan* requires sustained, coordinated, and complementary efforts of individuals and groups around the world, including healthcare providers, healthcare leaders, veterinarians, agriculture industry leaders, manufacturers, policymakers, and patients."[3]

FDA, CDC and USDA have pursued and implemented programs designed to reduce the overall use of antibiotics in humans and animals and to improve their stewardship. In addition, CDC and FDA are supporting additional limitations on physicians and veterinarians. EPA believes a corresponding approach to reducing the impacts on resistance from the use in crop agriculture is warranted. As part of this national approach, EPA has evaluated the risk of antibiotic resistance for this final decision. Throughout the review process, the Agency consulted with our federal partners at CDC, FDA, and USDA to discuss the extent of the problem and potential mitigation efforts for the antibiotic use in agriculture. The science of resistance is evolving and there is a high level of uncertainty in how and when resistance occurs. Our federal partners expressed a number of concerns on expanding uses of antibiotics in plant agriculture. Overall, they recommend judicious use, prevention of drift to neighboring fields/water bodies, and additional protection of agricultural pesticide handlers from exposure. Limiting unnecessary environmental and human exposure can reduce the potential for development of antibiotic resistance. Therefore, EPA has imposed the following restrictions to address concerns for the potential development of antibiotic resistance for pathogens.

Use Parameters and Restrictions for the End-Use Label (*Agri-Seed 50 WP; EPA Registration No. 80990-3)*

- "Not for residential use."
- REI: 12 hours
- PHI; citrus: 60 days

Elements Proposed to Reduce Potential for Selection of Bacterial Resistance

- **Agri-Seed 50 WP** contains a Group 25 (fungicide/bactericide). Fungal isolates/bacterial strains with acquired resistance to Group 25 may eventually dominate the fungal/bacterial population if Group 25 fungicides/bactericides are used repeatedly in the same field or in successive years as the primary method of control for targeted species. This may result in partial or total loss of control of those species by **Agri-Seed 50 WP** or other Group 25 products.

  To delay antibiotic/fungicide/bactericide resistance, take one or more of the following steps:

  - Use only the specified and full-strength application rates.
  - The streptomycin pesticidal mode of action is inhibition of protein synthesis. This product should be used to treat or prevent infection that are proven or strongly

[3] https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

suspected to be caused by the indicated target bacteria. To reduce the likelihood of bacteria developing resistance to streptomycin, follow the crop specific resistance management and use direction information present on this labeling. Use of this product should conform to resistance management practices/strategies established for the crop and use area (for example, the use of IPM, disease forecasting models, resistance crop varieties, etc.) Consult your local extension/crop consultant or State agricultural authority if reduced efficacy is suspected.

- Adopt an integrated disease management program that includes scouting, uses historical information related to pesticide use, and crop rotation, and which considers host plant resistance, impact of environmental conditions on disease development, disease thresholds, as well as cultural, biological and other chemical control practices.
- Where possible, make use of predictive disease models to effectively time applications.
- Avoid the consecutive use of **Agri-Seed 50 WP** or other target site of action Group 25 products that have a similar target site of action, on the same pathogens.
- Use tank-mixtures or premixes with products from different target site of action Groups as long as the involved products are all registered for the same use and are both effective at the tank mix or prepack rate on the pathogen(s) of concern. Do not use any product that has a prohibition on tank mixing and follow the more restrictive use directions.
- When feasible, **Agri-Seed 50 WP** should be alternated with a comparable bactericide with a different mode of action.
- Base use on a comprehensive IPM program.
- Monitor treated bacterial/fungal populations for loss of field efficacy.
- Contact your local extension specialist, certified crop advisors, and/or manufacturer for fungicide/bactericide resistance management and/or IPM recommendations for specific crops and resistant pathogens.
- For further information or to report suspected resistance contact AgroSource, Inc. at 908-931-9001."

- "Do not apply more than two consecutive applications before alternating with another fungicide/bactericide of a different mode of action."
- "Do not apply streptomycin in orchards in which the soil has been fertilized with animal waste/manure or human biosolids."
- "Animal Grazing in treated areas is prohibited. The public must be notified by posting restriction signs along the perimeter of the treatment area."
- "Not to be used for medical, veterinary or human purposes."
- "To reduce the development of drug-resistant bacteria and maintain the effectiveness of this and other fungicide/bactericide products, this product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria or fungi."

<u>Elements Proposed to Reduce Environmental Exposure:</u>

- For airblast application: "To help reduce off-target drift, direct spray into the canopy, and turn off outward pointing nozzles at row ends and when spraying outer rows." *(The Agency believes*

this drift statement will help reduce drift from the target application site for ground airblast use.)*

- "Do not apply this product through any type of irrigation system, including chemigation."
- "Do not apply this product by aerial application" *(this statement will replace the current restriction on the label that reads, "Do not apply this product by aircraft."*)*

Elements Proposed to Reduce Exposure to Handlers:

- The Personal Protective Equipment section of the label reads as follows:

"**PERSONAL PROTECTIVE EQUIPMENT**

All applicators and other handlers must wear a minimum of:
• Protective eyewear (goggles, safety glasses or face shield);
• Coveralls over short-sleeved shirt and short pants;
• Chemical-resistant gloves
• Socks and shoes; and
• NIOSH approved particulate filtering facepiece respirator with any N[1], R or P filter (TC-84A); OR an elastomeric NIOSH approved particulate respirator with any N[1], R or P filter (TC-84A)[2] OR a NIOSH approved powered air purifying respirator with an HE filter (TC-21C)[2]. Higher level respirators that are NIOSH approved for particulates that contain oil may also be used.

Applicators must also wear:
• Chemical-resistant headgear ensuring full coverage of the neck.

Applicators do not have to wear the protective eyewear, chemical-resistant gloves, chemical-resistant headgear, or a respirator when using closed cab systems that meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.607(e)].

When handlers use closed systems or enclosed cabs in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.607(d) and (e)], the handler PPE requirements may be reduced or modified as specified in the WPS.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables are available, use detergent and hot water. Keep and wash PPE separately from other laundry.

[1]*Note to registrant: Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.**

[2] *Note to registrant: The TC designation must be included for the first respirator listed. The other TC designations that are shaded can be included or not at the registrant's discretion."**

**comments in italics are not to appear on the label*

Supporting Documents

All supporting documents can be found in docket ID number EPA-HQ-OPP-2016-0067.