Streptomycin

Crops

Identification of Petitioned Substance

Chemical Name:
O-2-deoxy-2-methylamino-α-L-glucopyranosyl-(1- >2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1- >4)-N,N′-bis(aminoiminomethyl)-D-streptamine

Other Names:
D-Streptamine
dtreptamine
streptomycin A
streptomycine
streptomycin sulfate

Trade Names:
Agrept
Agri-mycin 17
Ag-Streptomycin
Agri-Strep
Phytomycin
Plantomycin
Rimosidin
Strepcin

CAS Numbers:
57-92-1
3810-74-0 (streptomycin sulfate)

Other Codes: Streptomycin
X1002030-7 (ACX number)
1768 (HSDB number)
006306 (USEPA PC Code)

Other Codes: Streptomycin Sulfate
X1009163-9 (ACX number)
006310 (USEPA PC Code)

Characterization of Petitioned Substance

<u>Composition of the Substance</u>:
Streptomycin ($C_{21}H_{39}N_7O_{12}$) is a human antibiotic drug originally derived from the soil bacteria *Streptomyces griseus*; it is also used to control bacteria, fungi, and algae in agricultural crops (EPA 1988, EXTOXNET 1995). The chemical structure of streptomycin is shown in Figure 1.

This review considers "streptomycin" to include streptomycin, streptomycin sulfate, and mixtures of both; PAN (2005a,b) lists pesticides containing one or both chemicals. The chemical formula for streptomycin sulfate is $2(C_{21}H_{39}N_7O_{12}) \bullet 3(H_2SO_4)$. It is an ionic compound that results from the interaction between negatively charged sulfate ions from sulfuric acid (H_2SO_4) and streptomycin. The current National Organic Program (NOP) National List of Allowed and Prohibited Substances (National List) regulations refer to both streptomycin (see NOP §205.601(i)(10)) and streptomycin sulfate (see NOP Preamble[1]) for use in plant disease control in organic crop production. Furthermore, many data sources (e.g., EXTOXNET 1995, HSDB 2002) and regulatory documents (EPA 1988, 1992a) use the term "streptomycin" generically to include plant disease control agents that include "streptomycin-related substances." The most commonly referred to substance is streptomycin sulfate (a.k.a., Agri-mycin 17) (e.g., EPA 1992a, Greenbook 2004).

<u>Properties of the Substance</u>:
Streptomycin is an odorless or nearly odorless, white to off-white (pink to tan) powder that is easily soluble in water (EPA 1988, HSDB 2002). It is most commonly produced as a dust, wettable powder, emulsifiable[2]

[1] http://www.ams.usda.gov/nop/NOP/standards/ListPre.html.
[2] An emulsion is a mixture of two immiscible (unblendable) substances; one substance (the dispersed phase) is dispersed in the other (the continuous phase).

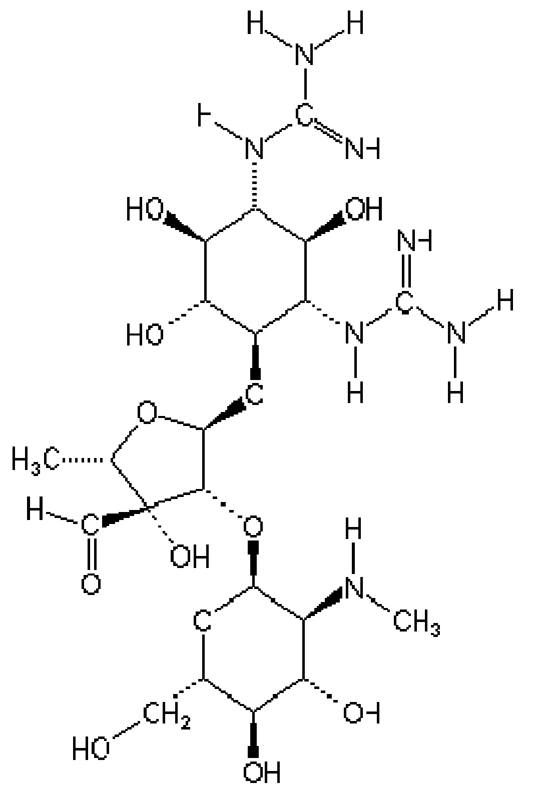

Figure 1. Chemical Structure of Streptomycin

concentrate, pelleted/tablets, and in a liquid (colorless to yellow, viscous) ready-to-use form. See response to Evaluation Question #1 for more information on the commercial production of streptomycin.

Streptomycin is insoluble in ethanol, isopropanol, ether, and carbon tetrachloride (EXTOXNET 1995). Neutral aqueous solutions of streptomycin are stable for weeks at temperatures below 25° C, but streptomycin is unstable/incompatible with strong acids and alkalis and deteriorates if heated (HSDB 2002).

<u>Specific Uses of the Substance</u>:
Streptomycin is currently included on the National List as a synthetic substance allowed in organic crop production for "fire blight[3] control in apples and pears only" (NOP §205.601(i)(10)). Sprays of agricultural streptomycin, typically applied at early bloom at 3- to 4-day intervals to help prevent infection, have been the standard commercial control for several decades (Guerena et al. 2003, McManus and Heimann 1997). As noted previously, "streptomycin" refers to pesticides for which streptomycin (USEPA PC Code 006306), streptomycin sulfate (USEPA PC Code 006310), or both are the active ingredient(s).

In addition to controlling fire blight in pears and apples (which accounts for 58% of its total use), streptomycin controls bacterial and fungal diseases of many other fruits, vegetables, seeds, and ornamental crops; it is also used to control algae in ornamental ponds and aquaria (EPA 1992a). Other significant uses

[3] Fire blight is a widespread and often damaging bacterial disease (caused by *Erwinia amylovora*) that can severely damage apples, pears, and other ornamental shrubs and trees in the apple sub-family (Pomodidae). Affected branches wither and turn black or brownish-black, as if burned. Blossoms, fruits, and twigs are also affected, which can result in the death of an entire tree. Under the tree bark, bacteria form a canker where they can survive the winter and emerge to infect more trees the following year. Fire blight can be transmitted by bees, aphids, or other insects. Pruning (especially during the growing season) and blowing wind and rain can also spread the disease. See Boyd and Jacobi (2005), Hagan and Akridge (1999), and Ritchie and Sutton (2002) for further information about fire blight and controlling fire blight.

of streptomycin are for nursery stock and in landscape maintenance (17% of use) and on tobacco (7% of use).

Streptomycin was first isolated from soil bacteria in 1944 and was the first of a class of drugs called aminoglycoside[4] antibiotics to be discovered (Borders 1992). Historically, streptomycin was the first drug found to be active against *Mycobacterium tuberculosis*—the cause of pulmonary tuberculosis (ACS 2005). Medical use of streptomycin has diminished in recent decades due to widespread use of other aminoglycoside antibiotics (e.g., gentamicin, tobramycin) and is now generally reserved for medical treatment (via intramuscular injection) in combination with other antibiotics (e.g., penicillin) for cases of active tuberculosis and for other specific bacterial diseases; Anaizi (2002) provides further information.

Approved Legal Uses of the Substance:

Streptomycin is a registered pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which is administered by the U.S. Environmental Protection Agency (EPA). It was first registered in 1955 for use in controlling bacterial and fungal diseases of certain agricultural and non-agricultural crops. EPA issued a Registration Standard for streptomycin in September 1988 (EPA 1988) and a reregistration eligibility decision (RED[5]) in September 1992 (EPA 1992a, 1992b). A TRED[6] for streptomycin is scheduled for May 2006 (EPA 2005a).

Streptomycin is regulated by the U.S. Food and Drug Administration (FDA) as a prescription drug (FDA 1998); it is to be prescribed and administered only by or under the immediate supervision of a physician (MedlinePlus 2002). Veterinary use of streptomycin is also regulated by FDA (CFR 21, Chapter I, Part 520, § 520.2158a). A tolerance of zero has been established by FDA for residues of streptomycin in uncooked edible tissues of chickens, turkeys, and swine as well as in eggs (HSDB 2002).

Action of the Substance:

Aminoglycoside antibiotics, including streptomycin, irreversibly bind to cellular components of bacteria, slowing down or inhibiting their ability to synthesize proteins needed for growth and survival (see Ophardt 2003 for further information). In general, aminoglycosides and streptomycin are effective on many aerobic Gram-negative and some Gram-positive bacteria; they are not useful for anaerobic or intracellular bacteria. (Guerena et al. (2003) and Steiner (1998) present options and measures to preserve and improve the effectiveness of streptomycin on the fire blight microorganism, *Erwinia amylovora* — especially as related to stabilizing risks for the development antibiotic resistance.)

Status

International

Streptomycin is not specifically listed for the petitioned use or other uses in the following international organic standards:

- Canadian General Standards Board
- CODEX Alimentarius Commission
- Japan Agricultural Standard for Organic Production

[4] Aminoglycosides are a group of antibiotics that are effective against certain types of Gram positive and Gram negative bacteria. Those that are derived from *Streptomyces* species are named with the suffix -mycin (e.g., streptomycin); those that are derived from *Micromonospora* are named with the suffix -micin (e.g., gentamicin).

[5] When EPA completes the review and risk management decision for a pesticide that is subject to reregistration (i.e., one initially registered before November 1984), EPA generally issues a Reregistration Eligibility Decision or RED document. The RED document summarizes the risk assessment conclusions and outlines any risk reduction measures necessary for the pesticide to continue to be registered in the United States (see EPA 2005b for further information).

[6] TRED documents are reports on FQPA (Food Quality Protection Act) Tolerance Reassessment Progress and (Interim) Risk Management Decisions (see EPA 2005b for further information).

The European Economic Community (EEC) Council Regulation 2092/91 prohibits the use of all antibiotics in organic crop production; furthermore, U.S. organic crop producers that use antibiotics (including streptomycin) are not eligible to label and sell their products as "organic" within the European Union. The use of antibiotics is also prohibited in crop production under the Basic Standards of the International Federation of Organic Agriculture Movements (IFOAM). (See CCOF 2005 and WSDA 2005 for a comparison of current U.S. NOP standards with EEC and IFOAM standards, including lists of prohibited substances in organic crop production.)

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1*:* Is the petitioned substance formulated or manufactured by a chemical process? (From 7 U.S.C. § 6502 (21))

Commercial quantities of streptomycin and streptomycin sulfate are produced via fermentation (DSIR 1991, HSDB 2002, Sengha 1993). Although various chemicals are used in the processes for isolating and purifying the substance, it is not clear whether the final end product results from chemical modification of the naturally occurring product. See response to Evaluation Question #3 below for further detail.

Evaluation Question #2: Is the petitioned substance formulated or manufactured by a process that chemically changes the substance extracted from naturally occurring plant, animal, or mineral sources? (From 7 U.S.C. § 6502 (21).)

As discussed under Evaluation Question #1 above, commercial fermentation is used to produce large quantities of streptomycin and/or streptomycin sulfate. Yet, it is unclear whether the naturally occurring product is modified chemically to produce the final end product. See Evaluation Question #3 below for further detail.

Evaluation Question #3: Is the petitioned substance created by naturally occurring biological processes? (From 7 U.S.C. § 6502 (21).)

Streptomycin is created through a naturally occurring process—it is produced by naturally occurring bacteria, but the processes used to isolate and purify the substance are not naturally occurring. Streptomycin and streptomycin sulfate, like many commercial antibiotics, are manufactured by an aerobic fermentation process (Dale and Mandelstam 2005, HSDB 2002, Sengha 1993).[7] The microorganisms used to produce the compounds are *Streptomycin griseus* and other *Streptomycin* species. The manufacturing process comprises three major steps: (1) preparation of inoculum (i.e., substance containing the microorganism), (2) fermentation, and (3) extraction, recovery, and purification (DSIR 1991). The first step is the preparation of inoculum from the original culture of *Streptomycin* species. The inoculum is transferred to a series of incubators where the total quantity of *Streptomycin* is greatly increased. The inoculum is then added to large, enclosed stainless steel or nickel-chrome vat fermentation tanks (often holding thousands of gallons) to maintain optimum growing conditions (DSIR 1991, USDA/NOSB 1995). The growth medium contains a suitable source of carbohydrates (e.g., glucose or lactose), a nitrogen source (e.g., soybean flour or urea), and various salt solutions to provide nutrients to optimize growth and yield of streptomycin. The fermentation process usually takes about two to seven days (DSIR 1991, Sengha 1993). To extract the compound, the mixture is filtered to remove the bacteria, diluted, and passed through ion exchange resin columns where streptomycin is adsorbed. It is further treated with several chemicals (e.g., solvents, antifoaming agents), activated carbon, and de-ashed in the resin column to remove impurities. Streptomycin is typically extracted from the resin column as streptomycin sulfate (DSIR 1991). Purified streptomycin (or streptomycin sulfate) solution is then concentrated and dried for the subsequent addition of other active and inert ingredients and packaging.

[7] Very few references were available on the manufacturing process for streptomycin and streptomycin sulfate; these references also do not clearly differentiate between the manufacture of streptomycin and streptomycin sulfate.

Evaluation Question #4: Is there environmental contamination during the petitioned substance's manufacture, use, misuse, or disposal? (From 7 U.S.C. § 6518 (m) (3).)

Dzhedzhev et al. (1975) reported that the manufacture of streptomycin resulted in high atmospheric concentrations of the solvents butyl alcohol and butyl acetate in the workplace. In 1998, EPA revised its water effluent limitations guidelines and standards for the pharmaceutical manufacturing industry to control water pollution discharged from these facilities (EPA 1998). Based on information EPA collected from 244 facilities, fermentation operations may use solvents to isolate the substance from the broth and other impurities. Usually, the solvents are recovered and reused, but small amounts of the solvents may remain in the broth "washes" that are discharged in the plant's wastewater. The solvents most frequently used in fermentation operations according to the data collected include acetone, methanol, isopropanol, ethanol, amyl alcohol, and methyl isobutyl ketone. Specific information for the production of streptomycin was not provided, so it is unclear whether manufacturers of streptomycin actually use solvents. Other pollutants that could be discharged from pharmaceutical fermentation processes include detergents and disinfectants used to clean equipment. Nitrogen and sulfur oxide gases may be produced by the fermenters, which are regulated by EPA. Assuming streptomycin manufacturers comply with applicable water and air regulations, it is unlikely that environmental contamination will result from fermenting processes. The *Pollution Prevention and Abatement Handbook: Pharmaceuticals Manufacturing* (IFC 1998) also provides a general discussion of environmental pollution and opportunities to diminish pollution associated with the manufacture of pharmaceuticals, including antibiotics such as streptomycin. No other specific information was found on the potential for environmental contamination resulting from the manufacture of streptomycin.

Because streptomycin is unstable when heated and does not accumulate/persist in the soil, disposal by incineration or burial should not result in harm to the environment (HSDB 2002). However, discharging streptomycin to sewers (for subsequent treatment in a wastewater treatment facility) is not recommended. (See response to Evaluation Question #5 below for further discussion of environmental effects.) See EPA 1998 for the final effluent (i.e., regulated disposal of wastes to surface waters) guidelines and standards for the pharmaceutical manufacturing industry.

Gardan and Manceau (1984) reported that no surface residue of streptomycin was detectable on pear or apple trees after four to six weeks following spray application. Furthermore, EPA (1988) concluded that streptomycin "residues are non-detectable (< 0.5 ppm [parts per million]) in or on crops when treated according to label use rates and directions." EPA (1988) also cited study data indicating that bacteria in the water and soil degrade streptomycin in two to three weeks. One study showed that that the major degradation products were carbon dioxide and urea, while another study found that the major degradation product was methyl amine. These products are found naturally in the environment. Therefore, if applied to apples and pears to help control fire blight in organic crop production in accordance with labeled instructions (EPA 1992a), it is unlikely that streptomycin will contaminate the environment.

Evaluation Question #5: Is the petitioned substance harmful to the environment? (From 7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i).)

EPA determined that "Streptomycin products, when labeled and used as described in the RED, should not pose unreasonable risks or adverse effects on non-target species or the environment…They also should not pose a significant risk to threatened or endangered species…" (EPA 1992a, 1992b). However, streptomycin is quite toxic to algae and, for this reason, is often used to control algae in ornamental ponds and aquaria (EPA 1992a). As a result, EPA (1992a) requires that all pesticide products containing streptomycin, except those specifically used as algicides in ornamental aquaria and ponds, include in the environmental hazards labeling section the following statement: "This product may be hazardous to aquatic plants…Do not apply directly to water, areas where surface water is present…Do not contaminate water by cleaning of equipment or disposal of wastes."

In addition, EPA (1992a) concluded that there are no environmental concerns associated with the release and use of naturally-produced streptomycin as a pesticide, when it used in accordance with labeled instructions. EPA's conclusion can be applied to fire blight control in organic crop production, as presently allowed by the National List, which is a pesticidal use. Thus, for the specific proposed use (i.e., fire blight control), information available from EPA (1992a) suggests that streptomycin and its breakdown products are unlikely to harm non-target organisms or the environment (see also Evaluation Question #10 below).

Evaluation Question #6: Is there potential for the petitioned substance to cause detrimental chemical interaction with other substances used in organic crop or livestock production? (From 7 U.S.C. § 6518 (m) (1).)

No published information was found to assess whether streptomycin or its byproducts cause detrimental chemical interaction with other substances used in organic crop production. Because EPA noted no environmental concerns with naturally-produced streptomycin and streptomycin residues are not detectable in or on crops when treated according to label use rates and directions (EPA 1988, 1992a, EXTOXNET 1995), it seems unlikely that streptomycin, if used in accordance with NOP regulations and labeled instructions, would cause detrimental chemical interaction with other substances used in organic farming.

Evaluation Question #7: Are there adverse biological or chemical interactions in the agro-ecosystem by using the petitioned substance? (From 7 U.S.C. § 6518 (m) (5).)

No specific information was found to assess whether spray-applied streptomycin or its byproducts have adverse biological or chemical reactions in the agro-ecosystem. As noted in Evaluation Question #4, when properly labeled and used in accordance with labeled instructions (EPA 1992a, 1992b), streptomycin should not pose a significant risk to the environment or to endangered species. Therefore, it seems unlikely that proper use of streptomycin would cause any adverse chemical or biological interactions in the agro-ecosystem.

Evaluation Question #8: Are there detrimental physiological effects on soil organisms, crops, or livestock by using the petitioned substance? (From 7 U.S.C. § 6518 (m) (5).)

Although streptomycin, as an antibiotic, has the potential to be toxic to some microorganisms in the soil, it is produced by naturally occurring bacteria. Ingham and Coleman (1984) showed that commercial rates of application of streptomycin to soil did not have significant effect on total bacterial and fungal numbers in the short term (i.e., several weeks). However, streptomycin is quite toxic to algae and is often used to control algae in ornamental ponds and aquaria (EPA 1992a). Thus, EPA (1992a) requires all pesticide products containing streptomycin, except those specifically intended for use as algicides, to be labeled as potentially hazardous to aquatic plants and to not be applied to water or in areas where surface water is present.

No published information was found to assess whether streptomycin (or its byproducts) used in organic crop production cause detrimental physiological effects on crops or livestock. As previously noted, however, when properly labeled and used in accordance with labeled instructions (EPA 1992a, 1992b), streptomycin should not pose a significant risk to the environment or to endangered species. Therefore, it seems unlikely that proper use of streptomycin would cause any adverse effects on crops or livestock.

Evaluation Question #9: Is there a toxic or other adverse action of the petitioned substance or its breakdown products? (From 7 U.S.C. § 6518 (m) (2).)

EPA determined that streptomycin is practically non-toxic to birds, freshwater invertebrates, and honey bees (EPA 1992a); it is slightly toxic to cold water and warm water species of fish (EPA 1988, 1992a, EXTOXNET 1995). Therefore, EPA classified it as a Toxicity Category IV pesticide, indicating the lowest level of acute toxicity. Pesticides containing streptomycin sulfate as an active ingredient are classified as "moderately toxic" for acute toxicity on EPA product labels (PAN 2005b).

A number of studies have been conducted with animals to determine the potential adverse effects of streptomycin in humans from medicinal use (EPA 1992a, EXTOXNET 1995, HSDB 2002). For example, cats that received intramuscular injections of streptomycin lost the righting reflex in three weeks, while those receiving oral doses did not (EPA 1992a). A study in pregnant rabbits indicated that streptomycin does not have the potential to cause birth defects (EXTOXNET 1995), and a chronic feeding study in rats indicated that streptomycin does not cause cancer in these animals (EPA 1992a). Streptomycin sulfate has been found to exhibit negative to weakly positive results in a series of tests designed to show whether chemicals interact with DNA or damage chromosomes—indicating that it is unlikely to cause cancer (NTP 2005).

Streptomycin has been used as a beneficial human and animal drug for many decades. HSDB (2002), Anaizi (2002), and MedlinePlus (2002) summarize side effects and contraindications associated with the medical use of streptomycin. Such adverse health effects include ototoxicity (e.g., temporary or permanent loss of hearing, ringing or buzzing in the ears); nephrotoxicity (e.g., greatly increased or decreased frequency of urination or amount of urine); and neurotoxicity (e.g., muscle twitching, numbness, seizures, tingling). In addition, a variety of allergic reactions have been observed in patients treated with streptomycin, including redness of the skin, rashes, hives, drop in blood pressure, headache, nausea and vomiting (EPA 1992a).

Evaluation Question #10: Is there undesirable persistence or concentration of the petitioned substance or its breakdown products in the environment? (From 7 U.S.C. § 6518 (m) (2).)

No. Streptomycin residues are not detectable in or on crops when treated according to label use rates and directions (EPA 1988, EXTOXNET 1995). EPA (1988) also cited data that showed that streptomycin biodegrades relatively quickly in soil and water. The breakdown products include carbon dioxide, urea, and methyl amine, all of which occur naturally in the environment. Therefore, if applied to apples and pears to help control fire blight in organic crop production in accordance with labeled instructions (EPA 1992a), it is unlikely that streptomycin will persist in the environment.

Evaluation Question #11: Is there any harmful effect on human health by using the petitioned substance? (From 7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4).)

EPA (1988) concluded that no significant dietary exposure is anticipated to occur from agricultural use of streptomycin due to the lack of detectable residues and the long pre-harvest intervals[8] (PHIs) for pears (30 days) and apples (50 days). Current tolerances or maximum residue limits for residues of streptomycin in or on foodstuffs (including apples and pears) were established at 0.25 ppm in 40 CFR 180.245 (EPA 1988, 1992a). EPA (1992a, 1992b) determined that the dietary risk from pesticide products containing streptomycin appears to be minimal.

Workers may be exposed to streptomycin while applying products containing this pesticide or while working in fields where crops have been recently treated (EPA 1988, 1992a). Some workers have developed an allergic response (e.g., rash, hives) to pesticides containing streptomycin (EXTOXNET 1995). For this reason, products containing streptomycin registered for commercial use on agricultural crops and ornamentals must include following statement on the label (EPA 1992a):

> Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Do not breathe dust or spray mist. Wear a MSHA/NIOSH approved TC-21C dust/mist filtering respirator, long sleeved shirt, pants, shoes, and chemical resistant gloves while handling or applying this product. Wash thoroughly after handling or applying.

Antibiotic-resistant bacteria are a significant public health concern; therefore, EPA considered whether use of streptomycin as a pesticide has the potential to encourage human pathogen resistance to streptomycin (EPA 1992a). EPA found no data indicating that streptomycin pesticide residues remaining in the food supply have a significant or even measurable potential for increasing resistance to that drug through oral

[8] The PHI for a pesticide governs the time between the application of the chemical pesticide and harvesting of the crop for subsequent consumption (Sunding and Zivin 2000).

exposures (EPA 1992a). However, EPA recognized a potential risk of agricultural workers developing antibiotic-resistant respiratory microorganisms as result of inhaling repeatedly pesticides containing streptomycin during and immediately after its application. To lessen this risk, EPA requires through product labeling several exposure and risk reduction measures including the use of protective clothing during application and the observation of a 12-hour reentry interval (i.e., REI of 12 hours) after application (EPA 1992a).

<u>Evaluation Question #12:</u> Is there a wholly natural product which could be substituted for the petitioned substance? (From 7 U.S.C. § 6517 (c) (1) (A) (ii).)

Using fire blight-resistant pear or apple plants (cultivars) can be considered a good and effective start to managing fire blight (Boyd and Jacobi 2005, Guerena et al. 2003, McManus and Heimann 1997). For example, there are several European-type and Asian-type pears with a comparatively high level of fire blight resistance that are adapted to most of the contiguous United States (Guerena et al. 2003). However, actual blight resistance for many of these cultivars appears to vary with growing conditions and cultivation practices.

The use of biological control methods has long been an attractive goal for integrated crop management programs and, in some cases, they have proven to be effective. There are several bacterial antagonists that have shown good effectiveness in protecting against fire blight (Steiner 1998). For example, one such material has been marketed since the mid-1990s as Blight Ban uses a strain (A506) of the bacterium, *Pseudomonas fluorescens* (Guerena et al. 2003, Steiner 1998). This bacteria multiplies rapidly and colonizes open flowers and thereby excludes significant subsequent colonization by *Erwinia amylovora*. However, many tests have shown that if this treatment is applied after *Erwinia amylovora* is already present, it is not as dependable or as effective as streptomycin (Steiner 1998). Steiner also warns that "…it is important to understand the nature of biological control in that we are depending on a living organism to grow, multiply, and be dispersed as well and as rapidly, if not more so, than the pathogen or pest we hope to control…Just as the populations and dispersal of the fire blight bacterium vary with the weather, we can expect similar effects on most bioantagonistic microorganisms."

<u>Evaluation Question #13:</u> Are there other already allowed substances that could be substituted for the petitioned substance? (From 7 U.S.C. § 6518 (m) (6).)

Yes. NOP (§205.601(i)(7) allows "Peracetic acid - for use to control fire blight bacteria" (USDA 2000) and (§205.601(i)(11) allows "Tetracycline (oxytetracycline calcium complex), for fire blight control only." However, tetracycline, unlike streptomycin, is not limited to use on apple and pear trees. More broadly, §205.601(i) allows eight other synthetic substances and groups of related substances for plant disease control. For example, "Bordeaux mix" (copper sulfate and lime; both approved for use under (§205.601(i)) has been used successfully to control fire blight of pears and apples (Boyd et al. 2005, Steiner 1998). The effectiveness of copper against various pathogens is attributed to the availability of copper ions that inactivate many different microorganism enzymes and other proteins essential to cell membrane function. However, this broad mode of action is not restricted to microorganisms and can also damage foliage and fruit on the crop plant, especially apples (Steiner 1998). Indeed, the potential for phytotoxicity to apples is the single most important factor limiting the effective use of Bordeaux mix and other copper-containing mixtures against fire blight. These and other copper formulations (see §205.601(i)(1)), however, sprayed at, or before, green-tip stage (i.e., buds showing ¼" of green tissue), provide some protection of pears from fire blight infection (Guerena et al. 2003, McManus and Heimann 1997).

<u>Evaluation Question #14:</u> Are there alternative practices that would make the use of the petitioned substance unnecessary? (From 7 U.S.C. § 6518 (m) (6).)

Because fire blight infestation is greatly favored by the presence of young, succulent tissues, cultural practices that favor moderate growth of trees are recommended (Boyd and Jacobi 2005, Guerena et al. 2003). Such practices include use of drip irrigation and limiting or excluding the use of manure (as allowed under NOP §205.203 (d)(5)), which can limit fast-growing succulent tissue. The structure and mineral content of the soil are important in managing fire blight because trees planted in poorly drained soil are more susceptible to fire blight. In addition, careful pruning, disinfection of all tools used in pruning, and/or pruning during the winter, when lower temperatures render the bacteria inactive, can help prevent spreading the disease from infected to uninfected trees.

References

ACS (American Chemical Society). 2005. The Pharmaceutical Century: 1940s. ACS Publications. http://pubs.acs.org/journals/pharmcent/Ch3.html.

Anaizi, N. 2002. The Drug Monitor: Streptomycin. http://www.thedrugmonitor.com/streptomycin.html.

Borders, D. 1992. Antibiotics (Survey). Kirth-Othmer Encyclopedia of Chemical Technology, Volume 2 (Fourth Edition). New York: John Wiley & Sons.

Boyd, J.E., Jacobi, W.R. 2005. Fire Blight. Report #2.907. Colorado State University Cooperative Extension. http://www.ext.colostate.edu/pubs/Garden/02907.html.

CCOF (California Certified Organic Growers International). 2005. CCOF's Draft Manual III: Global Market Access Program. http://www.ccof.org/pdf/GlobalMarketAccessDraftForReview.pdf.

Dale, M.M., Mandelstam, J. 2005. Antiobiotics. Microsoft Encarta Online Encyclopedia. http://encarta.msn.com/encnet/refpages/RefArtTextonly.aspx?refid=761577894&find=1.

Dzhedzhev, A., Mukhtarova, M., Koen, E., Karadzhova, N., Naidenov, I. 1975. Problems of work hygiene in the manufacture of penicillin and streptomycin [in Bulgarian]. Probl Khig. 1:61-69.

DSIR (Department of Scientific & Industrial Research; India). 1991. Technology in Indian Streptomycin Rifampicin Industry. Technical Status Report 67. http://dsir.nic.in/reports/techreps/tsr067.pdf.

EPA (U.S. Environmental Protection Agency). 1988. Streptomycin (Agri-Strep, Agrimycin) EPA Pesticide Fact Sheet 9/88. EPA/540/FS-88-096. Available online at: http://pmep.cce.cornell.edu/profiles/fung-nemat/febuconazole-sulfur/streptomycin/fung-prof-streptomycin.html.

EPA. 1992a. R.E.D. FACTS: Streptomycin and Streptomycin Sulfate. EPA-738-F-92-009. Office of Prevention, Pesticides And Toxic Substances. http://www.epa.gov/oppsrrd1/REDs/factsheets/0169fact.pdf.

EPA. 1992b. Reregistration Eligibility Document (RED): Streptomycin and Streptomycin Sulfate. Office of Pesticide Programs. http://www.epa.gov/oppsrrd1/REDs/old_reds/strep_sulfate.pdf.

EPA 1998. Development Document for Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category. EPA-821-R-98-005. Office of Water. http://www.epa.gov/guide/pharm/techdev.html.

EPA. 2005a. Pesticide Reregistration Status. http://cfpub.epa.gov/oppref/rereg/status.cfm?show=rereg.

EPA 2005b. Definitions: REDs, IREDs, and TREDs. http://www.epa.gov/oppsrrd1/reregistration/definitions.htm.

EXTOXNET (Extension Toxicology Network). 1995. Pesticide Information Profiles: Streptomycin. http://extoxnet.orst.edu/pips/streptom.htm.

FDA (U.S. Food and Drug Adminstration). 1998. Prescription and Over-the-Counter Drug Product List - 18th Edition - Cumulative Supplement Number 6: June 1998. http://www.fda.gov/cder/rxotcdpl/pdpl_698.htm#rx.

Gardan, L., Manceau, C.H. 1984. Persistence of streptomycin in pear and apple trees. ISHS (International Society for Horticultural Science). Acta Horticulturae 151:179-186.

Greenbook. 2004. Material Data Safety Sheet: Agri-Mycin 17 Agricultural Streptomycin. http://www.greenbook.net/docs/msds/M75805.PDF.

Guerena, M., Born, H., Mumma, T. 2003. Organic Pear Production: Horticulture Production Guide. ATTRA--National Sustainable Agriculture Information Service. http://attra.ncat.org/attra-pub/pear.html#Diseases.

Hagan, A., Akridge, R. 1999. Fighting fireblight: Agrimycin provides control of fireblight on crabapple. Alabama Agricultural Experiment Station. Highlights of Agricultural Research. Volume 46, Number 2. http://www.ag.auburn.edu/aaes/communications/highlightsonline/summer99/crabapple.html.

HSDB (Hazardous Substances Data Bank). 2002. Streptomycin. http://toxnet.nlm.nih.gov/.

IFC (International Finance Corporation). 1998. Pollution Prevention and Abatement Handbook: Pharmaceuticals Manufacturing. http://ifcln1.ifc.org/ifcext/enviro.nsf/AttachmentsByTitle/gui_pharmmfg_WB/$FILE/pharma_PPAH.pdf.

Ingham, E.R., Coleman, D.C. 1984. Effects of streptomycin, cycloheximide, fungizone, captan, carbofuran, cygon and PCNB on soil microorganisms. Microbial Ecology 10:345-358.

McManus, P.S., Heimann, O.S.F. 1997. Apple, Pear, and Related Tree Disorders: Fire Blight. Report A1616. University of Wisconsin Cooperative Extension. http://cecommerce.uwex.edu/pdfs/A1616.PDF.

MedlinePlus. 2002. Drugs & Supplements: Aminoglycosides (Systemic). http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202027.html.

National Toxicology Program (NTP). 2005. NTP Studies on Streptomycin Sulfate. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.ntpstudiesforchemical&cas_no=3810-74-0.

Ophardt, C.E. 2003. Introduction to Drug Action: Other Antibiotics. http://www.elmhurst.edu/~chm/vchembook/654antibiotic.html.

PAN (Pesticides Action Network). 2005a. PAN Pesticides Database - Pesticide Registration Status: Streptomycin. http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC34481.

PAN (Pesticides Action Network). 2005b. PAN Pesticides Database - Pesticide Registration Status: Streptomycin Sulfate. http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC34901.

Ritchie, D.F., Sutton, T.B. 2002. Fire Blight of Apple and Pear. Fruit Disease Information Note 3. Plant Pathology Extension. North Carolina State University. http://www.ces.ncsu.edu/depts/pp/notes/oldnotes/fd3.htm.

Sengha, S. 1993. Fermentation. Kirth-Othmer Encyclopedia of Chemical Technology, Volume 10 (Fourth Edition). New York: John Wiley & Sons.

Steiner, P.W. 1998. How Good Are Our Options With Copper, Bio-controls and Alliette for Fire Blight Control? West Virginia University, Kearneysville Tree Fruit Research and Education Center. http://www.caf.wvu.edu/kearneysville/articles/SteinerHort2.html.

Sunding, D., Zivin, J. 2000. Insect Population Dynamics, Pesticide Use, and Farmworker Health. American Journal of Agricultural Economics 82:527-540. http://www.columbia.edu/~jz126/word/phi_ajae.pdf.

USDA (U.S. Department of Agriculture,). 2000. TAP Review: Peracetic Acid. USDA National Organic Program. http://www.ams.usda.gov/nop/NationalList/TAPReviews/PeraceticAcid.pdf.
USDA/NOSB (National Organic Standards Board). 1995. NOSB/National List. Crops. #3 Antibiotics.

WSDA (Washington State Department of Agriculture). 2005. Organic Food: European Organic Verification Program (EOVP). http://agr.wa.gov/FoodAnimal/Organic/default.htm.