

**TITLE**

Request for Establishment of a New Exclusive Use Period (Provided by FIFRA § 3 (c) (1) (F)  
(VI)) for Oxytetracycline Hydrochloride on English Walnuts and Black Walnuts  
for FireLine™ 45 WP, (EPA Reg. No. 80990-6)

**REFERENCE**

EPA Pesticide Registration Notice (PR) 2018-1

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Aug. 14, 2020

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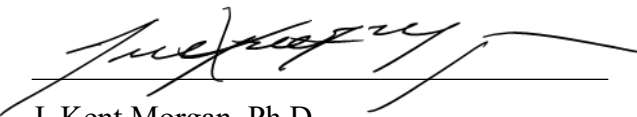
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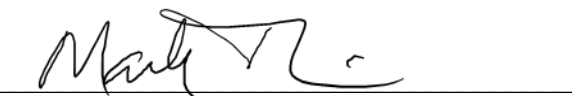
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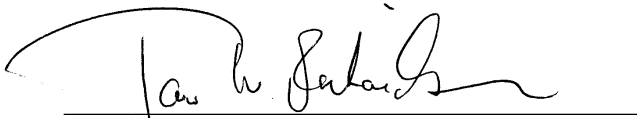
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## Introduction

A bacterial disease, walnut blight (*Xanthomonas juglandis*) seriously affects US commercial walnut production. Currently EPA-approved methods using conventional pesticides to control walnut blight are copper-based fungicides and a single bactericide (discussed below). These have limited-to-no ability to forestall the development of bacterial resistance since at least two bactericides, each with a different mode of action, are required for effective resistance management. To meet this essential condition, AgroSource is supporting a submission by The IR-4 Project to request a new minor use of a second bactericide (oxytetracycline) for the control of walnut blight on walnuts (English and black).

According to USDA NASS 2018 statistics, there are 344,848 bearing walnut acres in the United States. Although this figure exceeds the 300,000-acre threshold for minor crop designation under FIFRA §2 (II) (1), as registrant of FireLine™ 45 WP, (EPA Reg. No. 80990-6, active ingredient oxytetracycline hydrochloride), in accordance with FIFRA §2 (II) (2), AgroSource requests approval of FireLine™ 45 WP as a minor use pesticide for control of walnut blight in walnuts for the following reasons:

- there is insufficient economic incentive for AgroSource to support the initial registration or continuing registration of FireLine™ 45 WP for use on walnuts to control walnut blight, and
- the proposed use of FireLine™ 45 WP on walnuts to control walnut blight, satisfies criteria for minor use status.

In addition, AgroSource requests exclusive use of four reports prepared by AgroSource and submitted to support The IR-4 Project request for a new minor use on walnuts (English and black). These reports (MRIDs to be assigned) are:

1. Request for Establishment of a New Exclusive Use Period (Provided by FIFRA § 3 (c) (1) (F) (VI)) for Oxytetracycline Hydrochloride on English Walnuts and Black Walnuts for FireLine™ 45 WP (EPA Reg. No.: 80990-6), (this document);
2. Benefits Discussion and Rationale Supporting the Addition of Walnuts to the Section 3 Label for FireLine™ 45 WP (Oxytetracycline Hydrochloride);

3. Oxytetracycline: Exposure and Risk Assessments for a Proposed New Use on Walnuts and New Tolerances, and
4. FDA #152 Resistance Risk Assessment for Foliar Applications of FireLine™ 45 WP (active ingredient, Oxytetracycline Hydrochloride) to Walnuts.

**FIFRA §2 (II) (2) – “... *the use does not provide sufficient economic incentive to support the initial registration or continuing registration of a pesticide for such use ...*”**

Per EPA Pesticide Registration Notice (PR) 2018-1, AgroSource has conducted a thorough economic analysis of the proposed use of FireLine™ 45 WP (EPA Reg. No. 80990-6) on commercially grown walnuts for control of walnut blight (*Xanthomonas juglandis*). The following economic/financial metrics were used in making this assessment:

- Net Present Value (NPV),
- Revenue to Cost Ratio (R/C) and
- Internal Rate of Return (IRR).

In conducting the economic analysis, the following baseline information was used:

- Crop: Walnuts (English and Black)
- Bearing Acres<sup>1</sup>
  - US, total: 344,898
  - California: 343,062 (99%+ of US total).
- Product Used: FireLine™ 45 WP, 48.8% active ingredient (oxytetracycline hydrochloride)
- Application Rate: 0.5625 lbs. per acre
- Average No. Applications/Year: 2.33
- Time period analyzed: 7 years<sup>2</sup>

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<sup>1</sup> Acreage data are from USDA NASS, Noncitrus Fruits and Nuts, 2018 Summary. Accessed on August 7, 2020:  
URL:

[https://www.nass.usda.gov/Publications/Todays\\_Reports/reports/ncit0619.pdf#:~:text=8%20Noncitrus%20Fruits%20and%20Nuts%202018%20Summary%20%28June,percent%20from%20the%20comparable%2021%20crops%20in%202017.](https://www.nass.usda.gov/Publications/Todays_Reports/reports/ncit0619.pdf#:~:text=8%20Noncitrus%20Fruits%20and%20Nuts%202018%20Summary%20%28June,percent%20from%20the%20comparable%2021%20crops%20in%202017.)

<sup>2</sup> Analysis over 7 years was selected to be consistent with the most recent Section 3 registration for FireLine™ 17 WP (EPA Reg. No.: 80990-1), full name FireLine™ 17 WP Fungicide/Bactericide Agricultural Oxytetracycline.

- Initial expenses associated with pursuing registration (expenses at Year 0): \$234,000
- Expenses associated with supporting registration in Years 1-7, as a percentage of gross profit, each year.:
  - Marketing & Sales: 25%
  - Regulatory: 10%
  - Management Overhead: 10%
  - Technical Support: 5%
  - Total: 50%
- Market Penetration
  - Number of acres treated with FireLine™ 45 WP by Year 7:
    - 62,084 acres (18% market penetration)
- Economic Analysis
  - A discount rate of 10%<sup>3</sup> has been used to calculate NPV, R/C and IRR based on the above conditions and assumptions. Results from this analysis are:
    - NPV: -\$37,794
    - R/C: 0.3802
    - IRR: -0.1%
  - Results from this economic analysis indicate insufficient economic incentive exists for AgroSource to accept the inherent risks involved with pursuing an expanded registration for FireLine™ 45 WP and then supporting the product's use on walnuts over the forecast 7-year period.

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<sup>3</sup> A discount rate of 10% was used to reflect the relatively high-level uncertainty associated with the approval for the expanded use of FireLine™ 45 WP.



**FIFRA §2 (II) (2) (A) – “*There are insufficient efficacious alternative registered pesticides available for the use.*”**

Most commercial walnuts in the United States are grown in the state of California. Presently the University of California (UC) Integrated Pest management (IPM) Pest Management Guidelines<sup>4</sup> for control of walnut blight recommend walnut growers use the following (organized by “most effective and least likely to cause resistance”):

- A) Mancozeb<sup>®</sup> (e.g. Dithane<sup>®</sup> F-45, etc.) combined with fixed copper
- B) Kasugamycin (active ingredient of Kasumin<sup>®</sup> 2L; EPA Reg. No.: 66330-404)
- C) Fixed copper (e.g. Kocide<sup>®</sup> 3000; EPA Reg. No.: 91411-2-70051)
- D) Bordeaux (a mixture containing a combination of copper and calcium hydroxide use as a preventative measure)

Except for “B) Kasugamycin” each of the other recommendations (A, C, and D) include a form of copper as a part of the walnut blight management system.

Interestingly, in the case of “C) Fixed copper” the UC IPM indicates that: “*Resistance to copper is common in Sacramento Valley orchards and has been found in a few San Joaquin Valley orchards...If resistance is known to occur in the orchard, use higher label rates.*”. With copper resistance in walnut blight becoming more prevalent in California, this leaves only kasugamycin as the only viable options for walnut blight management.

Given the copper limitations for the walnut industry the EPA approved for use of kasugamycin hydrochloride hydrate the active ingredient of Kasumin<sup>®</sup> 2L (EPA Reg. No.: 66330-404) on March 1, 2018 for use on walnuts for treatment of walnut blight. Currently

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<sup>4</sup> See “Agriculture: Walnut Pest Management Guidelines Walnut Blight”  
<https://www2.ipm.ucanr.edu/agriculture/walnut/walnut-blight/>, accessed February 28, 2020.

Kasumin<sup>®</sup> 2L (FRAC<sup>5</sup> Group 24 fungicide/bactericide) is the only antibiotic-based bactericide registered for management of walnut blight; however, it is limited to only 2 applications a year in California (4 applications allowed everywhere else in US). Realizing the limitations of having a limited use of kasugamycin and the copper resistance issues, The IR-4 Project agreed to fund the studies necessary for oxytetracycline use for walnut blight to provide a second viable option for walnut growers to work together with kasugamycin for treatment of walnut blight.

Based on these reasons, there is a strong justification and need for granting the minor use of oxytetracycline hydrochloride for walnuts to provide options for growers to have sufficient efficacious alternative registered pesticides available for use on walnuts to manage/treat walnut blight disease.

**FIFRA §2 (II) (2) (C) – *The minor use pesticide plays or will play a significant part in managing pest resistance.***

The current University of California (UC) Integrated Pest management (IPM) Pest Management Guidelines recommends walnut blight chemical controls that include the use of a “Bordeaux” mixture containing a combination of copper and calcium hydroxide (use as a preventative measure), along with “Fixed Copper” (e.g. Kocide<sup>®</sup> 3000, etc.) or the combination of Mancozeb<sup>®</sup> (e.g. Dithane<sup>®</sup> F-45, etc.) with fixed copper. In cases where resistance to copper is known to occur the current UC IPM Pest Management Guidelines indicate to “use higher label rates”<sup>6</sup> of copper. From a resistance management perspective,

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<sup>5</sup> FRAC Group Code: Fungicide Resistance Action Committee are codes assigned to commercial fungicides and bactericides according to their mode of action (MOA). See at: <https://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2019.pdf>, accessed October 17, 2019. Note: Effective resistance management will always utilize at least two pest control products – each having a different mode of action (as designated by different FRAC Codes).

<sup>6</sup> See “Agriculture: Walnut Pest Management Guidelines Walnut Blight” <https://www2.ipm.ucanr.edu/agriculture/walnut/walnut-blight/>, accessed February 28, 2020.

elevating the rates of fixed copper where copper resistance is present is likely only a temporary reprieve that long-term practice should select for increased copper resistance development.

Heavy reliance on copper is used for walnut blight control; however, copper itself only acts as a disease protectant and therefore does not control the disease once an infection has been established. Also, copper has largely been the only active ingredient used to control this disease while evidence mounts showing resistance to copper is becoming more apparent [1-3]. Furthermore, copper is not readily redistributed on surfaces of growing (expanding) leaves and is easily washed off leaf surfaces by rainfall and must be continually applied to maintain its preventative effect on disease.

The widespread dependence on copper-based bactericides for control of foliar diseases has been associated with the following unwanted conditions:

- 1) potential or actual emergence of copper tolerant, i.e., copper resistant, disease pathogens since resistance management options available to implement with copper against walnut blight disease is limited;
- 2) the continued accumulation of metallic copper in the environment from the yearly, season-long, applications of copper-based bactericides.

Current studies of pesticide-based alternatives to copper treatment of walnut blight is limited in the open literature; however, with the prevalence of copper resistant *Xaj* now reported in walnuts [1-3] by Dr. Jim Adaskaveg *et al* from 1994-1995, and 1997-2018; there has begun a more active pursuit of copper alternatives to control walnut blight. These have included both oxytetracycline and kasugamycin based fungicide/bactericides that each have proved efficacious in treating walnut blight by killing *Xaj* [1].

Given the limited options available for the walnut industry the EPA approved for use of kasugamycin hydrochloride hydrate the active ingredient of Kasumin<sup>®</sup> 2L (EPA Reg. No.: 66330-404) on March 1, 2018 for use on walnuts for treatment of walnut blight. Currently

Kasumin<sup>®</sup> 2L (FRAC<sup>7</sup> group 24 fungicide/bactericide) is the only antibiotic-based bactericide registered for management of walnut blight. FireLine<sup>™</sup> 17 WP and FireLine<sup>™</sup> 45 WP contain the active ingredient oxytetracycline hydrochloride (FRAC group 41 fungicide/bactericide) that is efficacious against walnut blight [1-3] and when oxytetracycline is used with or in rotation with kasugamycin provides a viable mechanism for resistance management. However, as discussed, the known copper resistance of walnut blight at the current time reduces the viable treatment for walnut growers to kasugamycin alone. This is problematic as kasugamycin alone is insufficient to maintain a resistance management program where copper is failing. Therefore, the minor use addition of oxytetracycline hydrochloride (in FireLine<sup>™</sup> 45 WP) for use in conjunction with kasugamycin (in Kasumin<sup>®</sup> 2L) to treat walnut blight is necessary to maintain a practical resistance management program to allow long term treatment options for walnut blight for the US walnut industry.

Regarding management of resistance rationale to support a minor use status for oxytetracycline hydrochloride on walnuts the following are important:

- 1) The active ingredient oxytetracycline hydrochloride of FireLine<sup>™</sup> 45 WP has established bactericidal efficacy and systemic activity against the pathogens responsible for walnut blight.
- 2) Oxytetracycline has a different mode of action (MOA) than copper and kasugamycin and since these each have different MOAs effective resistance management strategies against this disease can be employed.

Based on these rational, there is a strong justification and need for the minor use of oxytetracycline hydrochloride to have a significant part in managing pest resistance with

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<sup>7</sup> FRAC Group Code: Fungicide Resistance Action Committee are codes assigned to commercial fungicides and bactericides according to their mode of action (MOA). See at: <https://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2019.pdf>, accessed October 17, 2019. Note: Effective resistance management will always utilize at least two pest control products – each having a different mode of action (as designated by different FRAC Codes).

its inclusion into existing resistance management programs established for control of walnut blight in walnuts.

**FIFRA §2 (II) (2) (D) – *The minor use pesticide plays or will play a significant part in an integrated pest management program.***

From the IR-4 Website (Food Request Database) for the walnut project it states for IPM Compatibility the following<sup>8</sup>:

*“Per requester: Very good IPM fit; can be integrated into management program and reduce total load of any one pesticide on the crop and in the environment; copper resistance levels are increasing and rotational products to mancozeb are needed to keep mancozeb activity high; once Kasumin is registered a rotational product will help to prevent overuse and selection of resistance.”*

Most registered products for walnut blight are copper based or biological in nature. Recently kasugamycin hydrochloride hydrate active ingredient of Kasumin® 2L (FRAC group 24 fungicide/bactericide; EPA Reg. No.: 66330-404) was approved in 2018 by the EPA as the first antibiotic-based bactericide for treatment of walnut blight. Its approval was necessary as evidence of copper resistant walnut blight bacteria are emerging in California (as discussed previously); this coupled with less effective treatment alternatives of biologicals (NOTE: the UC Pest Management Guidelines does not list any biologicals in their recommendations for management of walnut blight<sup>9</sup>), served to justify the approval of kasugamycin. However, because of the emergence of copper resistance, kasugamycin is now one of the only viable option for growers to treat copper resistant walnut blight bacteria. At present kasugamycin lacks an effective resistance management partner (as indicated previously in the IR-4 statement at the beginning of this section. Oxytetracycline

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<sup>8</sup> See <http://ir4app.rutgers.edu/Ir4FoodPub/prnum.aspx?prnum=11876>, accessed February 28, 2020.

<sup>9</sup> See “Agriculture: Walnut Pest Management Guidelines Walnut Blight” <https://www2.ipm.ucanr.edu/agriculture/walnut/walnut-blight/>, accessed February 28, 2020.

hydrochloride in FireLine™ 45 WP will provide a viable alternative for use to treat walnut blight and act in concert with kasugamycin to manage resistance development. In fact, studies showed that these together worked very well to control the disease [2, 3].

A separate factor for consideration of oxytetracycline playing a significant role in an integrated IPM program is that it is rapidly degraded in the environment. Due to this the resultant residue is minimal and has minimal impact on the environment. Together this also supports its role as an important part of an IPM strategy for management of walnut blight.

Regarding IPM rationale to support a minor use status for oxytetracycline hydrochloride on walnuts the following are important:

- 1) The addition of oxytetracycline into an IPM program for control of walnut blight potentially reduces the amount of metallic copper added to the environment each season.
- 2) The addition of oxytetracycline added into an IPM program for control of walnut blight serves to be an effective rotational partner with kasugamycin.
- 3) Oxytetracycline rapidly degrades in the environment and the rates and levels proposed will leave zero residue in the target crops leaving minimal to no lasting impact on the environment when employed in an integrated IPM management program.

Based on these reasons, there is a strong justification and need for the minor use of oxytetracycline hydrochloride allowance on walnuts to provide options to growers to have alternative modes of action for IPM programs and that oxytetracycline would be a significant part in the management for control of walnut blight in walnuts.

## Summary

Justifications for minor use status of oxytetracycline hydrochloride (a.i. of FireLine™ 45 WP) on walnuts per FIFRA §2 (II) (2) (A) (C) or (D); are:

- 1) Calculation of Net Present Value (NPV), Revenue to Cost Ratio (R/C) and Internal Rate of Return (IRR) using expected market penetration over a 7-year investment period each indicate there is insufficient economic incentive for AgroSource to pursue and support the expanded label use of FireLine™ 45 WP for walnuts.
- 2) Current registered products for walnut blight treatment are limited to mainly copper, biologicals, and kasugamycin hydrochloride hydrate. With the presence of copper resistance and the general ineffectiveness of biologicals; kasugamycin has become the de facto option for growers to treat walnut blight leaving a strong need for oxytetracycline hydrochloride to provide an efficacious alternate registered product available for use on walnuts to manage walnut blight.
- 3) The active ingredient oxytetracycline hydrochloride of FireLine™ 45 WP has established bactericidal efficacy and systemic activity against the pathogens responsible for walnut blight.
- 4) Oxytetracycline has a different mode of action (MOA) than copper and kasugamycin and since these each have different MOAs effective resistance management strategies against this disease can be employed.
- 5) The addition of oxytetracycline into an IPM program for control of walnut blight potentially reduces the amount of metallic copper added to the environment each season.
- 6) The addition of oxytetracycline added into an IPM program for control of walnut blight serves to be an effective rotational partner with kasugamycin.
- 7) Oxytetracycline rapidly degrades in the environment and the rates and levels proposed will leave zero residue in the target crops leaving minimal to no lasting impact on the environment when employed in an integrated IPM management program.

Based on justifications presented in this document, AgroSource, Inc. submits that oxytetracycline hydrochloride applications to walnuts for control of walnut blight complies with FIFRA §2 (II) (2) (A) (C) or (D) as a new minor use; additionally, that a new Exclusive Use Period applies to four studies (including this document) prepared by AgroSource and submitted in support of The IR-4 Project petition to expand the label use of FireLine™ 45 WP (EPA Reg. No.: 80990-6) on walnuts to manage walnut blight.



## Literature Cited

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