Tetracycline (Oxytetracycline Calcium Complex)

Crops

Identification of Petitioned Substance

Chemical Names:
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydro-6-methyl-1,11-dioxo-2-naphthacenecarboxamide calcium

Other Names:
agricultural terramycin
calcium oxytetracycline
oxytetracycline calcium complex

Trade Names:
Fireman
Mycoject
Mycoshield
Oxytetracycline calcium technical
Tree Tech OTC-CA

CAS Number:
7179-50-2

Other Codes:
X1039009-9 (ACX number)
006321 (USEPA PC Code)
3145 (HSDB number; oxytetracycline)

Related Compounds:
Oxytetracycline (CAS # 79-57-2)
Oxytetracycline hydrochloride (CAS # 2058-46-0)
Tetracycline (CAS # 60-54-8)

Characterization of Petitioned Substance

<u>Composition of the Substance</u>:
Oxytetracyline calcium complex ($C_{22}H_{22}N_2O_9 Ca$) is an agricultural antibiotic pesticide (microbiocide) derived from *Streptomyces* soil bacteria; it is used to control bacteria and fungi in agricultural crops (EPA 1993a). The chemical structure of the parent compound, oxytetracycline, is shown in Figure 1.

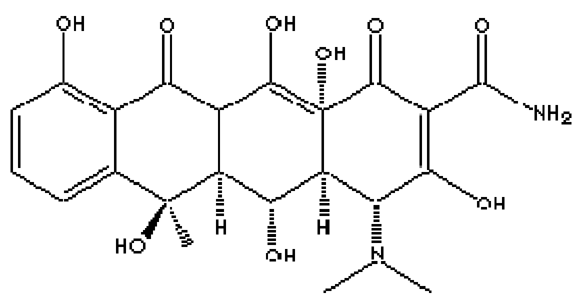

Figure 1. Chemical Structure of Oxytetracycline

This review focuses on "calcium oxytetracycline" (oxytetracycline calcium complex; CAS # 7179-50-2) and pesticides that contain calcium oxytetracycline for use in plant disease control in organic crop production (PAN 2006a provides a list of the pesticides). In cases where no information is available specifically for calcium oxytetracycline, related and relevant information for the parent compound oxytetracycline (CAS # 79-57-2) and/or oxytetracycline hydrochloride (CAS # 2058-46-0), a closely related compound, is provided and cited accordingly. The term "oxytetracycline[1]" is often used broadly to include oxytetracycline itself, calcium oxytetracycline, and oxytetracycline hydrochloride, which all have unique CAS numbers and EPA Pesticide

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[1] For regulatory purposes, EPA uses the term "oxytetracycline" to refer to pesticides containing calcium oxytetracycline or hydroxytetracycline monohydrochloride (oxytetracycline hydrochloride); there are currently no active pesticide registrations that contain oxytetracycline as the active ingredient (EPA 1993a, 2005a, PAN 2006b).

Chemical Codes (EPA 1988, 1993a, HSDB 2003a).[2] The term "tetracycline" refers to tetracycline (CAS # 60-54-8) and many tetracycline-derivatives that are used for a wide variety of medical, veterinary, and, to a much lesser extent, agricultural applications (HSDB 2003b).

Properties of the Substance:

Calcium oxytetracycline is an odorless light to dark brown powder that is most commonly produced as a wettable powder (EPA 1993a, Greenbook 2004a). Calcium oxytetracycline is slightly soluble in water (Greenbook 2004a). It is stable under normal use and storage conditions; light and extreme heat should be avoided. At high temperatures, it can decompose and form toxic gases (no information available as to specific gases formed).

Specific Uses of the Substance:

Oxytetracycline calcium complex (calcium oxytetracycline) is currently included on the National List as a synthetic substance allowed in organic crop production "for fire blight control only" (NOP §205.601(i)(11)).[3] Calcium oxytetracycline is typically formulated as a wettable powder and is most often spray-applied on pear trees (and to a lesser extent, apple trees) at early bloom to help prevent fire blight infection using ground or aircraft equipment (EPA 1988, 1993a, Guerena et al. 2003, PAN 2006a).

In addition to controlling fire blight, calcium oxytetracycline and/or oxytetracycline hydrochloride are used to control pear decline, bacterial spot on peaches and nectarines, lethal yellowing of coconut palm, and lethal decline of pritchardia palm (EPA 1993a). They are also used as an antifoulant when added to marine paints to prevent the growth of barnacles.

Oxytetracycline was first isolated from soil containing the bacteria *Streptomyces rimosus* in 1948 and was the second of the tetracycline antibiotics to be discovered (Hlavka et al. 1992, Klajn 2001). It and its many derivatives (including calcium oxytetracycline) have been used extensively for over fifty years in medical and veterinary practice and agriculturally as pesticides for over 30 years (EPA 1993a, HSDB 2003a). It is also an important drug for use at public and private fish hatcheries, including facilities culturing threatened and endangered fish (DEPA 2002, USGS 2003). Oxytetracycline, like other tetracyclines, is used to treat bacterial infections, both common (e.g., respiratory tract, sinuses, middle ear, urinary tract) and rare (e.g., anthrax, plague, cholera, Legionnaire's disease) (Dale and Mandelstam 2005) As with other tetracyclines, however, its use for treating these infections has become less common in the past decade due to its reduced effectiveness from increased resistance to its antibiotic action among targeted pathogens.

Approved Legal Uses of the Substance:

Calcium oxytetracycline is a registered pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which is administered by the U.S. Environmental Protection Agency (EPA). EPA issued a Registration Standard for oxytetracycline, oxytetracycline hydrochloride, and calcium oxytetracycline in December 1988 (EPA 1988) and a reregistration eligibility decision (RED[4]) in March 1993 (EPA 1993a, 1993b). A TRED[5] for oxytetracycline (i.e., calcium oxytetracycline and oxytetracycline hydrochloride) is

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[2] EPA has concluded that "the toxicity of all three oxytetracyclines [oxytetracycline, calcium oxtetracycline, oxytetracyline hydrochloride] is expected to be similar, and data generated on one compound can be used to assess exposure/risks of the other two" (EPA 1993a).

[3] Fire blight is a widespread bacterial disease caused by *Erwinia amylovora* that can severely damage apples, pears, and other ornamental shrubs and trees. Affected branches and twigs wither and turn black or brownish-black, as if burned. Under the 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, and can spread by pruning (especially during the growing season) and blowing wind and rain. Boyd and Jacobi (2005), McManus and Heimann (1997), and Ritchie and Sutton (2002) provide further information about fire blight and options for its control.

[4] 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).

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

scheduled for May 2006 (EPA 2005a). Tolerances (maximum legal residue levels) of 0.35 parts per million (ppm) are established for residues of these oxytetracycline pesticides in or on raw peaches, nectarines, and pears (40 CFR 180.337; EPA 1995).

Calcium oxytetracycline is regulated by the U.S. Food and Drug Administration (FDA) as an oral and injectable prescription drug (FDA 1999) and is to be prescribed only by a physician (MedlinePlus 2001). Veterinary and aquaculture use of oxytetracycline hydrochloride is also regulated by the FDA (CFR 21, Chapter I, Part 520, §520.2158a).

Action of the Substance:
Tetracyclines, including calcium oxytetracycline, are characterized by their antimicrobial efficacy against a wide range of Gram-positive and Gram-negative bacteria (Klajn 2001). They inhibit several processes essential for the survival and growth of bacterial cells, most notably synthesis of bacterial proteins (Klajn 2001, Ophardt 2003). Tetracyclines also alter bacterial membranes and cause the leakage of genetic material and other compounds out of the cells (Klajn 2001).

Status

International
Calcium oxytetracycline 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

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 calcium oxytetracycline) 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). CCOF (2005) and WSDA (2005) compare 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))

No specific information was available on the commercial manufacture of calcium oxytetracycline. The parent compound, oxytetracycline, is produced in commercial quantities through a fermentation process in which naturally occurring bacteria produce the substance; the manufacturer then uses chemical processes to isolate and purify the substance (Hlavka et al. 1992). Presumably, a further chemical treatment would be needed to form calcium oxytetracycline. Klajn (2001) provides a detailed discussion of the chemical synthesis of several tetracyclines, including oxytetracycline; see also Evaluation Questions #2 and #3 below.

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 stated above, no specific information was available on the commercial manufacture of calcium oxytetracycline. The parent compound, oxytetracycline is a naturally occurring substance and is produced in commercial quantities through a fermentation process (Hlavka et al. 1992). Presumably, chemical alteration of the parent compound would be required to yield calcium oxytetracycline. See Evaluation Question #3 below for further detail.

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

The parent compound, oxytetracycline, is created by naturally occurring soil bacteria (*Streptomyces* species) and is produced in commercial quantities through a fermentation process (Hlavka et al. 1992, HSDB 2003a, Klajn 2001). However, the processes used to extract and purify the substance from the bacteria and growth media are not naturally occurring. No specific information was available on the commercial manufacture of calcium oxytetracycline from the parent compound oxytetracycline (see also Evaluation Questions #1 and #2).

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

No specific information was available on environmental contamination resulting from the manufacture of calcium oxytetracycline or the parent compound oxytetracycline. However, the commercial fermentation of antibiotics usually takes about two to seven days and may require the use of several chemicals, such as solvents and antifoaming agents (Sengha 1993). 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 into the facility'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 oxytetracycline was not provided, so it is unclear whether manufacturers of calcium oxytetracycline actually use solvents. Other pollutants that could be discharged from fermentation processes include detergents and disinfectants used to clean equipment. Nitrogen and sulfur oxide gases may also be produced, which are regulated by EPA. Assuming calcium oxytetracycline 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) includes a general discussion of environmental pollution and opportunities to diminish pollution associated with the manufacture of pharmaceuticals, including antibiotics such as calcium oxytetracycline.

EPA waived all environmental fate data requirements for calcium oxytetracycline pesticides due to their limited pesticide use patterns and the availability of published literature that showed that oxytetracycline pesticides are absorbed and inactivated in soils, especially soils with high clay content (EPA 1993a, 1993b). EPA's determination 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), it is unlikely that calcium oxytetracycline will contaminate the environment.

Furthermore, the labeling and safety information on pesticides that is provided to users is intended to help prevent environmental contamination. Spilled calcium oxytetracycline materials should be swept up and placed in a container for onsite disposal or at an approved waste disposal facility (Greenbook 2004a, 2004b). Contaminated surfaces should be scrubbed with hard water detergent and water.

<u>Evaluation Question #5:</u> 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 "use of the active ingredients hydroxytetracycline monohydrochloride [oxytetracycline hydrochloride] and oxytetracycline calcium in accordance with approved labeling will not result in unreasonable adverse effects to…the environment" (EPA 1993a). EPA further noted that there are no environmental concerns associated with naturally-produced tetracycline. Thus, if used in accordance with NOP regulations and labeled instructions, it is unlikely that calcium oxytetracycline or its breakdown products will be harmful to non-target organisms or the environment (see also Evaluation Question #10 below).

<u>Evaluation Question #6:</u> 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 available to assess whether spray-applied calcium oxytetracycline or its byproducts can cause detrimental chemical interaction with other substances used in organic crop production. EPA (1993a) cited studies that indicate that oxytetracycline was absorbed and inactivated by clays. Because there are no concerns with naturally-produced tetracycline (EPA 1993a), it seems unlikely that calcium oxytetracycline, if used in accordance with NOP regulations and labeled instructions, would cause detrimental chemical interaction with other substances used in organic farming.

<u>Evaluation Question #7:</u> 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 information was available to assess whether spray-applied calcium oxytetracycline or its byproducts can have adverse biological or chemical reactions in the agro-ecosystem. As noted in Evaluation Question #5, when properly labeled and used in accordance with labeled instructions (EPA 1993a, 1993b), calcium oxytetracycline should not pose a significant risk to the environment. Therefore, it seems unlikely that proper use of calcium oxytetracycline to control fire blight in organic crop production would cause any adverse chemical or biological interactions in the agro-ecosystem.

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

No information was available to assess whether spray-applied calcium oxytetracycline or its byproducts can cause detrimental effects on soil organisms, crops, or livestock. However, the toxicity of veterinary oxytetracycline to bacteria that has accumulated in the sediment of fish farms has been shown to decline rapidly over time (DEPA 2002). Binding of the antibiotic to positively charged ions (e.g., magnesium) and other substances in the sediment has been proposed as a possible explanation for the biological inactivation of oxytetracycline. Furthermore, although calcium oxytetracycline has the potential to be toxic to microorganisms in the soil, it is also produced by naturally occurring soil bacteria (EPA 1993a).

As noted previously (see Evaluation Question #5), EPA determined that use of calcium oxytetracycline in accordance with approved labeling will not result in unreasonable adverse effects to the environment, which includes the subsurface environment.

<u>Evaluation Question #9:</u> 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 (1993a) stated that the toxicity of all three oxytetracyclines is expected to be similar, and data generated on one compound can be used to assess exposure/risks of the other two.

Based on acute toxicity studies in the published literature, calcium oxytetracycline is practically non-toxic to birds, fish, aquatic invertebrates, and non-target insects such as honey bees (EPA 1993a, 1993b). Therefore, EPA classified it as a Toxicity Category IV pesticide, indicating the lowest level of acute toxicity. Several studies have been conducted using laboratory animals to determine the potential adverse effects of oxytetracyclines in humans from their medicinal use and in other animals from veterinary use (EPA 1988, 1993a, HSDB 2003a, NTP 2006). For example, 14-day feeding studies of oxytetracycline hydrochloride in mice and rats showed no adverse health effects (EPA 1993a). One developmental toxicity study with oxytetracycline hydrochloride in rats showed a high incidence of maternal deaths and adverse health effects in offspring; however, extremely high dose levels were used. A similar experiment with mice yielded no effects. Carcinogenicity studies showed no evidence of cancer in mice and some equivocal evidence of cancer in male and female rats orally administered oxytetracycline hydrochloride in extremely high doses. Oxytetracycline hydrochloride has been found to exhibit mostly negative results in a series of tests designed to show whether chemicals interact with DNA or damage chromosomes, indicating it is unlikely to cause cancer (NTP 2006). In this regard, EPA has classified calcium oxytetracycline as a "Group D" carcinogen—one that is "not classifiable as to human carcinogenicity."

Calcium oxytetracycline, related oxytetracyclines, and tetracyclines in general have been used as beneficial human and animal drugs for several decades. MedlinePlus (2001) summaries side effects and contraindications associated with the medical use of tetracyclines. Such adverse health effects commonly include increased sensitivity of skin to sunlight and uncommonly include abdominal pain, headache, loss of appetite, nausea and vomiting, and yellowing skin. In addition, medical use of oxytetracycline has produced allergic reactions in some patients (EPA 1993a).

<u>Evaluation Question #10:</u> 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).)

Veterinary oxytetracycline has been found to have a half-life of 30 days in fresh water (pH = 7) but only 30 hours in sea water (pH = 8) (DEPA 2002). While abiotic degradation of antibiotics is the dominant breakdown process in the water, microbial degradation appears to be the main breakdown pathway in sediments. For example, the persistence of oxytetracycline in anoxic (no oxygen) bottom sediment deposits of fish farms has been investigated and found to be relatively high (estimated half-life of approximately 10 weeks); degradation occurs much more slowly in deeper layers of the sediment compared to top layers. Although the factors affecting the degradation of antibiotics in water and sediments are not completely understood, temperature, water flow, bacterial activity, chemical composition, and depth of the sediment will affect the decomposition and/or leaching of antibiotics, including oxytetracyclines. Oxytetracycline pesticides are absorbed and inactivated in dry soils, especially those with high clay content (EPA 1993b).

<u>Evaluation Question #11:</u> 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 (1993a) concluded that risks from dietary and occupational exposure to pesticides containing calcium oxytetracycline are negligible and that chronic dietary risks posed by all food uses of oxytetracycline pesticides are well below tolerance levels that would reasonably cause public health concern.

Workers (pesticide mixers, loaders, and applicators) are likely to be exposed to greater amounts of calcium oxytetracycline than the general public during its application to pears, peaches, and nectarines using foliar application methods[6]; fieldworkers also can be exposed post-application (EPA 1988). As stated above, EPA (1993a) concluded that risks from such exposures are negligible. EPA further concluded that label requirements will address concerns with potential allergic responses in oxytetracycline-sensitive people as well as the potential development of microbial resistance to oxytetracyclines. For this reason, pesticides containing calcium oxytetracycline registered for use on agricultural crops by foliar application methods must include the following restricted entry after application and protective clothing statements on the label (EPA 1993a):

- Entry into treated orchards (or "areas") is prohibited for 12 hours following application.
- Prolonged or frequently repeated exposure 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.

[6] The process of spraying a liquid onto the leaves of plants, such as fruit trees using a spray gun attached to a tank.

Evaluation Question #12: 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 fruit trees (cultivars) can be considered an effective start to managing this plant disease (Boyd and Jacobi 2005, Guerena et al. 2003, McManus and Heimann 1997). For example, there are several strains of pears and apples with a comparatively high level of fire blight resistance that are adapted to most of the contiguous United States. However, blight resistance for many of these cultivars appears to vary with growing conditions and cultivation practices, and none are completely immune (see Evaluation Question #14).

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 biological agent multiplies rapidly, colonizes open flowers, and excludes any significant subsequent colonization by the fire blight microorganism (*Erwinia amylovora*). However, tests have shown that this biological antagonist is not effective if applied after *Erwinia amylovora* is already present; it is, however, about as effective as calcium oxytetracycline (Stockwell et al. 2004).

Evaluation Question #13: 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)(10) allows "Streptomycin [streptomycin and streptomycin sulfate], for fire blight control in apples and pears only." More broadly, §205.601(i) allows eight other synthetic substances and groups of related substances for plant disease control in organic crop production. 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, if sprayed at, or before green-tip stage (i.e., buds showing ¼" of green tissue), provide some protection to apples and pears from fire blight infection (Guerena et al. 2003, McManus and Heimann 1997).

Evaluation Question #14: 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 development 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, McManus and Heimann 1997). Such practices include use of drip irrigation and limiting or excluding the use of fertilizers (including manure as currently allowed under NOP §205.203 (d)(5)), which can limit fast-growing succulent tissue (McManus and Heimann 1997). 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 (Boyd and Jacobi 2005). 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.

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