Formal Recommendation
From: National Organic Standards Board (NOSB)
To: the National Organic Program (NOP)

Date: April 11, 2013

Subject: Petition to remove the expiration date for Tetracycline on 205.601

Chair: Mac Stone

The NOSB hereby recommends to the NOP the following:

Rulemaking Action: ☐

Guidance Statement: ☐

Other: ☐

Statement of Recommendation: (Motion # 1) Failed

Amend the listing for tetracycline to remove the expiration date of October 21, 2014 and add the following annotation: 205.601 Synthetic substances allowed for use in organic crop production
(i) As plant disease control.
(12) Tetracycline, for fire blight control in apples and pears only until October 21, 2016. Tetracycline may only be used if the grower has implemented an integrated system of practices and materials to control fire blight. Orchard management systems must demonstrate an annual increase in the extent or number of alternative practices for managing fire blight.

Rationale Supporting Recommendation (including consistency with OFPA and NOP):

The support for the extended expiration date was to allow time for current testing of potential organic replacement materials to be completed by researchers and then time for implementation by growers into their Organic farm systems plans. This is a material already on the National List as approved.

The support for not allowing an extension and allowing it to expire as scheduled on October 21, 2014 is based on consumer concerns surrounding the use of antibiotics in organic crop production and the impacts that it may possibly have on human health. There was concern that as research progressed that there could be no certainty that further requests for extension of the expiration date would not occur and because of the need to restore consumer confidence the current expiration date should be upheld.

Committee Vote:

Moved: Harold Austin

Seconded: Nick Maravell

Yes: 9 No: 6 Abstain: 0 Absent: 0 Recuse 0

Statement of Recommendation: (Motion # 2)

Passed

Resolution:
The National Organic Standards Board is committed to the phase out of tetracycline. In addition, the Board strongly advocates to USDA a high priority for increased support for research into the alternative practices and materials for control of fire blight.

Rationale Supporting Recommendation (including consistency with OFPA and NOP):

The NOSB wishes to make its intent very clear to the entire organic community and recognize the need for research in this area.

Committee Vote:

Moved: Zea Sonnabend

Seconded: Colehour Bondera

Yes: 15 No: 0 Abstain: 0 Absent: 0 Recuse: 0

Statement of Recommendation: (Motion # 3)

The NOSB requests that the NOP investigate the ability of the Secretary to invoke its authority under the "Emergency Spray Programs" provision of the Organic Foods Production Act, 7 U.S.C. 6518(k)(6) and 7 C.F.R section 205.672, to allow the emergency use of oxytetracycline for fire blight during the period of October 21, 2014 to October 21, 2017.

Rationale Supporting Recommendation (including consistency with OFPA and NOP):

In order to minimize potentially devastating loss of trees during the period that growers believe is necessary to make the transition, the NOSB recommends that the NOP facilitate use of emergency provisions under OFPA.

See attached "Request from NOSB to NOP to investigate the emergency use of oxytetracycline for fire blight during the period of October 21, 2014 to October 21, 2017."

Committee Vote:

Moved: Jay Feldman

Seconded: Jean Richardson

Yes: 14 No: 1 Abstain: 0 Absent: 0 Recuse: 0

Rationale for request from NOSB to NOP to investigate the emergency use of oxytetracycline for fire blight during the period of October 21, 2014 to October 21, 2017.

In order to minimize potentially devastating loss of trees during the period that growers believe is necessary to make the transition, the NOSB recommends that the NOP facilitate use of emergency provisions under OFPA.

Under OFPA, 7 U.S.C. 6518(k)(6), the NOSB is given broad authority to advise the Secretary on "Emergency Spray Programs." The statute states: "The Board shall advise the Secretary concerning rules for exemptions from specific requirements of this chapter (except the provisions of section 6511 [additional guidelines residue testing] of this title) with respect to agricultural products produced on certified organic farms if such farms are subject to a Federal or State emergency pest or disease treatment program." Therefore, the authority to exempt an organic farmer from the specific requirements of OFPA is limited to a Federal or State emergency.

However, the National Organic Program is a federal program under the umbrella of the USDA. It stands to reason that USDA (under direction from the NOP) is in the position to issue such a federal emergency pest treatment program if organic farmers do indeed have a problem with fire blight during the three year transition.

The National Organic Regulations anticipated this situation and created the following rules in 7 C.F.R. 205.672 (in relevant part):

"When a prohibited substance is applied to a certified operation due to a Federal or State emergency pest or disease treatment program and the certified operation otherwise meets the requirements of this part, the certification status of the operation shall not be affected as a result of the application of the prohibited substance: Provided, That:

(a) Any harvested crop or plant part to be harvested that has contact with a prohibited substance applied as the result of a Federal or State emergency pest or disease treatment program cannot be sold, labeled, or represented as organically produced…"

Since tetracycline is permitted in conventional agriculture, the emergency pest treatment program will not require approval by EPA under FIFRA as long as the application is in accordance with tetracycline's registration. (FIFRA Section 18 only authorizes EPA to allow an unregistered use of a pesticide for a limited time if EPA determines that an emergency condition exists.)

The situation presented by the tetracycline sunset is unique. The emergency spray program would not require use of an unregistered pesticide, nor would it protect against a plant pest or noxious weed as defined by APHIS. Therefore, USDA-NOP must be the agency to create the exception, under the plain language of the statute.

National Organic Standards Board
Crops Subcommittee
Petitioned Material Proposal
Oxytetracycline

February 5, 2013

Summary of Proposed Action:

The Crops Subcommittee proposes to:
Remove the existing expiration date of October 21, 2014 for oxytetracycline and replace that with a new expiration date of October 21, 2016. This would be for use in both apples and pears for control of fire blight.

The Crops Subcommittee would also like to put forward this resolution:
Resolution: The National Organic Standards Board is committed to the phase out of this material. Between now and 2016 the Board urges growers and certifiers to include in organic systems plans an annual increase in the extent and/or number of alternative practices and materials that are trialed for controlling fire blight. In addition, the board strongly advocates to USDA a high priority for increased support for research into these alternative practices and materials.

Introduction

A Petition to the National Organic Standards Board (NOSB) was received for Removal of the Expiration Date (October 21, 2014) for the Authorized Use of Tetracycline for the Control of Fire Blight in Apples and Pears. It was furthermore requested by the petitioner to reinstate Tetracycline to the sunset process.

Because this subject is complex and there are two different positions to be represented, this recommendation is organized to include a brief history of previous NOSB decisions involving this substance, followed by two separate discussion sections from those for (Majority Position) and against (Minority Position) an extension. These are designed to supplement the points raised in the checklist.

The sub-committee acknowledges the concerns of consumers and previous NOSB members who feel that it is time to phase this material out from organic agriculture. The two positions represented in the discussion section of this document differ on the timing of the phase-out. Additional concerns are being put forward in a separate resolution on the subject.

Background

NOSB History on Tetracycline in Fruit Production

1995- A TAP review on “Antibiotics” was reviewed by the NOSB. All three reviewers thought that tetracycline and streptomycin were non-synthetic. Voted on Nov. 1995 as three separate Listings:

Antibiotics (Avermectin) – failed 3-6-4

Antibiotics (Streptomycin sulfate) – Determined to be synthetic; vote – unanimous. The NOSB's decision is to allow this material for use in organic crop production; vote: 10 aye/3 opposed. Annotation: Permitted for use as a fire blight control in apples and pears only. To be reviewed again in two years.
Antibiotics (Terramycin – Oxytetracycline calcium complex) – Determined to be synthetic; vote – unanimous. The NOSB's decision is to allow this material for use in organic crop production; vote: 10 aye/ 1 opposed/2 abstentions. Annotation: To be reviewed again in two years.

No discussion was given in transcript except that the NOSB was to set up a task force to look further into these materials in the two year time frame.

2006 - A TR commissioned by the NOSB for the sunset review was received in January 2006. Sunset review of Tetracycline and Streptomycin in April 2006. (discussion 4/20/06 pp.41-78) Discussion is worth reading because of the wide variety of concerns raised from the concern of the CDC for antibiotics in the environment to the quantity of pear trees being cut down in Romania and other European Union (EU) countries. Mr Neal from the NOP stated that the board should not be making changes in annotation during sunset especially because nobody presented any economic impact data in the Sunset Federal Register notice for removal of these materials.

The Crops Committee recommends renewing the materials listed in Section (i) as plant disease control. Streptomycin and tetracycline for fire blight control in apples and pears. 7-4-1-2 (p.411)

2007- A petition was received to add Oxytetracycline hydrochloride to the National List. Oxytetracycline calcium complex is the form already on the list and the petitioned form is similar but from a different manufacturer.

2008 - The NOSB reviews the new petition for adding another form of tetracycline (Oxytetracycline hydrochloride) at their public meeting November 19, 2008. The 2006 TR was used for the checklist, with some supplemental references. The committee recommendation to add oxytetracycline hydrochloride for fire blight control only to NL §205.601 (i) failed: 0-6-0-0. The committee recommendation states: "Considering the intense on-going public comment that the committee has been receiving on the negative public health impacts of these materials, the committee anticipates that a petition will be filed for the removal of tetracycline and streptomycin from the National List before their sunset date of October 2012. Adding a new form of tetracycline to the list at this time would be counterproductive".

At the NOSB meeting, Dr. Robinson indicated that adding a new form to the existing listing would "reset the clock" for another 5 years until sunset. The motion to add the Oxytetracycline hydrochloride failed unanimously. However, an NOSB member then moved to reconsider the listing vote because of "new information regarding possible action on this petition….." The NOSB then voted to reconsider the vote before it was stated what the new information was. This passed: 11-0-1-2.

The next motion was "to change….the listing and annotation of tetracycline to read: tetracycline for use only in organic crop production for fire blight control until October 21st, 2012". After an effort to change the date to December 2009, but the NOP stated that they could not get a rule change out by then, this motion was voted with no further public comment. Vote was: 13-0-1-1 to amend the original recommendation. On the motion to add tetracycline for fire blight control only on the National List Section 205.601 (I) until October 21st, 2012. Vote: 13-0-1-1.

2010 – A petition was submitted to remove the Expiration Date for Tetracycline, in accordance with 75 FR38696 where the NOP states: "…*we note the NOSB's recommendation to only allow the continued use of tetracycline for fire blight control until October 21, 2012. Though some commenters have requested the removal of the expiration date from the use of tetracycline, the NOP recommends that such interested parties petition the NOSB using the petition process outlined in 72 FR 2167* (January 18, 2007) *to have the expiration date removed from the authorized use of the substance".*

2011 – Review of Petition to remove Expiration Date for Tetracycline. A new TR was commissioned. The Crops Committee did not receive it before issuing their recommendation, but did review their decision in light of the TR. The TR was posted for public view on the last day of the written comment period.
At the April 2011 meeting the NOSB recommended to:

> "Adopt the petition to amend the listing for tetracycline to remove the expiration date of October 21, 2012 and be annotated as follows:
>
> §205.601 Synthetic substance allowed for use in organic crop production.
> (i) As plant disease control.
> (12) Tetracycline, for fire blight control in apples and pears only until October 21, 2014.
>
> The NOSB expects that members of the industry will collaborate and coordinate efforts in preparing for the eventual removal of this material from the National List, specifically optimizing the use of resistant rootstocks and cultivars, preventive management methods, and the use of alternative, allowed biological and chemical controls, whenever warranted".

Discussion Regarding NOSB History
From the perspective of 2012 looking back on the previous actions of the NOSB and NOP, there are inconsistencies and errors along the way. A few of the most apparent are:

- The task force and two year review was never implemented after the 1995 recommendation.
- The vote to re-list in the first sunset review in 2006 was not a 2/3 majority as is required today.
- The 2008 decision to change from adding another form of tetracycline to the National List to a firm expiration of all forms in 2012 was done without a written public comment period. What happened at the meeting was different from the recommendation on the petition that was posted in advance.
- The proposed rule that followed the 2008 decision received some public comment about economic harm but not enough to trigger a USDA economic impact review, even though the 2006 statement from the NOP indicated such impact must be considered.
- The public did not have access to the TR during the written public comment period prior to the 2011 recommendation, but NOSB members did.
- The 2011 proposed rule to extend the sunset date to 2014 again did not result in an economic impact review by the USDA.

<u>Discussion of the Extension Position</u> (Majority Position)

Because of the very large investment of time and money that establishing an orchard entails, the variety of locations that apples and pears are grown, and the very rudimentary state of research on alternatives to this material in that variety of locations, we are supporting slowing down the removal of tetracycline from the National List.

Since the organic pear industry is more at risk to fire blight than apples (see Pear Perspective later in this document) there is concern that pear research and control measures are lagging behind and that an expanded time frame will be needed.

A slightly extended date of 2016 will benefit consumers and growers alike. The few more seasons of research will enable new products to be tested in both apples and pears in a variety of weather conditions. Allowing the new EPA data to be reviewed will inform many of the unanswered questions stakeholders may have about oxytetracycline.

Because of the need to make sure that this material is phased out, a resolution motion has been added to affirm the commitment by the NOSB to all organic stakeholders. The NOSB must ensure that the decisions made reflect due consideration of the various needs and concerns of the vast array of all our organic stakeholders, especially when dealing with complicated issues, such as this one.

This section focusses on how the material is used in the context of both plant and human health. Specific portions address Checklist categories as noted.

Introduction

In 2009, about 15% of the total apple area and 40% of the pears (organic and conventional) were treated with streptomycin or oxytetracycline for control of fire blight, the disease caused by the bacteria *Erwinia amylovora*.

The core issue here is whether there is a risk of enhancing antibiotic resistance in human pathogens. The most astute and experienced scientists in this area realize that science and medicine have to find a way to co-exist with resistance, including managing reservoirs of resistance in the environment and preventing development of new forms of resistance. (Am. Academy of Microbiology, 2009)

While oxytetracycline is used to treat a wide variety of human bacterial infections and diseases, the 2011 TR (lines 593-597) cites the Centers for Disease Control and Prevention (CDC) as indicating that resistance has not yet occurred for these drugs. Also mentioned is that there are alternative antibiotics to oxytetracycline for human illness.

In fact, the American Academy of Microbiology review of Antibiotic Resistance (2009) states that biocides, such as triclosan or quaternary ammonium compounds, may represent a more important threat to the future of antibiotics than antibiotics themselves. Because they have become so widespread in consumer products at sub-lethal concentrations, they promote the evolution of bacterial resistance. Other environmental factors that can contribute to resistance include the use of sewage sludge and water from sewage facilities, overuse of non-antibiotic drugs, and other chemical stressors that contribute to selective pressure such as heavy metals in animal feeds.

The EPA is reviewing the pesticide registration for oxytetracycline. (US EPA, 2008) Part of this review will include environmental fate data as well as the potential for antibiotic resistance transfer from plant pathogens to human pathogens. The EPA's final registration review decision and information is scheduled for 2014. (TR lines 609 - 612) While the EPA studies only a risk assessment point of view which is not the same as the full spectrum of criteria that the NOSB considers, this review is particularly important because it is calling for additional ecological data, such as aquatic toxicity to both plants and animals, terrestrial plant toxicity, honeybee toxicity, and avian reproduction studies. They are expecting an immunotoxicity study to determine whether repeated exposure from oxytetracycline will affect the immune system. After the docket closes in June 2014 the EPA will develop a final work plan and schedule for registration review of oxytetracycline, expected in September of 2014.

Quantity and Use Patterns

In 2009 in the US, 16,465 kg (active ingredient) was applied to orchards, which is 0.12% of the total antibiotics used in animal agriculture (Stockwell and Duffy, 2012)

In the USA, the preharvest interval for application of oxytetracycline and streptomycin varies from between 21 and 60 days, depending upon the compound and the crop. (McManus & Stockwell, 2001)

Resistance in *Erwinia amylovora* (Fire Blight)

While there are three major strategies for developing tolerance, efflux pumps, alteration of the ribosome to block binding, and production of enzymes to inactivate the material, resistant strains to tetracyclines have not been detected in orchards in the USA (McManus et al., 2002)

This plant pathogen does not develop resistance in the laboratory during exposure to oxytetracycline. In laboratory experiments, E. amylovora will be resistant to tetracycline if resistance genes are introduced. Nonetheless, there are no examples of acquisition of tetracycline-resistance genes by E. amylovora in orchards. This, in part, may be due to low populations of tetracycline-resistant plant associated bacteria on flowers in fruit orchards that could be a potential source of resistance genes. (Schnabel and Jones, 1999) In orchards treated with antibiotics, only 5% of the bacteria isolated from flowers or leaves was resistant to oxytetracycline (10 µg/ml). (Schnabel and Jones, 1999)

Checklist Discussion:

Category 1, Questions 8 and 9: Mode of Action, Breakdown, and Residues

Mode of Action
Oxytetracycline inhibits the multiplication of bacterial cells by binding reversibly to the bacterial ribosome and blocks proteins while bound. (McManus et al., 2002)

Bacteria from the environment migrate to the flowers over time given favorable environmental conditions. As flowers develop and form fruit tissues, detectable populations of bacteria decrease and are restricted to the stem end and the calyx end of the fruit. Intact waxy surface of the fruit does not support bacterial growth.

Breakdown
Even though they can be detected on plant surfaces for up to a month after application, their capacity to inhibit bacterial growth is lost within a week after application. Oxytetracycline is thermostable on leaves, but rapidly degrades when exposed to natural sunlight. 44% within 1 day, 92% within 4 days, and near the detection limit of 50 ppb by a week after application. (Christiano et al., 2010) It is not rainfast on leaves: 2 minutes of simulated rain reduced residual concentrations by 67% and an hour reduced it near the detection limit. (Christiano et al., 2010)

The 2011 TR points to a study by Chander et al. (2005) that tetracycline remains biologically active even while tightly adsorbed to clay particles in soil. (lines 322 – 323) This is used to bolster the concern that the residues persist in the environment and may contribute to bacterial resistance. This study however was done in a lab using soil that was centrifuged and innoculated for 24 hours at concentrations many times higher than even a manure application would contribute, much less a foliar spray. This 24 hour time frame tells nothing about persistence in environmental conditions, nor does it acknowledge the role of light in breaking down the material. Other research indicates that the bioavailability of tetracyclines is limited in soil because it forms strong bonds with metals and organic matter. (Lui et al, 2009; Popowska et al, 2012) The relative activity and breakdown is strongly influenced by soil composition, shifts in microbial populations, exposure to light and other environmental factors (TR lines 458- 467).

The petitioner, in their rebuttal to the NOSB 2011 recommendation (submitted with the 2012 petition), states that tetracycline breaks down into 3 by-products found in the soil and much lower levels than the parent compound and with much reduced antibacterial potencies. The tetracycline molecule has a strong affinity to form chelates or complexes with divalent cations. This action reduces the bioavailability of oxytetracycline as well as its antibacterial effects, rendering it inactive in soils through a combination of degradation, absorption, and chelation. (Halling-Sorensen et al., 2002) This research was done on tetracycline being applied in animal manure, at much higher concentrations and with a lot of supplemental nitrogen than would be found in tree fruit applications.

A statement in the NOSB 2011 recommendation checklist (Category 1, Question 9) for tetracycline states that "Tetracycline is taken up by plants and appears in all tissues and exudates." This is not fully borne out in literature. While it has recently been shown that it can be taken up by annual plants from soil after a manure application (Kumar et. al., 2005), it is not always the case for all plants and has not been shown for perennials.

Residue on Fruit
For oxytetracycline the residue tolerance level on tree fruit crops is 0.35 ppm. To date there are no reports of fruit with residues greater than this. In a risk assessment study the EPA states that typical pharmaceutical oxytetracycline exposure to humans would be 50,000 to 200,000 times greater that the theoretical dietary exposure. (US EPA 2008)

Residue data for oxytetracycline were reported by the U.S. EPA (2005) as part of the process to allow the material to be used on apples. Field trials were conducted in various parts of the country. Oxytetracycline was applied at rate from 0.5 to 11 times the proposed seasonal rate of 1.53 lb a.i./acre, and at 49-60 days before harvest. The Limit of Quantification was 0.013 ppm. Most samples were at or below this limit, while the highest residue level detected was 0.252 ppm. There was no dose response to increasing rates in the residue data. No data were reported for trees treated only once or twice during bloom, which is the most common use pattern in the western U.S. (Stockwell and Duffy 2012)

Category 1, Question 10

Potential for Humans to build Resistance to Medical Tetracyclines
There are numerous reports that the use of antibiotics in animal production is associated with increase of antibiotic-resistant bacteria in animals, waste-water, and manure (for some examples see Larsen 2010, Wright 2010). A direct linkage was reported between infection and colonization of humans by antibiotic resistant bacteria from farm animals. (Larsen et al 2010) No direct linkage has been demonstrated between antibiotic resistant bacteria in humans and antibiotic sprays on plants. (Stockwell and Duffy, 2012)

The TR from 2011 cites an article by Rezzonico et al. (2009) that other countries have placed restrictions on antibiotics due to concerns about horizontal transfer of resistance genes from bacterial in the agricultural setting to clinically relevant bacteria. However such a link has never been documented (2011 TR lines 614 - 616) and this article only referred to streptomycin and not to oxytetracycline.

Models generated by the EPA indicate that the potential for direct exposure of humans and their microflora to antibiotics deployed for crop protection is several thousand-fold less than for the medical use of antibiotics. (US EPA 2006a, 2006b, 2008)

For humans, tetracyclines are administered at doses between 1000 mg to 2000 mg daily for at least a week (http://www.drugs.com/dosage/tetracycline.html) or a minimal exposure of 7,000 to 14,000 mg during a prescribed cycle. To date, there are no reports of fruit with residues at or above the permitted tolerance for oxytetracycline at 0.35 mg/kg fruit.

In the Code of Federal Regulations (21CFR556, Sec. 556.720: Tetracycline), the acceptable daily intake (ADI) for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) is 25 micrograms per kilogram of body weight per day. The ADI is an estimate of the amount of a substance which can be ingested daily over a lifetime by humans without appreciable health risk. For a 100 kg person, the ADI for tetracyclines is 2.5 mg. If a person ate fruit with oxytetracycline residues of 0.35 mg/kg fruit, then they would need to consume 7 kg of fruit daily or 47 apples (150 g) each day to reach the ADI. (Stockwell et al., 2013)

Human pathogens have not been detected in surveys (Pusey et al., 2009) of genera of bacteria on flowers of fruit trees. Given this, direct enrichment of antibiotic-resistant human pathogens from antibiotic sprays on plants is unlikely.

It is well established that bacteria harboring transmissible antibiotic resistance genes are common in the environment, even in environments that have never been exposed to exogenous antibiotics. (Duffy et al., 2011; Popowska, et al., 2012; Sundin and Bender, 1996) Given that human pathogens are not common colonizers of pome fruit flowers, the probability of direct acquisition of antibiotic resistance genes from resident phyllosphere bacteria in the tree canopy is reduced. (Stockwell and Duffy, 2012)

Even those most concerned about spread of antimicrobial resistance state that the molecular details of the emergence of resistance genes "...suggest that an enormous number of encounters between agent and germs have been needed to produce the first emergence of most resistance genes." (O'Brien, 2002) Presumably, this resistance would first be seen in the target organism, *Erwinia amylovora*, since it has far more "encounters" than any human pathogen organism would have in an orchard. Yet this has not been the case. This same article continues that resistance in the bacteria for the first host is key to making it more likely to transfer to a second strain on another host. The implication is that the resistance gene has to come into contact with human or animal pathogenic bacteria in order to move out of the orchard environment. Since plant hosts are not mobile in the way humans or animals are, the chances of this happening mean that the alternate host has to come into the orchard while the material is still active.

During the process of spraying, a portion of the material lands on the orchard floor. The supposition that resistance genes could build up in the soil has not been supported by recent studies. (Duffy et al., 2011; Popowska, et al., 2012; Walsh, et al., 2011) Tetracycline is absorbed onto soil particles and rapidly rendered inactive. (Subbiah et al., 2011) The authors of this study speculate that antibiotic residues from foliar applications would have minor effects, if any, in increasing antibiotic resistance genes in soils.

Conclusion
There is no evidence that applications of antibiotics to orchards during bloom contributes to antibiotic-resistance in human pathogens. Human pathogens have not been found in orchards and would have to be present for the resistance genes to transfer. (Stockwell and Granatstein, 2013) The fire blight organism has not shown any signs of resistance itself, thus negating the first step in the transfer of potential resistance genes. The tetracycline is active for a very short time period on plant tissues and it is long before harvest. (Christiano et al, 2010) Naturally occurring tetracycline resistant bacteria may be minor components of the overall bacterial communities found on apple flowers and in soils, but their presence is independent of the antibiotic application. The amount and timing of the use of this material in an orchard environment does not contribute to any human health concerns.

Checklist Discussion Continued:
Category 2 Questions 9 and 10: The Pear Perspective

Fire blight disease caused by *Erwinia amylovora* poses unique challenges in pears. Because pears bloom earlier than apples in general and the bloom can last for a longer period, they are often more susceptible to fire blight. This discussion focusses on some issues unique to pears because their production will be more challenged by the expiration of oxytetracycline.

Pear growers use integrated management to control fire blight that includes removing infected wood during pruning and spraying copper at early green-tip help to reduce inoculum levels before the growing season. Preventive sprays of oxytetracycline and/or streptomycin are used because applications before infection are known to be more effective than those applied after infection. (Adaskaveg, 2010; Keil & Wilson, 1962) These preventive sprays are based on predicted weather conditions from computer models such as Cougar Blight or Maryblyt Model. However these models are better at predicting high-infection risk from in the primary bloom that is relatively short but not in the secondary (rat tail) bloom that can last two months. (Holtz et al., 1999; Holtz et al., 2002) They also failed to predict warm dew infection periods during rainless weather in the Central Valley of California. (Holtz et al., 2002) The Zoller Degree Hour Model (Zoller, 2000) is widely used in pears and can predict the build-up of the causal bacteria in blossoms, as well as suggesting risk-based changes in treatment frequency needed during rainless infection periods. Refinements of all the models is ongoing, but each pear region needs a model tailored to the local specific growing conditions; something not currently available.

Pear varieties show less variation in resistance than apples and are generally more susceptible to fire blight. (Granatstein et al., 2011) A few "blight resistant" cultivars have been developed but these have not shown full resistance in all locations and have not been popular with consumers.

The alternatives to oxytetracycline and streptomycin are not as well researched in pears as in apples, but some of the same limitations are more pronounced in pears. Coppers are being tested at green-tip stage in pears but cannot be used at bloom or after on clear-skinned fruit because they cause fruit russetting, rendering the fruit unmarketable. The biological antagonists such as *Pseudomonas fluorescens* A506, or *Pantoea agglomerans* strains C9-1 and E25 have either not been tested for as long a period of time in pears and/or the results have been inconsistent. The new yeast product, Blossom Protect, has only been tested for one year in pears. The biological products also must be separated in time from the use of coppers or lime-sulfur, thus possibly interfering with scab treatments. The use of alternative treatments has also resulted in increased russet and loss of fresh market quality. (Zoller, 2011)

In general organic production of pears has lagged behind that of apples largely because of the fire blight problems. Pears take 6 to 7 years to bear their first significant commercial crop and live for 50 to 80 years, so a planting is a larger investment in time and not as easy to replace as apples, which can produce in 3 to 4 years and live 20 to 50 years. A very limited quantity of pears is now produced without antibiotics for the EU market. These blocks often have to be removed from an EU program periodically to address fire blight infections.

Conclusion for Majority Position

The organic farming sector is committed to developing and implementing a non-antibiotic approach to controlling fire blight in organic apples and pears. Some progress has been made in recent years to identify research needs, secure some research funding, and take an initial look at some promising alternative controls. Because apple and pear growers are spread throughout a majority of the country and are decentralized in organization, the relevant regional research and extension of those results will not reach all the growers by the 2014 expiration date.

Retaining that date could potentially cause immense financial loss for a variety of organic stakeholders and could cause many producers to go out of business. Their fruit could potentially be replaced with organic fruit from Chile, China, and various other countries where there is no fire blight, or with conventionally grown fruit containing a full array of chemicals.

A short extension will benefit organic stakeholders that could be affected by this decision, such as consumers, producers, handlers, and retailers. Giving producers a chance to have good access and experience with other control methods will make sure that consumers have a choice of variety of organic fruit in the marketplace that they have grown accustom to having.

Discussion of the Position to Allow Expiration of Oxytetracycline Listing in October 2014 (Minority Position)

It has been clear for several sunset and expiration reviews that environmental and consumer groups do not support another extension of the listings for antibiotics (oxytetracycline –referred to as tetracycline– and streptomycin) in apple and pear production. This position is based on the analysis that antibiotics for fire blight fail the three NOSB review criteria for materials used in organic production—(i) environmental and health impacts, (ii) compatibility with organic principles, and (iii) essentiality.

Basis for Urgent Action to Remove Antibiotics from Organic Production

There are several principal understandings that form the foundation in science and law for acting to remove antibiotics from organic apple and pear production in an urgent manner:

i. Tetracycline is an antibiotic considered by the World Health Organization to be of critical importance to human medicine.[1]

ii. Tetracycline is used in a way—broadcast spray on trees—that exposes bacteria in the orchard, particularly in the soil, to the antibiotic.[2]

iii. Current science shows that environmental exposure to antibiotic use in the environment is the major cause of development and spread of antibiotic resistance in human pathogens.[3]

iv. The spread of antibiotic resistance does not require contact between the antibiotic and human pathogens because the major means of spreading antibiotic resistance is through the transfer of genes between different bacteria.[4]

vi. Uses resulting in low residues (subtherapeutic or subinhibitory levels) can create a high health risk.[5]

vii. Tetracycline resistance is evident and expected to grow if urgent use precaution is not exercised.[6]

viii. Organic National List standards require adherence to practices and inputs that ensure, “Production practices implemented in accordance with this subpart must maintain or improve the natural resources of the operation, including soil and water quality.” (7 CFR §205.200**)**

NOSB Review Criteria

I. Environmental and Health Effects.
Finding: Antibiotic use in organic agriculture —in both animal and plant production— contributes to the spread of antibiotic resistance in human pathogens, while infectious disease are a critical human health issue increasingly uncontrolled. Organic standards are intended, by statute and rulemaking, to lead in the adoption of practices that reverse threats. Several hazards associated with the use of antibiotics in fruit production have been documented in technical reviews.

Summary
Agricultural use of antibiotics—including the spraying of tetracycline in orchards—increases the proportion of antibiotic resistant bacteria through the well-known mechanisms of selection and horizontal gene transfer. [7] This is affirmed in standard scientific texts and is part of the extensive record of NOSB proceedings,[8] which has supported extensive efforts and votes by the NOSB to end the use of antibiotics in organic agriculture. The mechanism of antibiotic resistance –the use of antibiotic anywhere increases the proportion of antibiotic resistant bacteria everywhere– is a fact well-known to all microbiologists and has been crucial to the development of strategies to reduce antibiotic resistance in bacteria that produce human disease.[9] Tetracycline and streptomycin are both considered “critically important antimicrobials”[10] and according to federal guidance, the risk to human health from their use is “high.”[11]

Tetracycline Resistance
Resistance to an antimicrobial agent such as tetracycline is promoted when microbes (in this case, bacteria) are exposed to an antimicrobial agent.[12] When bacteria are exposed to tetracycline, two things happen: (1) the bacteria that are susceptible to tetracycline are killed, while those not susceptible survive,[13] and (2) conjugation with other bacteria increases.[14] This conjugation is a sharing of genetic material known as “horizontal gene transfer,” and it does not need to be between related bacteria.[15] It can be between an innocuous soil bacterium and *Escherichia coli* (E-coli), for example*.*[16] Those bacteria receiving genes through conjugation may, in turn, share those genes with other bacteria, including human pathogens not present in the orchard.[17]

Therefore, spraying tetracycline in an orchard will increase the proportion of bacteria that are resistant to tetracycline, and increase the likelihood that human pathogens –which may not be in direct contact with tetracycline, but may be in contact with bacteria that were in direct contact with tetracycline –will end up with genes for tetracycline resistance. This is why the primary strategy for maintaining the effectiveness of antibiotics is to eliminate all non-therapeutic use.[18]

This is not a theoretical issue or a problem of scientific uncertainty. The consequences of spreading genes for resistance to tetracycline are considered severe by the World Health Organization (WHO). WHO has classified tetracycline as a “critically important antimicrobial” because it meets two criteria: (1) it is used as the sole therapy or one of few alternatives to treat serious human disease (limited therapy for infections due to *Brucella*, *Chlamydia* spp. and *Rickettsia* spp.), <u>and</u> (2) it is used to treat diseases caused either by organisms that may be transmitted via non-human sources or by organisms that may acquire resistance genes from non-human sources (transmission of *Brucella* spp. from non-human sources). [19]

Although the promotion of resistance to tetracycline in human pathogens does not require direct contact between those pathogens and the sprayed tetracycline in the orchard, there is evidence that such direct contact does occur. First of all, tetracycline may be taken up by plants, so that pathogens may be exposed when a person consumes the fruit.[20] Second, there is an EPA food residue tolerance for tetracycline on the fruit, supported by field studies that found residues on fruit after harvest--which is another way for pathogens in a person to be exposed to tetracycline.[21] Finally, tetracycline maintains its antibiotic activity as it is adsorbed to soil particles and later released, allowing direct exposure to tetracycline through soil in air, water, or on fruit.[22] Workers, of course, are at higher risk of direct exposure.[23]

Other Impacts on Human Health

The major impact on human health from tetracycline use is the increase in the pool of antibiotic resistant bacteria that can lead to resistance in human pathogens.[24] However, other health effects are associated with exposure to tetracycline, such as developmental toxicity, and full formulations applied to orchards, which contain the known human carcinogen crystalline silica.[25]

Environmental Contamination and Ecological Impacts

The 2006 TR (TR1) lists a number of substances that may be released in the manufacture of tetracycline, including solvents, detergents, disinfectants, and oxides of nitrogen and sulfur.[26]

Quoting from the 2011 TR (TR2),

> "Thiele-Bruhn (2003) reported that, in general, the effects of an antibiotic on soil organisms are essentially influenced by the bioavailability of the antibiotic, which depends on soil properties, availability of nutrients, and presence of root exudates. Tetracyclines exhibit strong adsorption to soil components such as clay and organic matter and form strong bonds with metals in the soil. These interactions limit the bioavailability of tetracyclines to microorganisms in the soil. (Lui et al., 2009) Tetracycline can persist in soil for long periods of time without showing antimicrobial activity, and high concentrations can be achieved. (Popowska et al., 2010) Upon later release from soil components, it can exhibit antimicrobial activity. Factors that may result in a release of tetracycline from the soil include changes in organic material composition of the soil, shifts in microorganism populations, or changes in soil pH (Aga et al., 2005)."[27] The TR also mentions reductions in fungi, fungal/bacteria biomass, rate of soil nitrification, nodulation of legumes, length of fungal hyphae of mycorrhizal fungi, and bacterial diversity.[28] The TR cites a study that found no direct effects on three species of soil fauna, but "the authors noted that it is not possible to exclude the possibility of indirect effects on soil fauna caused by changes in the microbial community following application of oxytetracycline."[29]

Key Elements of Scientific Understanding

The concerns about the human health impacts of tetracycline use are based on an understanding of the mechanisms by which antibiotic resistance develops and spreads and is directly associated with antibiotic resistance. In this context, the NOSB assesses whether an allowed material in organic production is contributing to an adverse impact even though it may be permitted under statutes other than the Organic Foods Production Act (OFPA). The standard of protection in OFPA and its overriding commitment to sustainability and improvement of the environment means that NOSB decisions must seek to exceed risk minimization standards of other statutes by looking to eliminate dependencies on practices and inputs that cause harm. This is captured in 7 CFR 205.200, “Production practices implemented in accordance with this subpart must maintain or improve the natural resources of the operation, including soil and water quality.” Thus, it is the intent, spirit, and letter of OFPA that puts organic systems at the forefront of rejecting practices that are not sustainable and puts us on a path detrimental to the environment and health.

(i) Horizontal gene transfer and the American Academy of Microbiology, 2009.[30] The American Academy of Microbiology (AAM) report, cited above in the pro-extension majority position discussion, must be read in full to glean a complete understanding of its position and urging that antibiotic resistance be treated as an urgent matter to prevent the spread of resistance in the environment and preserve the efficacy of antibiotics for human therapeutic use. Therefore the elements of the report are cited here:

- “If science and medicine cannot win a war against antibiotic resistance, what CAN be done? We have to find a way to co-exist with resistance. To minimize the loss of life, we can develop strategies to prevent new resistance from spreading and, where resistance already exists, identify the strains we need to protect against, find ways to treat resistant infections effectively in patients, and manage reservoirs of antibiotic resistant strains in the environment. Preventing development of new forms of resistance should rely, in part, on prudent use of antibiotics with an eye to the ecologies of pathogens and other microorganisms.”[31] (pp.5-6)
- “It is mandatory to prevent the needless use of antibiotics…” (p.2)
- “Horizontal gene transfer, in which genetic information is passed between microbes, allows resistance determinants to spread within harmless environmental or commensal microorganisms and pathogens, thus creating a reservoir of resistance.” (p.1)
- “Horizontal gene transfer—the movement of genetic material from one organism to another—is the primary mechanism by which bacteria acquire antibiotic resistance. Antibiotics promote this genetic exchange by inducing the transfer of conjugative elements.” (p.8)
- “[A]ntibiotics always select naturally resistant bacteria and the strains which have acquired resistance…” (p.3)
- “The rate of antibiotic resistance emergence is related to all uses of these drugs, not just misuse…” (p.4)
- “Most organisms can be sources of resistance genes, but selection for antibiotic resistance most often takes place in non-pathogenic microorganisms, since they comprise the vast majority of the microbial world.” (p.5)
- “Developing resistance to antibiotics increases the cache of genes available to microorganisms and impacts many other genes as well, thereby contributing to the evolutionary possibilities available to them. Once a microorganism derives a genetic tool for resistance, it can pass that gene on to its progeny by clonal replication or to other microbes through horizontal gene transfer…” (p.5)
- “Selection for antibiotic resistance takes place anywhere an antibiotic is present: in the skin, gut, and other areas of the bodies of humans and animals and in the environment…” (p.7)

(ii) Importance of low concentrations of antibiotics to resistance and other factors. While there are certainly many contributory factors to antibiotic resistance, such as widespread use of the antimicrobial triclosan (not allowed in organic systems), this factor does not minimize the critical role that low level concentrations of antibiotics play in enhancing resistance.

The NOSB review process seeks to remove the hazards under assessment, recognizing that there may be other hazards as well, many outside the control of the board. While multiple factors may contribute to the development of resistance, the NOSB considers the various factors individually under the National List review process and assesses whether they contribute to harm individually.

Additionally, the standards of material review require an assessment of harm associated with its manufacture, use, and disposal.

In this regard, AAM says the following:

- The use of sub-inhibitory (or sub-MIC) concentrations of antibiotics plays several important roles in the development of resistance. Like low concentrations of biocides (see *Anti-Infective Strategies and Antimicrobials*, above), low concentrations of antibiotics could enrich for resistance genes in a population while having little effect on overall mortality."[32]
- "The tendency to mutate also increases upon exposure to sub-inhibitory concentrations of antibiotics. Pathogens can initiate an SOS response (a DNA repair pathway) when subjected to low concentrations of antibiotics like quinolones, which affect DNA synthesis. This may make them more prone to develop resistance in the future. Low concentrations of antibiotics can also select for strains that increase expression of their existing resistance genes, further enhancing their resistance.[33]

(iii) Consideration of EPA findings. While regulatory agencies, such as EPA, register materials permitted by National List criteria, the standard by which EPA registers materials that are used in chemical-intensive agricultural production do not necessarily meet the standards of OFPA. EPA has registered tetracycline in fruit production and its ongoing review through its reregistration process (with timelines subject to change) cannot be the basis for delaying NOSB action based on the board's statutory mandated technical review and assessment process. Nor can the NOSB rely on judgments that EPA makes under other statutory standards, including "no unreasonable adverse effects" or "reasonable certainty of no harm," both governed by risk assessments. Therefore, EPA's pesticide registration of tetracycline (2008) and open docket until June 2014, with an expected completion date of September 2014, does not necessarily add additional information beyond the Technical Review and cannot delay action under OFPA.

(iv) Higher exposure to tetracycline in therapeutic context. A higher use rate of tetracycline in a therapeutic context does not justify its allowance in organic agricultural production systems that seek to break the cycle of dependency on inputs and practices known to have deleterious effects on health and the environment. The fact that typical pharmaceutical exposures to humans are 50,000 to 200,000 times greater than the theoretical dietary exposure[34] does not justify an acceptable relative risk standard by which toxic inputs are allowed in organic production. If it were, reduced uses of virtually all hazardous synthetics would be allowed in organic production, based on the assessment that less is used than in chemical-intensive agriculture. Of course, that analysis does not justify the use of National List materials.

Again, as explained above, the issue with respect to antibiotic resistance is <u>not</u> only direct human exposure to tetracycline, but the exposure of bacteria to tetracycline in the environment.[35] And, as explained above, subinhibitory doses lead to increased antibiotic resistance.

(v) Resistance associated with orchard use has been found.
The pro-extension majority position, citing Schnabel and Jones (1999), points out that, "In orchards treated with antibiotics, only 5% of the bacteria isolated from flowers or leaves was resistant to oxytetracycline (10 µg/ml)." Even if this were the only finding in the study, it would be a significant finding, establishing the resistance mechanism and the threat that it presents. However, the authors also found higher levels of tetracycline resistance in the orchard that had a history of five years use of tetracycline before the experiment. In addition, to become problematic, resistance associated with tetracycline use in apple and pear production does not have to start with the fire blight bacterium becoming resistant. There are many bacteria in an orchard environment, including those resident in

orchard workers, which can contribute to the spread of resistance. See discussion of AAM 2009 above.

(vi) Laboratory studies provide useful data in conjunction with field studies, show tetracycline persistence for "long periods"[36] . . .upon later release from soil components."[37] The extension proponents have criticized the TR's treatment of individual studies in the section dealing with the persistence of tetracycline in soils. The complete text from the TR is helpful in understanding both the laboratory and field data:

> Although oxytetracycline, as an antibiotic, is toxic to some microorganisms in the soil, it is already present in soil due to production by naturally occurring bacteria. Thiele-Bruhn (2003) reported that, in general, the effects of an antibiotic on soil organisms are essentially influenced by the bioavailability of the antibiotic, which depends on soil properties, availability of nutrients, and presence of root exudates. Tetracyclines exhibit strong adsorption to soil components such as clay and organic matter and form strong bonds with metals in the soil. These interactions limit the bioavailability of tetracyclines to microorganisms in the soil (Lui et al., 2009). Tetracycline can persist in soil for long periods of time without showing antimicrobial activity, and high concentrations can be achieved (Popowska et al., 2010). Upon later release from soil components, it can exhibit antimicrobial activity. Factors that may result in a release of tetracycline from the soil include changes in organic material composition of the soil, shifts in microorganism populations, or changes in soil pH.[38] (Aga et al., 2005)

Laboratory studies can be helpful, especially in the context of field studies. See 2011 TR lines 502-511:

> Popowska et al. (2010) demonstrated in a laboratory experiment that the presence of tetracycline in three different types of soils affected the ecological balance in the soil, causing the elimination of some bacterial populations. In this study, varying concentrations of tetracycline (1 – 9 ppm) were added to three different soil types in a laboratory setting: forest soil from a pine forest, fertile arable agricultural soil, and garden compost. The soils were then incubated for 14 days. The authors found that 2 ppm and higher concentrations of tetracycline caused a significant reduction in bacterial count and many bacterial species were eliminated from the soils. The eliminated species were described as beneficial bacteria involved in various metabolic processes, mineralization of organic compounds, degradation of toxic compounds, or creating soil structure. This study also isolated from the soils many strains of bacteria demonstrating resistance to tetracycline, including opportunistic pathogens of humans and/or animals.

(vii) Tetracycline has been shown to be taken up by a range of plants, both annual and perennial, and residuals are found in or on fruit. Kong et al. found the uptake of oxytetracycline by alfalfa, a perennial plant.[39] "In an energy-dependent process," Sinha et al. showed that leafhoppers feeding on plants grown in a medium treated with tetracycline also absorbed tetracycline from the plants.[40] Nevertheless, there is agreement that tetracycline residues are found, albeit at low levels, in or on the treated fruit. According to the 2011 TR, "The current tolerance (maximum residue limit) for oxytetracycline on or in apples and pears is 0.35 ppm."[41]

(viii) The linkage of agricultural use to antibiotic resistance is identified by FDA, absent direct exposure to the use pattern. Horizontal gene transfer is the central issue of concern relative to tetracycline use in apple and pear production and antibiotic resistance in humans. As stated earlier, tetracycline is considered a "critically important antimicrobial" by the World Health Organization.[42] FDA's Guidance 152 for evaluating the impact of animal drugs on human health considers the risk to human health to be "high" when an antibiotic is "critically important" even if the probability that the use of the antimicrobial will result in the emergence or selection of resistant bacteria is low and the probability of direct exposure to humans is low.[43]

Nevertheless, human beings can be found in orchards, and humans carry human pathogens. However, the presence or absence of human pathogens in orchards is not the prime consideration since the primary mechanism of the spread of antibiotic resistance is horizontal gene transfer, and the primary site of development of antibiotic resistance is the "environment."[44]

There is no need for contact with a human or animal pathogen in order for the resistance genes to move out of the orchard environment. As long as the bacteria in the orchard are exposed to tetracycline, the selection for resistance will continue. Those bacteria may move out of the orchard in dust on fruit, airborne dust, dirt attached to workers' shoes, or in many other ways. O'Brien (2002) says, "The abundance of *E. coli* implicates them as the likely predominant vehicles for the spread of resistance genes and vectors, as opposed to the spread of infection, between the bacterial populations of animals and humans…"[45]

(ix) The finding of resistant bacterial in soils is troubling. The focus of mechanism of antibiotic resistance is necessarily focused on the huge number of bacteria in the soil, even though there may be some research showing short tetracycline activity on plant tissue. With a focus on soil tests, such as those conducted by Popowska, it was found that, "Bacteria with the highest MICs [minimum inhibitory concentrations] were detected in manure-amended soils or soils from agricultural systems with a history of antibiotic use."[46] MICs are the indicator that is used to confirm antibiotic resistance. Meanwhile, as indicated in the scientific literature cited in this section, a finding of resistant bacteria in the phylosphere is not required for resistant genes to have adverse impact on human health. And, the existence of naturally occurring tetracycline does not address the effect of additional applied tetracycline and the biological impact that it has on the bacterial resistance to antibiotics. In fact, the fire blight organism is not necessarily the first to develop resistance.

II. The use of antibiotics in organic production is incompatible with organic principles.[47]

Rather than relying on practices central to organic production —such as the choice of resistant cultivars and rootstocks[48]— the antibiotic-dependent system relies on synthetic off-farm inputs.[49] The use of antibiotics to control fire blight is not sustainable[50] and does not promote the long-term viability of organic farm operations because resistance to antibiotics will ultimately develop.[51] This has already been experienced with streptomycin resistance to fire blight in the northwest.[52] The use of antibiotics in organic fruit production is inconsistent with the prohibition against antibiotics in organic livestock production.[53] It is inconsistent with organic standards in the European Union and Canada.[54] The use of antibiotics in organic fruit production does not satisfy consumer expectations regarding the authenticity and integrity of organic products.[55] As reported in "Organic pome and cherry production and marketing issues: Past, present and future," and presented to IFOAM, "Over the last ten years, the Hartman Group (Bellevue, Washington, USA) has studied changes in consumer attitudes, backgrounds, and buying characteristics related to the organic market. The Hartman Group surveyed about two thousand household consumers across four regions of the USA. They found that the 'traditional' properties suggested by 'organic' were no longer the same properties held by the new organic consumer. The survey indicated that traditional properties such as 'locally-grown,' Fair Trade, 'tastes better,' and sustainable production ranked at the bottom. The new organic consumers made it clear that they want, plain and simple, a product centered around the 'absence of all health concerns,' and the absence of pesticides, growth hormones, GMO's, antibiotics, and BSE."[56]

The process surrounding antibiotics since the beginning of the National Organic Program has consisted of repeated acknowledgement of the public health hazard, accompanied by warnings that the tetracycline and streptomycin listings for apple and pear production were phasing out "the next time."[57] Each time, the use of these materials has been extended with great and increasing reluctance. While the sunset and expiration process has been used as a way of injecting continuous improvement into the organic systems approach to agricultural production and handling, the OFPA process requires that substances meet the three criteria identified at the beginning of this section —(i) environmental and health impacts, (ii) compatibility with organic principles, and (iii) essentiality[58] The OFPA standards require an assessment distinct from pesticide registration process under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and require the prohibition of inputs that cause adverse health and environmental effects, even in the face of production practices that are reliant on the material.

III. The use of antibiotics in organic fruit production is not essential.

Like most challenges in organic production systems, with fire blight there is no one material and no one practice that will eliminate the problem. Fire blight must be met with a truly organic systems approach.

With regard to the "essentiality" of tetracycline, not all organic apple and pear growers depend on antibiotics. In fact, there is a sizeable proportion of growers of both apples and pears who do not use antibiotics. However, many say that large scale, commercial, organic apple and pear production would end without tetracycline. In an organic market where consumers expect no antibiotic use, it is no small point that after years of NOSB debate and votes on discontinuing antibiotic use there is an expectation that the transition to less susceptible varieties and alternative practices would take place by the October 2014 expiration date adopted by the NOSB in 2011.

At the April 2011 meeting of the NOSB in Seattle, Katherine Withey of the Washington State Department of Agriculture's Organic Food Program said in a statement that, "In 2010 WSDA certified 719 producers. Of these producers, 361 were certified for apples and/or pears, and of these 361 producers 136 [38%] used tetracycline and 34 [9%] have used streptomycin."[59] Thus, it appears that a minority of apple and pear producers rely on these antibiotics. As of March 10, 2011, there were 96 businesses certified as EU-compliant organic producers of apples and/or pears in the state of Washington alone, representing about one third of the state's organic apple and one fourth of the state's organic pear production.[60] EU-compliant organic apple and pear growers cannot use antibiotics, and face a three-year ban from selling in the EU if they do. Instead, these growers rely on a number of other practices, allowing them to avoid fire blight damage to susceptible varieties:[61]

- Balancing nutrients and avoiding over-application of nitrogen fertilizers, especially on susceptible varieties of apples or pears;
- Avoidance of over-pruning in the dormant season;
- Use of pre-bloom foliar nutrient sprays even though there is no foliage;
- Use of copper materials on the trees between delayed dormant and tight cluster sages as preventive measures against overwintering FB;
- Use of lime sulfur during bloom to thin apples; and,
- Use of Serenade MAX (in the future, perhaps Blossom Protect) post-bloom and at petal-fall, with good spray coverage.

With some differences for pears:

- For the Bosc, use of low levels of copper only sprayed foliar during bloom and infection periods;

- For pear varieties Bartlett and Anjou which are subject to skin russetting, use of antagonistic bacterial products during bloom, followed by Serenade MAX or Blossom Protect at petal-fall; and,
- Copper and Lime Sulfur with oil.

In addition, Steiner's observations offer insight into how changes in the orchard environment[62] have contributed to epidemics of fire blight.[63] In response, the following is suggested:

- Increase species diversity;
- Decrease tree density;
- Use resistant cultivars and rootstocks;
- Plant a variety of cultivars on a variety of rootstocks.

<u>**Evaluation Criteria**</u>

(Applicability noted for each category; Documentation attached)	**Criteria Satisfied?**
1. Impact on Humans and Environment	☒Yes x [1]No ☐ N/A
2. Essential & Availability Criteria	☒ Yes x No ☐ N/A
3. Compatibility & Consistency	☒ Yes x No ☐ N/A
4. Commercial Supply is Fragile or Potentially Unavailable as Organic (only for § 205.606)	☐ Yes ☐ No ☒ N/A

Substance Fails Criteria Category:[ ]**Comments:**

Proposed Annotation (if any):

Basis for annotation:☐To meet criteria above☐Other regulatory criteria ☐Citation

Recommended Committee Action & Vote, including classification recommendation (state actual motion):

Classification Motion: N/A
Motion by: Seconded by:
Yes: No: Absent: Abstain: Recuse:

Listing Motion:

The Crops Sub-Committee recommends amending the listing for tetracycline to remove the expiration date of October 21, 2014 and add the following annotation:
§205.601 Synthetic substances allowed for use in organic crop production
(i)As plant disease control.
(12) Tetracycline, for fire blight control in apples and pears only until October 21, 2016.

Motion by: Nick Maravell Seconded by: Harold Austin
Yes: 5 No: 3 Absent: 0 Abstain: 0 Recuse: 0

Resolution:

[1] "No" check marks indicate minority viewpoint.

The National Organic Standards Board is committed to the phase out of this material. The board urges growers and certifiers between now and the 2016 expiration date to encourage an annual increase in the extent and/or number of alternative practices that are trialed for controlling fire blight. In addition, the board strongly supports increased support for the research into these alternative practices and materials.

Motion by: Nick Maravell Seconded by: Zea Sonnabend
Yes: 7 No: 0 Absent: 1 Abstain: 0 Recuse: 0

Crops	☒	**Agricultural**	☐	**Allowed**[1]	☐
Livestock	☐	**Non-synthetic**	☐	**Prohibited**[2]	☐
Handling	☐	**Synthetic**	x	**Rejected**[3]	☐
No restriction	☐	**Commercial unavailable as organic**	☐	**Deferred**[4]	☐

[1]Substance voted to be added as “allowed” on National List to § 205. with Annotation (if any):

[2]Substance to be added as “prohibited” on National List to § 205.with Annotation (if any):

Describe why a prohibited substance:

[3]Substance was rejected by vote for amending National List to § 205. Describe why material was rejected:

[4]Substance was recommended to be deferred because
If follow-up needed, who will follow up:

Approved by Subcommittee Chair to Transmit to NOSB

Jay Feldman Subcommittee Chair February 11, 2013

NOSB Evaluation Criteria for Substances Added To the National List

Category 1. Adverse impacts on humans or the environment? Substance: Oxytetracycline

Question	Yes	No	N/A 1	Documentation(TAP; petition; regulatory agency; other)
1. Are there adverse effects on environment from manufacture, use, or disposal? [§205.600 b.2]			x	
2. Is there		x		**[Majority Position]** Line 397 (April1, 2011 TR) states no

environmental contamination during manufacture, use, misuse, or disposal? [§6518 m.3]				current information can be found on possible contamination from the manufacture of agricultural oxytetracycline products. Lines 398-412 does state that the potential could be there because of the solvents used in the fermentation process. Lines 412-414 state that if the manufacturers comply with the applicable air and water regulations, it is unlikely that environmental contamination will result from fermenting processes. See above – if the label is followed and all applicable air and water regulations followed there should be no environmental contamination, other than from misuse. In the April 2011 Checklist it mentions “treated plants exude tetracycline”, the petitioner rebuts this stating that there is no data that they could find that shows apple and pear trees exude tetracycline. WSHA (the petitioner) states that scientific evidence supports the understanding that tetracycline does not freely translocate within an apple or pear tree, nor is it exuded from plants[2]. It is the majority opinion that the papers cited by the minority do not actually support these claims. **[Minority Position]** WSHA does not actually present any citations to support their claim that tetracycline is not translocated in or exuded by plants. Translocation of oxytetracycline is occurring as sprayed material on blossom ends up in fruit. See U.S. Environmental Protection Agency. 2005. Oxytetracycline. Section 3 Use on Apples. Summary of Analytical Chemistry and Residue Data. HED Records Center Series 361 Science Reviews, File R104981. Washington, DC. .http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-006304_3-Jan-05_a.pdf “Oxytetracycline tolerances are currently established on peaches and pears at 0.35 ppm in terms of oxytetracycline, only. A tolerance on apple is proposed, also at 0.35 ppm.TR1[3] lines 149-164; TR2 397-426. This is reinforced by label on another oxytetracycline product, Mycoject, while only registered for ornamental, indicates on its label that it is applied by injection and acts by translocation. See Mycoject label, http://www.mauget.com/ProductLabels/AnitiboticLabels/Mycoject.pdf TR1 (lines 149-164); TR2 (lines 397-426): Manufacture may result in discharges of solvents, detergents,

[2] Washington State Horticultural Association, 2011. Comment on the re-listing of tetracycline to docket AMS-NOP-11-0014, page 3.
[3] TR1 is TR dated January 27, 2006.

				disinfectants. Kumar et al, 2005; Kong et al, 2006; Sinha and Peterson, 1972; Daniels, 1982:[4] Treated plants may contain and exude tetracycline. TR2[5] 291-294: “Once released into the soil, oxytetracycline is expected to become strongly adsorbed to soil particles and have moderate to no mobility. (Kumar et al., 2005; HSDB, 2006) This means it can remain in soil for a long time following treatment. Furthermore, it is not likely to leach below the surface soil (Aga et al., 2005); however it can spread by surface run-off of sediment.” TR2 322-324: “Chander et al. (2005) demonstrated that even though tetracycline was tightly adsorbed to clay particles in soil, it was still biologically active” following a 24-hour incubation period.
3. Is the substance harmful to the environment and biodiversity? [§6517c(1)(A)(i);6517(c)(2)(A)i]	x	x		**[Majority Position]** April 29, 2011 Checklist refers to a report by Thiele-Bruhn and Beck, 2005 on the effects of tetracycline in soil microbial activity. This report is appears to refer to two soil groups representative of European soils. This report does not reflect typical soils or types of soil amendments found in the U.S[6], nor does it reflect the use pattern for this allowed substance as it is listed. **[Minority Position]** See complete reference to TR2 (lines 296-307) that cites scientific literature on limited to no oxytetracyline degradation in U.S. soils: “[T]he extent and kinetics of antibiotic degradation in soil is highly dependent on temperature, soil type, and antibiotic adsorption to soil (Thiele-Bruhn, 2003). One study reported no degradation of oxytetracycline in a soil and manure sample after 180 days (Thiele-Bruhn, 2003). In a field study with silt loam soil, the measured amount of oxytetracycline in the soil declined by 50% in three weeks following application of manure with oxytetracycline, however the amount of total tetracyclines did not significantly decline after 5 months (Aga et al., 2005). Another study showed that oxytetracyline residues were present in agricultural soil 10 months after fertilization with manure containing oxytetracycline (Cengiz et al., 2010). Wang and Yates (2008) found the half-life of

[4] K. Kumar, S.C. Gupta, Y. Chander, and C.J. Rosen, 2005. Antibiotic Uptake by Plants from Soil Fertilized with Animal Manure. J. Environ. Qual. 34:2082–2085 (2005).
W.D. Kong, Y.G. Zhu',, Y.C. Liang, J. Zhang, F.A. Smith, and M. Yang, 2007. Uptake of oxytetracycline and its phytotoxicity to alfalfa (*Medicago sativa* L.). **Environmental Pollution**, Volume 147, Issue 1, May 2007, Pages 187-193.
RC Sinha and EA Peterson, 1972. Uptake and persistence of oxytetracycline in aster plants and vector leafhoppers in relation to inhibition of clover phyllody agent, Phytopathology 62: 50-56.
MJ Daniels, 1982. Editorial: Possible effects of antibiotic therapy in plants. Reviews of Infectious Diseases 4 (Supp): 167-170.
[5] TR2 is TR dated April 1, 2011.
[6] Washington State Horticultural Association, 2011. Comment on the re-listing of tetracycline to docket AMS-NOP-11-0014, page 4.

				oxytetracycline to be 33 days in manure-amended soil and 56 days in non-amended soil. Yang et al. (2009) reported half-lives for oxytetracycline between 29 and 56 days for non-sterile treatments and 99 to 120 days for sterile treatments (aerobic conditions), and between 43 and 62 days in the non-sterile soil and 69 to 104 days in sterile soil (anaerobic conditions).” Thiele-Bruhn and Beck, 2005:[7] “The antibiotics significantly ($p < 0.05$) reduced numbers of soil bacteria, resulting in dose related shifts in the fungal: bacterial ratio, which increased during 14 d, as determined from analysis of ergosterol and EC. It was concluded that pharmaceutical antibiotics can exert a temporary selective pressure on soil microorganisms even at environmentally relevant concentrations.” Aminov, 2011:[8] “There is a substantial body of evidence suggesting that the sub- inhibitory concentrations of antibiotics may significantly increase the frequency of horizontal transfer of many types of MGEs [mobile genetic elements].” See #6 below. TR2 322-324: “Chander et al. (2005) demonstrated that even though tetracycline was tightly adsorbed to clay particles in soil, it was still biologically active” following a 24-hour incubation period. There is a concern that the persistence of oxytetracycline residues in the environment may contribute to the development of bacterial resistance to oxytetracycline and other tetracyclines (Arikan et al., 2007).”
4. Does the substance contain List 1, 2 or 3 inerts? [§6517 c (1)(B)(ii); 205.601(m)2]		x		
5. Is there potential for detrimental chemical interaction with other materials used? [§6518 m.1]		x		**[Majority Position]** TR 2 (page 9 lines 432-434) states that there is no information available to assess whether spray applications of tetracycline will cause chemical reactions or interaction with other materials used in organic crop production. **[Minority Position]** Burgos et al, 2003:[9] Bacteria with multiple resistances may result from use of oxytetracycline and manure treated with other antibiotics.
6. Are there adverse		x		**[Majority Position]** TR2 (lines 442-453): it was stated

[7] Sören Thiele-Bruhn' and Iris-Constanze Beck, 2005. Effects of sulfonamide and tetracycline antibiotics on soil microbial activity and microbial biomass. **Chemosphere**, Volume 59, Issue 4, April 2005, Pages 457-465
[8] Rustam I. Aminov, 2011. Horizontal gene exchange in environmental microbiota, Front Microbiol. 2011; 2: 158.
[9] Burgos JM, Ellington BA, Varela MF., 2005. Presence of multidrug-resistant enteric bacteria in dairy farm topsoil. J Dairy Sci. 2005 Apr;88(4):1391-8.

biological and chemical interactions in agro-ecosystem? [§6518 m.5]				that there were no available information on the interactions in the agro-ecosystems following the use of oxytetracycline specifically for foliar use to control fire blight in apples and pears. There are studies where tetracycline has been applied directly to the soil and usually are related to manure applications where tetracycline treatments of the animals have been used, or where it has been included in feed stocks. **[Minority Position]** Thiele-Bruhn and Beck, 2005: Oxytetracycline shifts fungal-bacterial balance at environmentally relevant concentrations.TR2 469-511: Application of oxytetracycline changed fungal and bacterial composition of soils and reduced the rate of nitrification.
7. Are there detrimental physiological effects on soil organisms, crops, or livestock? [§6518 m.5]		x		**[Majority Position]** The TR from 2006 (Lines 210-212): 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. The 2011 TR also indicates no negative interactions could be found in literature (2011 TR lines 432-436. **[Minority Position]** TR2:" No information could be found on interactions in the agro-ecosystem following the use of oxytetracycline specifically for control of fire blight in apples and pears." TR2 does present results of a number of laboratory studies.
8. Is there a toxic or other adverse action of the material or its breakdown products? [§6518 m.2]	x	x		**[Majority Position]** The 2011 Checklist and the petitioner have both combined answers and response to this question (8) and checklist question 10, listed below. (See additional information listed under question 10 of this section.)*See Checklist Discussion, Category1, Question 8 and 9: Mode of Action, Breakdown, and Residues, in the Introduction Document. **[Minority Position]** Mycoshield MSDS: **Other Acute Effects**: Oxytetracycline may cause severe allergic reactions (anaphalactic shock) in sensitive individuals. **Subchronic (Target Organ) Effects**: For oxytetracycline, gastrointestinal irritation with nausea, epigastric pain and burning, vomiting, abdominal pain, transitory yellowish-brown discoloration of the tongue, anorexia and diarrhea. Blood disorders (delay in coagulation) have been reported. Possible hypersensitization and superinfections due to overgrowth of resistant organisms not affected by the antibiotic. Three types of renal diseases are associated with overexposure: Acute Non-Oliguric Renal Failure (individuals with pre-existing pancreatitis or fatty liver); Uremia (individuals with pre-existing impaired renal function) and Reversible Nephrotoxicity (due to outdated or degraded tetracyclines). Inhalation of excessive

				amounts of kaolin dust may produce coughing, sneezing, and nasal irritation Chronic exposure to mica may cause persistent cough, possible difficulty in breathing. **Carcinogenicity/chronic effects**: Prolonged overexposure to oxytetracycline may cause effects to skin and digestive tract. Oxytetracycline did not cause cancer in laboratory animals. Long-term over-exposure to kaolin dust may affect lungs. The diluent as a whole is not listed as a carcinogen. However, it does contain crystalline silica (e.g. Quartz), a natural occurring component. Inhalation of crystalline silica may cause pulmonary fibrosis (silicosis). Crystalline silica has been classified by International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), by the US NTP as a known human carcinogen, and by ACGIH as a suspected human carcinogen (A2). **Developmental Toxicity:** Adverse effects were reported in mother (severe hepatic damage) and fetus (retardation of skeletal development, discoloration of teeth, and enamel hypoplasia.) See also #10 below.
9. Is there undesirable persistence or concentration of the material or breakdown products in environment?[§6518 m.2]		x		**[Majority Position]** The November 2008 recommendation and checklist states degradation half-life varies from 30 days (fresh water) to 10 weeks in pond sediments. It is absorbed and inactivated in dry soils. The 2011 TR (lines 535-543) states that according to EPA's (RED) Pesticides Registration Eligibility Document in 1993 that oxytetracycline products labeled and used according to EPA regulations will not pose unreasonable risks or adverse effects to the environment. Since that time (EPA 2006a &b) the agency noted that new environmental fate studies should be conducted. From the EPA-HQ-OPP-2008-RegReview Summary: "The environmental fate data currently under review, along with the data to be requested, are expected to address some of the uncertainties laid out in the 2006 oxytetracycline TRED regarding the potential for antibiotic resistance resulting from the pesticidal uses." This Re-review by EPA is currently underway and is scheduled to be completed in 2014[10].(also TR lines 542-543) The whole subcommittee recognizes that EPA risk assessments are a different standard than the criteria for the organic regulations, but the majority believes the EPA information will be an important resource contributing to evaluating our criteria. *See Checklist Discussion, Category 1, Questions 8 and 9: Mode of Action, Breakdown, and Residues, in the Introduction Document. **[Minority Position]** OFPA requires Board evaluation of

[10] United States Environmental Protection Agency. 2008. Oxytetracycline summary document registration review: initial docket December 2008. Docket number: EPA-HQ-OPP-2008-0686. Available at: www.regulations.gov

				adverse effects to determine the acceptability of material listing, taking into account compatibility with organic practices. EPA regulates to a different standard of no unreasonable risks, which does not include all OFPA checklist criteria. In this context, the question is whether organic practices should be contributing to antibiotic resistance. Schnabel and Jones, 1999[11]: Resistance to oxytetracycline is associated with use in orchard. To become problematic resistance associated with tetracycline use in apple and pear production does not have to start with the fire blight bacterium becoming resistant. Kumar et al, 2005; Kong et al, 2006; Sinha and Peterson, 1972; Daniels, 1982: Tetracycline may be taken up by plants and appear in all tissues and in exudates. TR2 291-294: Once released into the soil, oxytetracycline is expected to become strongly adsorbed to soil particles and have moderate to no mobility. (Kumar et al., 2005; HSDB, 2006) This means it can remain in soil for a long time following treatment. Furthermore, it is not likely to leach below the surface soil (Aga et al., 2005); however it can spread by surface run-off of sediment. TR2 322-324: "Chander et al. (2005) demonstrated that even though tetracycline was tightly adsorbed to clay particles in soil, it was still biologically active" following a 24-hour incubation period. Halling-Sørensen et al, 2002:[12] Degradation products have same activity as parent. TR2 463-465: Tetracycline can persist in soil for long periods of time without showing antimicrobial activity, and high concentrations can be achieved. (Popowska et al., 2010) Upon later release from soil components, it can exhibit antimicrobial activity.
10. Is there any harmful effect on human health? [§6517 c (1)(A)(i); 6517 c(2)(A)i; §6518 m.4]		x		The 2011 TR (lines 557-559) according to EPA's Tolerance Reassessment Progress and Risk Management Decision (TRED) for oxytetracycline there is reasonable certainty that no harm to any population subgroup will result from exposure to oxytetracycline (EPA, 2006b, p.4) The whole subcommittee recognizes that EPA risk assessment alone is not sufficient to replace the OFPA criteria and that other information must be looked at. However there is no direct evidence of negative human health impacts that have been proven to occur

[11] Elise L. Schnabel and Alan L. Jones, 1999. Distribution of tetracycline resistance genes and transposons among phylloplane bacteria in Michigan apple orchards. Appl. Environ. Microbiol., 65, 4898–4907.
[12] Halling-Sørensen B; Sengeløv G; Tjørnelund J, 2002**.** Toxicity of tetracyclines and tetracycline degradation products to environmentally relevant bacteria, including selected tetracycline-resistant bacteria.
Archives of environmental contamination and toxicology 2002;42(3):263-71.

				solely from the use of oxytetracycline in apples and pears.[13] [14] *See Checklist Discussion, Category 1, and Question 10: Potential for Humans to build Resistance to Medical Tetracyclines, in the Introduction Document. **[Minority Position]** Data submitted in support of EPA's establishment of a tolerance for tetracycline demonstrated residues of tetracycline in apples.[15] Levy, "Antibiotic resistance: an ecological imbalance" (1997) at p6": Dietary exposure of medical concern - "Tetracycline resistance in the faecal flora was high when the volunteers were eating normal, non-sterilized food for 21 days, but dropped dramatically when the diet was shifted to sterilized food for 17 days." TR163-71, 279-293: Workers are at risk of contracting tetracycline-resistant disease and suffering from allergic reactions. Lugo-Melchor et al, 2010:[16] As a consequence of the widespread use of tetracyclines, the emergence and spread of tetracycline-resistant bacterial pathogens, among them the foodborne pathogen Salmonella enterica, has become a serious health hazard worldwide. Levy et al, 1976:[17] Workers who handle feed with tetracycline have tetracycline-resistant flora in their intestines. http://en.wikipedia.org/wiki/Tetracycline_antibioticsTetracyclines remain the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), Rickettsia (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be used to treat anthrax, plague, tularemia, and Legionnaires' disease. They may have a role in reducing the duration and severity of

[13] Stockwell, V.O., and Duffy, B. 2012. Use of antibiotics in plant agriculture. Rev. Sci. Tech. Off. Int. Epiz., 31:199-210.

[14] Stockwell, V. and Granatstein, D. 2013. Lack of Evidence for Linkage of Plant Agriculture Use of Oxytetracycline to Antibiotic Resistance in Human Pathogens. unpublished report posted to Washington State University Tree Fruit Research and Education Center: http://www.tfrec.wsu.edu/pages/organic/fireblight

[15] United States Environmental Protection Agency. 2005. Oxytetracycline. Section 3 Use on Apples. Summary of Analytical Chemistry and Residue Data. HED Records Center Series 361 Science Reviews, File R104981. Washington, DC. http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-006304_3-Jan-05_a.pdf "Oxytetracycline tolerances are currently established on peaches and pears at 0.35 ppm in terms of oxytetracycline, only. A tolerance on apple is proposed, also at 0.35 ppm. The crop field trials were conducted from 0.5 to 11.6X the proposed seasonal rate of 1.53 lb ai/A and from 49 to 61 days PHI as compared to the proposed PHI of 60 days. Residues were largely at the limit of quantitation (LOQ) of 0.013 to 0.2 ppm up to 0.252 ppm for a 1X study in Region V [MI]. Adequate storage stability data were presented to indicate that the residues of oxytetracycline were stable for the duration of the residue field trial studies."

[16] Lugo-Melchor, Y., Quinones, B., Amezquita-Lopez, B.A., Leon-Felix, J., Garcia-Estrada, R., Chaidez, C. 2010. Characterization of tetracycline resistance in Salmonella enterica strains recovered from irrigation water in the Culiacan Valley, Mexico. Microbial Drug Resistance. 6(3):185-190.

[17] Stuart B. Levy, M.D., George B. FitzGerald, Ph.D., and Ann B. Macone, B.S., 1976. Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline-Supplemented Feed on a Farm. N Engl J Med 1976; 295:583-588.

				cholera, although drug-resistance is occurring, and their effects on overall mortality is questioned. “Prop 65 list” http://www.oehha.org/prop65/prop65_list/files/P65single3405.pdf Developmental toxin listed by the state of California. TR2 549-551: There is a high probability that oxytetracycline resistant bacteria are present in the environment as a consequence of pesticidal use of oxytetracycline which may have negative health consequences for humans (EPA, 2006). The World Health Organization (WHO) has recently changed its categorization of tetracyclines from “highly important” to “critically important””[18] See also #8 above.
11. Is there an adverse effect on human health as defined by applicable Federal regulations? [205.600 b.3]			x	
12. Is the substance GRAS when used according to FDA’s good manufacturing practices? [§205.600 b.5]			x	
13. Does the substance contain residues of heavy metals or other contaminants in excess of FDA tolerances? [§205.600 b.5]			x	

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

NOSB Evaluation Criteria for Substances Added To the National List

Category 2. Is the Substance Essential for Organic Production? Substance: Oxytetracycline

Question	Yes	No	N/A[1]	Documentation(TAP; petition; regulatory agency; other)
1. Is the substance formulated or manufactured by a chemical		x		TR2, lines 247-277: Oxytetracycline is a naturally occurring compound produced by the soil bacterium *Streptomyces rimosus.* It is produced on a large scale by aerobic fermentation followed by isolation and purification

[18] WHO, 2009. Report of the First Meeting of the Advisory Group on Integrated Surveillance of Antimicrobial Resistance. CDC, 2010. National Antibiotic Resistance Monitoring System: Enteric Bacteria-- 2010 Human Isolates Final Report.

process? [6502 (21)]				processes. The materials as formulated may or may not have gone through a chemical change during the manufacturing process.
2. Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral, sources? [6502 (21)]	x			See above – question #1. The two forms of tetracycline current on the National List as approved are listed as synthetic substances.
3. Is the substance created by naturally occurring biological processes? [6502 (21)]	x			See above answers to questions #1 & 2.
4. Is there a natural source of the substance? [§205.600 b.1]			x	
5. Is there an organic substitute? [§205.600 b.1]			x	
6. Is the substance essential for handling of organically produced agricultural products? [§205.600 b.6]			x	
7. Is there a wholly natural substitute product? [§6517 c (1)(A)(ii)]		x		**[Majority Position]** Available natural biological control materials have been proven to not adequately control the serious damage caused by the fire blight organism. (November 2008 recommendation/checklist) There are current trials being conducted on two different strains of yeast *Aureobasidium pullulans* that make up a product from Germany named, Blossom Protect. (2011 TR lines 636-641) (Kunz et al., 2011) TR2 622-725: other products include Bloomtime, Blight Ban A 506, Serenade Max that are listed for use in controlling fire blight. In the April 29, 2011 recommendation/checklist it mentions that there is a natural replacement *Pseudomonas* spp. (Stockwell and Stack, 2007)

				(Phytopathology 97:244-249) The petitioner rebuts this by addressing the inconsistency of control from the use of *Pseudomonas* spp. for control of fire blight in "*real world*" conditions. In the EPA's Oxytetracycline TRED (pages 5 of 15, June 2006) it states that the biological control agent, Blight Ban A506 (a.i. *Pseudomonas flourescens* strain A506) is used to complement an antibiotic pesticide and it is not a replacement for antibiotics. Blight Ban is to be used as part of an integrated control program. Also, there is another product similar to Blight Ban called Bloomtime (*Pantoea agglomerans*). **[Minority Position]** Since Blossom Protect is now available in the U.S.,[19] it should be noted that research reports from Washington state show its efficacy to be equal to or better than that of oxytetracycline.[20] Certainly, research on all of the known products as well as new ones can and should continue, but that should not preclude action by the NOSB. TR2 lines 713-714: "The results are mixed for biological control agents in the suppression of fire blight." Granatstein, 2013[21]: Blossom Protect has given results equal to tetracycline Stockwell and Stack, 2007:[22] BlightBan A506 provides significant control of fire blight caused by *E. amylovora*, russet caused by IAA-producing bacteria, and frost injury due to ice-nucleation active bacteria Glenn et al, 2001:[23] BlightBan A506 provides significant control of fire blight caused by *E. amylovora*, russet caused by IAA-producing bacteria, and frost injury due to ice-nucleation active bacteria
8. Is the substance used in handling, not synthetic, but not organically produced? [§6517 c (1)(B)(iii)]			x	
9. Are there any alternative substances? [§6518 m.6]	x			Peracetic acid is now registered for use against fire blight, but the TR2 (lines 747-748) says, "No information could be found on the efficacy of peracetic acid in control of fire blight." There are other products that currently

[19] See label at: http://westbridge.com/products-pdf-documents/BlossomProtectLabel.pdf
[20] Granatstein, 2013. Fire Blight Introduction, OTA Task Force Meeting, January 21, 2013. Powerpoint slides 13-14.

[21] Granatstein, D., 2013. Fire Blight Introduction, OTA Task Force Meeting, January 21, 2013. Powerpoint slides 13-14.
[22] Stockwell, V. O., and Stack, J. P. 2007. Using *Pseudomonas* spp. for integrated biological control. Phytopathology 97:244-249.
[23] Glenn, D. M., van der Zwet, T., Puterka, G., Gundrum, P., Brown. E. 2001. Efficacy of kaolin-based particle films to control apple diseases. Online. Plant Health Progress doi:10.1094/PHP-2001-0823-01-RS. http://ddr.nal.usda.gov/bitstream/10113/12139/1/IND43805958.pdf

				claim or have shown some control: Serenade, lime-sulfur, copper and the biological products. There are currently no stand- alone viable alternatives for reliable control of fire blight on apples and pears in organic production.(2012 Petition last paragraph page 11 of 13) *See Checklist Discussion, Category 2 Questions 9 & 10 for further discussion on Pears, in the Introduction Document. Granatstein, 2013: Blossom Protect has shown comparable efficacy to oxytetracycline in recent trials. However it has been shown to work much better in conjunction with a copper spray ahead of it to remove competing microbes from the flower before introducing the Blossom Protect. And the Blossom Protect does not give immediate results in extreme risk situations. TR1 lines 317-330 Phytotoxicity limits usefulness of copper compounds currently available for use. There are a couple of new copper compounds currently being looked at in research trials that may help to remove that limitation.
10. Is there another practice that would make the substance unnecessary? [§6518 m.6]	x	x		**[Majority Position]** There are other practices that could help as part of an integrated systems approach to controlling fire blight that could help to reduce the reliance upon oxytetracycline. But, these practices would not replace oxytetracycline by themselves. The April 1, 2011 TR (lines 757-762) mentions using resistant varieties of apples and pears. (Koski and Jacobi, 2009) There is no cultivar that is completely immune to fire blight. There are some rootstocks (Geneva) coming that are showing good resistance potential, but these are still several years away from being commercially available. (This would also not address the thousands of acres of organic apples and pears currently in production.) This is only the rootstock and not the cropping or cultivar part of the tree. Selection of soils and proper air and water drainage will aid in control. Pruning out cankers will help by removing some of the inoculum from the orchard. Fertility management will also help, by controlling vegetative growth of the tree. There are several detection models that are currently in use to assist in the identification of infection periods and their severity, as well as proper timing of control materials to maximize their efficacy in controlling fire blight. ("Fireblight Management in the Pacific Northwest USA") http://www.ncw.wsu.edu/treefruit/fireblight/principles.htm Everything listed here would work together as part of an organic systems approach to fire blight control, but not as a stand –alone. *See Checklist Discussion, Category 2 Questions 9 & 10

				for further discussion on Pears, in the Introduction Document. **[Minority Position]** TR1 297-302, 335-343. Resistant cultivars. Proper pruning, fertilization, watering, drainage. Aldwinckle et al, 1998[24]. "Serious fire blight damage can be avoided simply by not planting highly susceptible scion varieties and rootstocks." "Fireblight Management in the Pacific Northwest USA" (http://www.ncw.wsu.edu/treefruit/fireblight/principles.htm) Streptomycin "is no longer adequately effective in most of the Pacific Northwest" Ken Johnson[25]: 'Integrated control': … utilizing delayed dormant copper sanitation … in apples, using bloom thinners to further delay pathogen 'build-up' in flowers As of March 10, 2011, there were 96 businesses certified as EU-compliant organic producers of apples and/or pears in the state of Washington alone, representing about one third of the state's organic apple and one fourth of the state's organic pear production.[26] Testimony of Katherine Withey, Washington State Dept of Agriculture at Seattle NOSB meeting 4/2/2011 p. 380: "In 2010 WSDA certified 719 producers. Of these producers, 361 were certified for apples and/or pears, and of these 361 producers 136 used tetracycline and 34 have used streptomycin."

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

NOSB Evaluation Criteria for Substances Added To the National List

Category 3. Is the substance compatible with organic production practices? Substance : Oxytetracycline

Question	Yes	No	N/A[1]	Documentation (TAP; petition; regulatory agency; other)
1. Is the substance compatible with organic handling? [§205.600 b.2]			x	
2. Is the substance consistent with organic farming and handling? [§6517 c (1)(A)(iii); 6517 c (2)(A)(ii)]	x			**[Majority Position]** The substance, oxytetracycline is on the list of allowed exemptions in question 7 below. It is derived from a non-

[24] H. Aldwinckle, J Norelli, and MT Momol, 1998. Fire blight: the search for better control. IDFTA Compact Fruit Tree, Vol. 31, No. 4
[25] Ken Johnson, 2012. Fire Blight Control in Organic Pome Fruit Systems Under the Proposed Non-antibiotic Standard. http://www.extension.org/pages/62448/fire-blight-control-in-organic-pome-fruit-systems-under-the-proposed-non-antibiotic-standard
[26] Washington State Department of Agriculture printout, "International Organic Program—EU Compliant Operations, March 10, 2011.

				synthetic source organism, works in a similar fashion to other biologically based control organisms and has a history of safe use in organic farming systems for more than 20 years. The issues surrounding the use of antibiotics in animal agriculture have not been proven to pose the same threats when used in plants. **[Minority Position]** Ostenson, H.T. 2010, citing Hartman Group[27] study, which says antibiotic use is contrary to consumer expectations. Inconsistent with prohibition on antibiotics in livestock. TR2 lines 226-230: Inconsistent with European requirements.
3. Is the substance compatible with a system of sustainable agriculture? [§6518 m.7]	x			**[Majority Position]** The NOSB recommendation concerning assessing consistency and compatibility[28] lists 12 factors to be considered for determining this and the majority believes that over the time this has been on the National List, some factors have gained priority over others and thus acknowledges the need to phase the material out. However the majority feels that this needs to be done in a way that causes less disruption to the whole industry as alternatives are adopted. **[Minority Position]** Increases likelihood of antibiotic resistance in pathogenic organisms. The use of antibiotics to control fire blight is not sustainable[29]
4. Is the nutritional quality of the food maintained with the substance? [§205.600 b.3]			x	
5. Is the primary use as a preservative? [§205.600 b.4]			x	
6. Is the primary use to recreate or			x	

[27]Ostenson, H.T. 2010. Organic pome and cherry production and marketing issues: Past, present and future. Acta Hort. (ISHS) 873:137-144
[28] NOSB Policy and Procedures Manual p.32.
[29] NOSB Principles of Organic Production and Handling says, "Organic production and handling systems strive to achieve agro-ecosystems that are ecologically, socially, and economically sustainable." AAM, 2009. p.3. "The struggle against antibiotic resistance is a war we will never win."

improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk)? [205.600 b.4]				
7. Is the substance used in production, and does it contain an active synthetic ingredient in the following categories: a. copper and sulfur compounds;				
b. toxins derived from bacteria;	x			
c. pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals?				
d. livestock parasiticides and medicines?				
e. production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleaners?				

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

NOSB Evaluation Criteria for Substances Added To the National List

Category 4. Is the commercial supply of an agricultural substance as organic, fragile or potentially unavailable? [§6610, 6518, 6519, 205.2, 205.105 (d), 205.600 (c) 205.2, 205.105 (d), 205.600 (c)]
Substance: Oxytetracycline

Question	Yes	No	N/A[1]	Documentation (TAP; petition; regulatory agency; other)
1. <u>Is the comparative description provided</u> as to why the non-organic form of the material /substance is necessary for use in organic handling?			x	
2. Does the current and historical industry information, research, or evidence provided explain how or why the material /substance cannot be obtained organically in the appropriate **<u>form</u>** to fulfill an essential function in a system of organic handling?			x	
3. Does the current and historical industry information, research, or evidence provided explain how or why the material /substance cannot be obtained organically in the			x	

appropriate **quality** to fulfill an essential function in a system of organic handling?				
4. Does the current and historical industry information, research, or evidence provided explain how or why the material /substance cannot be obtained organically in the appropriate **quantity** to fulfill an essential function in a system of organic handling?			x	
5. Does the industry information provided on material / substance non-availability as organic, include (but not limited to) the following: a. Regions of production (including factors such as climate and number of regions);			x	
b. Number of suppliers and amount produced;			x	
c. Current and historical supplies related to weather events such as hurricanes, floods, and droughts that may temporarily halt production or destroy crops or supplies;			x	
d. Trade-related issues such as evidence of hoarding, war, trade barriers, or civil unrest that may temporarily restrict supplies; or			x	
e. Are there other issues which may present a challenge to a consistent supply?			x	

[1]If the substance under review is for crops or livestock production, all of the questions from 205.600 (b) are N/A—not applicable.

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Endnotes for Minority Position

[1] WHO, 2009. Critically Important Antimicrobials for Human Medicine, http://www.who.int/foodsafety/foodborne_disease/CIA_2nd_rev_2009.pdf See Table 1.
[2] Tetracycline TR, April 1, 2011. Lines 291-326. Mycoshield label http://www.cdms.net/ldat/ld246008.pdf
[3] American Academy of Microbiology, 2009. Antibiotic Resistance: An Ecological Perspective on an Old Problem. http://academy.asm.org/images/stories/documents/antibioticresistance.pdf (pp.1-5, 10.)
[4] American Academy of Microbiology, 2009. (p.8.)
[5] http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf See Table 6, p.22.
[6] 2011 TR lines 549-551: "There is a high probability that oxytetracycline resistant bacteria are present in the environment as a consequence of pesticidal use of oxytetracycline which may have negative health consequences for humans (EPA, 2006)." American Academy of Microbiology, 2009. p.2: "Controlling antibiotic resistant bacteria and subsequent infections more efficiently necessitates the prudent and responsible use of antibiotics. It is mandatory to prevent the needless use of antibiotics…"
[7] T.F. O'Brien, 2002. Emergence, Spread, and Environmental Effect of Antimicrobial Resistance: How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else, Clin Infect Dis. 34 Suppl 3:S78-84. "Use of an antimicrobial agent selects for overgrowth of a bacterial strain that has a gene expressing resistance to the agent. It also selects for the assembly and evolution of complex genetic vectors encoding, expressing, linking, and spreading that and other resistance genes. Once evolved, a competitive construct of such genetic elements may spread widely through the world's bacterial populations. A bacterial isolate at any place may thus be resistant—not only because nearby use of antimicrobials had amplified such a genetic construct locally, but also because distant use had caused the construct or its components to evolve in the first place and spread there. The levels of resistance at any time and place may therefore reflect in part the total number of bacteria in the world exposed to antimicrobials up until then."
K.M. Shea, 2003. Antibiotic Resistance: What is the Impact of Agricultural Uses of Antibiotics on Children's Health? Pediatrics 112: 253-258. http://pediatrics.aappublications.org/content/112/Supplement_1/253.full.html
[8] One time was in the 2008 testimony of former NOSB member Rebecca Goldburg, writing on behalf of Keep Antibiotics Working. She said, "A first concern is that the use of antibiotics on fruit trees likely makes at least a small contribution to the growing crisis of antibiotic resistance in human medicine. Modern molecular tools for tracking the movement of genes make clear that antibiotic resistance is an ecological and not just a medical problem. The use of antibiotics selects for resistant bacteria, whether in orchards or hospitals. Even if these resistant bacteria are not human pathogens, gene transfer mechanisms special to bacteria allow these microbes to spread their resistance genes to other, unrelated bacteria, including pathogens. Although the odds are very low that resistance genes from any particular orchard bacterium will end up in bacteria harmful to humans, such highly unlikely individual events become probable given the vast numbers of bacteria present in soil, water, and living organisms. In short, the use of antibiotics in orchards increases the load of antibiotic resistance genes in the environment, and thus likely contributes at least modestly to medical problems from resistant bacteria."
[9] American Academy of Microbiology, 2009. "Horizontal gene transfer—the movement of genetic material from one organism to another—is the primary mechanism by which bacteria acquire antibiotic resistance."
[10] WHO, 2009. See Table 1.
[11] http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf See Table 6, p.22.
[12] American Academy of Microbiology, 2009. p.10. "Selection takes place anywhere an antibiotic is present, especially in natural environments…"
[13] T.F. O'Brien, 2002. "The basic event in selection is simple. Enough molecules of the antimicrobial agent impinge on a bacterial cell that is about to divide to stop it from doing so, while in its place another cell divides that would not otherwise have divided. The second cell divides either because it was not inhibited by the same exposure (i.e., had some level of resistance) or because it did not quite get that same exposure (e.g., by being a bit away and coming into the space later)."
[14] American Academy of Microbiology, 2009 (p.8): "Horizontal gene transfer—the movement of genetic material from one organism to another—is the primary mechanism by which bacteria acquire antibiotic resistance. Antibiotics promote this genetic exchange by inducing the transfer of conjugative elements." T.F. O'Brien, 2002, p.1: "Use of an antimicrobial agent selects for overgrowth of a bacterial strain that has a gene expressing resistance to the agent. It also selects for the assembly and evolution of complex genetic vectors encoding,

expressing, linking, and spreading that and other resistance genes. Rustam I. Aminov, 2011. Horizontal gene exchange in environmental microbiota, Front Microbiol. 2011; 2: 158: “There is a substantial body of evidence suggesting that the sub-inhibitory concentrations of antibiotics may significantly increase the frequency of horizontal transfer of many types of MGEs [mobile genetic elements].”

[15] American Academy of Microbiology, 2009, p.8: “The transfer of antibiotic resistance genes is evident between bacteria or fungi of the same species, but transfer between organisms that bear limited phylogenetic relatedness, including transfer between gram-negative and gram-positive species, is also possible.”

[16] T.F. O’Brien, 2002 p.5:“The abundance of *E. coli* implicates them as the likely predominant vehicles for the spread of resistance genes and vectors, as opposed to the spread of infection, between the bacterial populations of animals and humans…”

[17] T.F. O’Brien, 2002. p.4: “A resistant strain made prevalent by selection in the bacterial populations of one host is more likely to be among the strains that the host transfers to a second host [15]. Similar selection in the second host would boost the strain’s chances of becoming established, amplified, and then transferred to a third host.”

[18] American Academy of Microbiology, 2009. p.2: “Controlling antibiotic resistant bacteria and subsequent infections more efficiently necessitates the prudent and responsible use of antibiotics. It is mandatory to prevent the needless use of antibiotics…” T.F. O’Brien, 2002. p.6: “Management of such systems necessitates restraint and understanding. The global interdependence of antimicrobial resistance requires that we restrain antimicrobial use to its essential minimum—not just locally, but everywhere in the world.”

[19] WHO, 2009. http://en.wikipedia.org/wiki/Tetracycline_antibiotics “Tetracyclines remain the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), Rickettsia (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be used to treat anthrax, plague, tularemia, and Legionnaires' disease… They may have a role in reducing the duration and severity of cholera, although drug-resistance is occurring, and their effects on overall mortality is questioned.”

[20] K. Kumar, S.C. Gupta, Y. Chander, and C.J. Rosen, 2005. Antibiotic Uptake by Plants from Soil Fertilized with Animal Manure. J. Environ. Qual. 34:2082–2085 (2005). W.D. Kong, Y.G. Zhu',, Y.C. Liang, J. Zhang, F.A. Smith, and M. Yang, 2007. Uptake of oxytetracycline and its phytotoxicity to alfalfa (*Medicago sativa* L.). Environmental Pollution, Volume 147, Issue 1, May 2007, Pages 187-193. RC Sinha and EA Peterson, 1972. Uptake and persistence of oxytetracycline in aster plants and vector leafhoppers in relation to inhibition of clover phyllody agent, Phytopathology 62: 50-56.

[21] United States Environmental Protection Agency. 2005. Oxytetracycline. Section 3 Use on Apples. Summary of Analytical Chemistry and Residue Data. HED Records Center Series 361 Science Reviews, File R104981. Washington, DC. http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-006304_3-Jan-05_a.pdf “Oxytetracycline tolerances are currently established on peaches and pears at 0.35 ppm in terms of oxytetracycline, only. A tolerance on apple is proposed, also at 0.35 ppm. The crop field trials were conducted from 0.5 to 11.6X the proposed seasonal rate of 1.53 lb ai/A and from 49 to 61 days PHI as compared to the proposed PHI of 60 days. Residues were largely at the limit of quantitation (LOQ) of 0.013 to 0.2 ppm up to 0.252 ppm for a 1X study in Region V [MI]. Adequate storage stability data were presented to indicate that the residues of oxytetracycline were stable for the duration of the residue field trial studies.”

[22] 2011 TR lines 291-294: “Once released into the soil, oxytetracycline is expected to become strongly adsorbed to soil particles and have moderate to no mobility (Kumar et al., 2005; HSDB, 2006). This means it can remain in soil for a long time following treatment. Furthermore, it is not likely to leach below the surface soil (Aga et al., 2005), however it can spread by surface run-off of sediment.” 2011 TR 322-325: “Chander et al. (2005) demonstrated that even though tetracycline was tightly adsorbed to clay particles in soil, it was still biologically active” following a 24-hour incubation period. There is a concern that the persistence of oxytetracycline residues in the environment may contribute to the development of bacterial resistance to oxytetracycline and other tetracyclines (Arikan et al., 2007).”

[23] Tetracycline TR, January 27, 2006, , lines 279-293: “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; fieldworkers also can be exposed post-application (EPA 1988).” Although EPA at the time judged these exposures to be “negligible”, this is not an appropriate judgment under OFPA, and as we have seen above, no exposure to an antibiotic is negligible. Lugo-Melchor, Y., Quinones, B., Amezquita-Lopez, B.A., Leon-Felix, J., Garcia-Estrada, R.,

Chaidez, C. 2010. Characterization of tetracycline resistance in Salmonella enterica strains recovered from irrigation water in the Culiacan Valley, Mexico. Microbial Drug Resistance. 6(3):185-190. "As a consequence of the widespread use of tetracyclines, the emergence and spread of tetracycline-resistant bacterial pathogens, among them the foodborne pathogen Salmonella enterica, has become a serious health hazard worldwide." Stuart B. Levy, M.D., George B. FitzGerald, Ph.D., and Ann B. Macone, B.S., 1976. Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline-Supplemented Feed on a Farm. N Engl J Med 1976; 295:583-588: "Chickens were fed tetracycline-supplemented feed (tet-feed), and, as expected, within one week their intestinal flora contained almost entirely tetracycline-resistant organisms. Increased numbers of resistant intestinal bacteria also appeared, but more slowly, in farm members, but not their neighbors. Within five and six months, 31.3 per cent of weekly fecal samples from farm dwellers contained greater than 80 per cent tetracycline-resistant bacteria as compared to 6.8 per cent of the samples from the neighbors (P less than 0.001)."

[24] 2011 TR lines 549-551: "There is a high probability that oxytetracycline resistant bacteria are present in the environment as a consequence of pesticidal use of oxytetracycline which may have negative health consequences for humans (EPA, 2006)."

[25] See Mycoshield MSDS a: http://www.cdms.net/LDat/mp246000.pdf

[26] 2006 TR Lines 154-162.

[27] Lines 458-467.

[28] Lines 469-511.

[29] Lines 521-522.

[30] American Academy of Microbiology, 2009.

[31] American Academy of Microbiology, 2009, pp.5-6.

[32] American Academy of Microbiology, 2009, p.12.

[33] American Academy of Microbiology, 2009, p.12.

[34] EPA, 2008. Oxytetracycline Summary Document Registration Review: Initial Docket, December 2008, p.8. "The Agency found that the pharmaceutical oxytetracycline exposure a user is expected to receive from a typical therapeutic dose is 50,000 to 200,000 times greater than the estimated dietary exposure from the pesticidal sources of oxytetracycline."

[35] American Academy of Microbiology, 2009., p.10: "Selection takes place anywhere an antibiotic is present, especially in natural environments…"

[36] 2011 TR line 463.

[37] 2011 TR line 464.

[38] 2011 TR lines 457-467.

[39] W.D. Kong, Y.G. Zhu',, Y.C. Liang, J. Zhang, F.A. Smith, and M. Yang, 2007. Pages 187-193.

[40] RC Sinha and EA Peterson, 1972.

[41] 2011 TR lines 452-453.

[42] WHO, 2009. See Table 1.

[43]http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf. See Table 6, p.21.

[44] American Academy of Microbiology, 2009, p.7.

[45] ." T.F. O'Brien, 2002, p.5.

[46] Popowska M., Rzeczycka M., Miernik A., Krawczyk-Balska A., Walsh F. & Duffy B. (2012). – Influence of soil use on prevalence of tetracycline, streptomycin and erythromycin resistance and associated resistance genes. Antimicrob. Agents Chemother., 56 (3), 1434–1443.

[47] See NOSB, 2008. Principles of Organic Production and Handling, adopted by the NOSB October 17, 2001, and NOSB Guidance Document on Compatibility with a System of Sustainable Agriculture and "Consistency with Organic Farming and Handling," adopted by the NOSB October 24, 2003, revised April 29, 2004.

[48] NOSB Principles of Organic Production and Handling says, "An organic production system is designed to… Utilize production methods and breeds or varieties that are well adapted to the region…"

[49] NOSB Principles of Organic Production and Handling says, "Organic agriculture is an ecological production management system that promotes and enhances biodiversity, biological cycles, and soil biological activity. It emphasizes the use of management practices in preference to the use of off-farm inputs, taking into account that regional conditions require locally adapted systems. These goals are met, where possible, through the use

of cultural, biological, and mechanical methods, as opposed to using synthetic materials to fulfill specific functions within the system."

[50] NOSB Principles of Organic Production and Handling says, "Organic production and handling systems strive to achieve agro-ecosystems that are ecologically, socially, and economically sustainable."

[51] American Academy of Microbiology, 2009, p.3. "The struggle against antibiotic resistance is a war we will never win. The strength of trillions upon trillions of microorganisms, combined with the ancient force of evolution by constant, unrelenting variation, will inevitably overpower our drugs."

[52] Streptomycin TR, March 8, 2011. Lines 506-507.

[53] See comments of former NOSB member Hubert Karreman on antibiotics 4/13/2011. http://www.regulations.gov/?source=govdelivery#!documentDetail;D=AMS-NOP-11-0014-2686 "As a veterinarian you cannot use antibiotics in organic livestock, I see the use of tetracycline and streptomycin as a sick joke. To allow them for use for non-sentient crops and not allow them to relieve pain and suffering in sentient animals is unethical at best and shockingly appalling at least."

[54] See 2011 Tetracycline Technical Report, lines 226-230.

[55] http://www.organicitsworthit.org/quick/antibiotics-101 "Go organic! By law, organic products must be made without the use of antibiotics." http://www.organicvalley.coop/why-organic/antibiotics/ "Organic Means No Antibiotics" http://www.earthsbest.com/products/product/2392320005 (Earth's Best First Pears): "USDA organic: no growth hormones, antibiotics, steroids or potentially harmful pesticides or herbicides." Even USDA expects it: http://www.usda.gov/wps/portal/usda/usdahome?navid=ORGANIC_CERTIFICATIO "U.S. producers are turning to certified organic farming systems as a potential way to lower input costs, decrease reliance on nonrenewable resources, capture high-value markets and premium prices, and boost farm income. Organic farming systems rely on ecologically based practices such as cultural and biological pest management, exclusion of all synthetic chemicals, antibiotics, and hormones in crop and livestock production." (Accessed 1/20/2013.)
NOSB Guidance on Compatibility with a System of Sustainable Agriculture and Consistent with Organic Farming and Handling, question number 5: Does the substance satisfy expectations of organic consumers regarding the authenticity and integrity of organic products?

[56] Ostenson, H.T. 2010. Organic pome and cherry production and marketing issues: Past, present and future. Acta Hort. (ISHS) 873:137-144

[57] In 1995, tetracycline and streptomycin were added to §205.601, but it was to be reviewed again in two years and a taskforce was to be organized to "explore antibiotic use in crop production. (NOSB minutes, Oct-Nov 1995 meeting, lines 594-604.) In 2006, there was much discussion, including presentation of a statement from CDC opposing the use of the antibiotics in crops, and the question, "Is it possible to put forth a recommendation that we would like to have it taken off of the list within two years?" The antibiotics failed to get a two-thirds majority, but were relisted. (Transcript April 20, 2006.) In 2008, board members noted the advantage of the 2012 expiration date as a final end to tetracycline as a reason for supporting the motion to expand the listing to all forms of tetracycline. (Transcript November 19, 2008.) And in 2011, board members expressed frustration, e.g., "feeling the need to see progress," "[T]he fact is that the committee now has twice in the period of time I've been on the Board, expressed itself, the beliefs that the antibiotics ought to come off the list…" "I wouldn't be able to vote for more than a two-year extension at this point." (Transcript April 29, 2011, pp.25, 32, 37.)

[58] §6517(c)(1): "The National List may provide for the use of substances in an organic farming or handling operation that are otherwise prohibited under this chapter only if -
(A) the Secretary determines, in consultation with the Secretary of Health and Human Services and the Administrator of the Environmental Protection Agency, that the use of such substances
(i) would not be harmful to human health or the environment;
(ii) is necessary to the production or handling of the agricultural product because of the unavailability of wholly natural substitute products; and
(iii) is consistent with organic farming and handling;

[59] NOSB transcript, April 26, 2011, p.380.

[60] Washington State Department of Agriculture printout, "International Organic Program—EU Compliant Operations, March 10, 2011. http://agr.wa.gov/FP/Pubs/docs/wsda_eu_compliant.pdf

[61] Johnson, Ken, Oregon State University, Fire Blight *control in Organic Pome Fruit Systems Under the Proposed Non-antibiotic Standard,* E-Organic Webinar, March 13, 2012. R.D. Koski and W.R. Jacobi *Fire Blight*. Colorado State University Extension. October 2009.

[62] Norelli, John L., Alan L. Jones, and Herb S. Aldwinckle. "Fire blight management in the twenty-first century: using new technologies that enhance host resistance in apple." *Plant Disease* 87.7 (2003): 756-765. "In the twentieth century, fundamental changes in the apple industry resulted in the adoption of high-density orchard systems, and recent planting of susceptible cultivars and rootstocks has increased the danger of fire blight in apple orchards to unprecedented levels."

[63] Paul W. Steiner, 2000. A Philosophy For Effective Fire Blight Management, Presented at the State Horticultural Association of Pennsylvania Annual Meeting, January 2000. http://www.caf.wvu.edu/kearneysville/articles/PHILOSOPHY2000.html