

<u>Title</u> Application for the Extension of the Exclusive Use Period for Cyflumetofen as Provided by FIFRA Section 3c(1)(F)(ii)

EPA Guideline(s)

Not Applicable

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Test Facility / Performing Laboratory

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GOOD LABORATORY PRACTICES STATEMENT

This report does not meet the definition of a study under 40 CFR part 160 and is not required to be conducted in compliance with 10 CFR part 160. As such, there is no study director or sponsor.

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Date December 14 2022



Application for the Extension of the Exclusive Use Period for Cyflumetofen as Provided by FIFRA Section 3c(1)(F)(ii)

December 2022

Introduction

BASF Corporation, the sole registrant of the proprietary miticide active ingredient cyflumetofen, is hereby petitioning the U.S. Environmental Protection Agency (EPA) for approval of the allowed third year of exclusive use of data supporting the registration of cyflumetofen on minor crops, as provided under FIFRA Section 3(c)(1)(F)(ii).

Cyflumetofen was first registered by EPA on May 9, 2014, under the registered names of Cyflumetofen Technical, Nealta[®] Miticide, and Sultan[®] Miticide (EPA Registration Numbers 7969-335, 7969-336, and 7969-337, respectively). The initial 10-year period for exclusive use of data extends until May 9, 2024. On May 30, 2017, BASF submitted to EPA a request for extension of our exclusive use based on approved minor crop uses as allowed under FIFRA. This submission, as required by FIFRA, was within the commencement of the required seven years of the original exclusive use period. EPA reviewed our submission and granted two of the three allowed years (refer to EPA letter dated October 9, 2018, for full EPA determination).

With this December 2022 submission, BASF is requesting EPA review new supporting data on 13 minor crops and then grant BASF the allowed third year of exclusive use of our cyflumetofen data–thus extending BASF's exclusive use period thru May 9, 2027.

The cyflumetofen-based products used to develop the minor use data supporting this extension, and on which these uses are registered, includes:

- Cyflumetofen Technical (EPA Reg. No. 7969-335)
- Nealta® Miticide (EPA Reg. No. 7969-336)
- Sultan[®] Miticide (EPA Reg. No. 7969-337)

The justification presented in this document is based on fulfillment of at least one of the four criteria identified in FIFRA 3c(1)(F)(ii) which states:

"The period of exclusive data use provided under clause (i) shall be extended 1 additional year for each 3 minor uses registered after August 3, 1996, and within 7 years of the commencement of the exclusive use period, up to a total of 3 additional years for all minor uses registered by the Administrator if the Administrator, in consultation with the Secretary of Agriculture, determines that, based on information provided by an applicant for registration or a registrant, that

- 1. There are insufficient efficacious alternative registered pesticides available for the use
- 2. The alternatives to the minor use pesticide pose greater risks to the environment or human health
- 3. The minor use pesticide plays or will play a significant part in managing pest resistance
- 4. The minor use pesticide plays or will play a significant part in an integrated pest management program."

Table 1 presents a summary of the minor uses cited to satisfy the Criterion for extending the exclusive use period.



Table 1 Summary of Rationale to Extend Exclusive Use for Cyflumetofen

	Target Minor Use Crop	Representative Crops for Crop Group	Cyflumetofen Use Pattern	Criteria used by EPA to Determine if Minor Crop is Counted for Data Exclusivity Extension			
Count				1. There are insufficient efficacious alternative registered pesticides available for the use	2. The alternatives to the pesticide use pose greater risks to the environment or human health	3. The minor use pesticide plays or will play a significant part in managing pest resistance	4. The minor use pesticide plays or will play a significant part in an integrated pest management program.
1	Greenhouse Tomatoes	Tomato	Fruiting Vegetables Group 8-10A Foliar application to control spider mites			x	x
2	Greenhouse Peppers / Non-bell Peppers	Pepper and Non- bell Pepper	Fruiting Vegetables Group 8-10B and 10C			x	x
3	Greenhouse Non-bell Peppers / Eggplants	Eggplant	Foliar application to control spider mites			x	x
4	Greenhouse Strawberries	Strawberry	Low growing berry subgroup 13-07G Foliar application to control spider mites			x	x
5	Greenhouse Cucumbers	Cucumber	Cucurbits Vegetables Group 11 (cucumber only) Foliar application to control spider mites			x	x
6	Peaches	Peach				x	x
7	Sweet and Tart Cherries	Cherry				x	x
8	Plums		Stone Fruit Group 12-12			x	x
9	Plumcots		Foliar application to			x	x
10	Nectarines		stone fruits			x	x
11	Prunes					x	x
12	Apricots					x	x
13	Hops	Hops	Foliar application to control spider mites in hops	x		x	x



Minor Crop Uses used to Satisfy the FIFRA 3c(1)(F)(ii) Criteria for Extending the Exclusive Use Period for Cyflumetofen

Each of the crops (or group of crops) listed in sections **I through XIII** of this document are minor crops within EPA crop groupings for which residue studies were conducted to establish permanent tolerances (MRLs) for cyflumetofen. These crops including:

- Greenhouse-grown fruiting vegetables (tomatoes, bell pepper, non-bell pepper, and eggplant crops)
- Greenhouse-grown strawberries
- Greenhouse-grown cucumbers
- stone fruits (peach, sweet & tart cherries, plum, plumcot, nectarines, prunes, and apricot)
- hops

All of these crop uses were developed in collaboration with The IR-4 Project having met their selection criteria for use in minor crops. Justifications for minor crop use data development cited by stakeholders/growers on IR-4's Pesticide Clearance Forms (part of their evaluation process) indicated one or more of the below key factors associated with Nealta® or Sultan® miticides:

- good IPM (Integrated Pest Management) fit
- alternative miticide for rotation efforts
- soft on beneficial insects
- growers need for more modes of action to better manage resistance to miticides

Mode of Action (MOA) for Cyflumetofen

Cyflumetofen belongs to the benzoylacetonitrile class of chemistry. Cyflumetofen is the only mitochondrial complex II mitochondrial electron transport inhibitor (IRAC Class 25A) registered in the U.S. (Table 2). This MOA is unique compared to the other miticides. It inhibits the mitochondrial electron transport complex II enzyme within mite cells. This inhibition interrupts the production of ATP, eventually depleting the cell of energy, leading to paralysis and death.

Table 2 List of miticides and respective Mode of Action

		IRAC
Miticide Active Ingredient	Mode of Action	Group/SubGroup
Abamectin	Chloride channel activator	6
Clofentezine, hexythiazox	Mite growth inhibitor	10A
Etoxazole	Mite growth inhibitor	10B
	Mitochondrial ATP synthase	
Propargite	inhibitor	12C
Fenazaquin, fenpyroximate, pyridaben	METI Complex I	21A
Acequinocyl	METI Complex III	20B
Spirodiclofen, spiromesifen,		
spirotetramat	Acetyl CoA carboxylase inhibitor	23
Cyflumetofen	METI Complex II	25A
Bifenazate	Unknown	

Cyflumetofen has demonstrated high efficacy against mites that have developed resistance to other acaricides ([1] Hu et al. 2010; [2] Stavrinides et al. 2010). No instances of target site cross-resistance have been observed. Because of its unique mode of action, cyflumetofen is an important miticide resistance management tool when used according to good agricultural practices and when local



resistance management recommendations are followed. The Insecticide Resistance Action Committee (IRAC) recommends rotating products, so the same mode of action is not used on successive pest generations.

► The unique mode of action of cyflumetofen, selectivity to mite pests, and it being the only registered Group 25A product in the U.S. satisfy FIFRA 3c(1)(F)(ii) Criterion 3 guidelines: The minor use pesticide plays or will play a significant part in managing pest resistance.

Contribution to Integrated Pest Management Programs

Cyflumetofen fits into integrate pest management (IPM) programs because of the low risk to honeybees, predatory mites, and other beneficial arthropods which may be used in biocontrol programs. Further, due to its highly selective nature, cyflumetofen is a good fit in IPM programs. Cyflumetofen's bee contact LD_{50} is >102 µg/bee, which is classified as "Practically non-toxic" by U.S. EPA standards. Standard laboratory bioassays indicate cyflumetofen has a low impact on a wide range of beneficial arthropods, including parasitic wasps, predatory mites, predatory bugs, ladybird beetles, rove beetles, and lacewings (Table 3) when the organisms are exposed to fresh residues on inert substrates. Because of cyflumetofen's relatively low aquatic, avian, and mammalian toxicity, impact on other non-target wildlife species is also low.

Unlike currently available spider mites control products, cyflumetofen is the only product combining low mammalian toxicity, control of all life stages of the target pest, low toxicity to honeybees, low toxicity to key beneficial insects and arthropods, and that provides these benefits while delivering a new mode of action for IPM without cross-resistance with other miticides.

Cyflumetofen's very selective activity against spider mites, with little or no effect on non-target arthropods, makes it an extremely effective tool in an IPM program–satisfying FIFRA 3c(1)(F)(ii) Criterion 4 guidelines: The minor use pesticide plays or will play a significant part in an integrated pest management program.



Table 3 Impact on Beneficial Insects, Predators, and Parasites^a

Independent comparison of miticide activity on beneficials. Of the three alternatives classified as harmless across all beneficial species evaluated, two (clofentezine and hexythiazox), share the same mode of action (mite growth regulator).

Active ingredient / MOA ^b	Amblyseius californicus (predatory mite)	Amblyseius cucumeris (predatory mite)	Amblyseius swirskii (predatory mite)	Aphidius colemani (aphid parasite)	Encarsia formosa (whitefly parasite)	Orius laevigatus (predatory bug)	<i>Phytoseiulus persimilis</i> (predatory mite)
cyflumetofen (Nealta [®])							
fenbutatin oxide							
clofentezine							
hexythiazox							
acequinocyl							
bifenazate							
spirodiclofen							
etoxazole [‡]							
fenpyroximate [‡]							
propargite							
pyridaben							
abamectin [‡]							

^aAll data from Koppert Biological Systems - Side effects database. http://side effects.koppert.nl/

Koppert Rating scale: Green = harmless (< 25% reduction), Yellow = slightly harmful (25 - 50% reduction), Pink = moderately harmful (50 - 75% reduction), Red = very harmful (> 75% reduction), Gray = no information. ^bIRAC mode of action classification.

METI Complex II
Mitochondrial ATP synthase inhibitor
Mite growth regulator
METI Complex III
Unknown
Lipid biosynthesis inhibitor
METI Complex I
Chloride channel activator

[‡] = Competitive targets Nealta[®] CA is expected to partially displace.



I thru III. Greenhouse-Grown Fruiting Vegetables

FIFRA 3c(1)(F)(ii) criterion satisfied \rightarrow 3 and 4

"The minor use pesticide plays or will play a significant part in managing pest resistance" **and** "The minor use pesticide plays or will play a significant part in an integrated pest management program."

Minor Use Crop	Minor Use Acreage ¹	Description of Specific Labeled Use Pattern	Reason Why Cyflumetofen Satisfies Criterion 3 and 4
Tomatoes	<300,000	Apply Sultan[®] Miticide at 13.7 fl oz/100 gallons of water (0.18	Sultan [®] Miticide (cyflumetofen) is
Bell Peppers	<300,000	lb ai). Make application at first sign of spider mite infestation.	and a good IPM fit in greenhouse- grown fruiting vegetables. Cyflumetofen offers a novel MOA as a tool to manage resistance to miticides.
Non-bell Peppers / Eggplant	<300,000	Consecutive applications not permitted without rotating to a different MOA. No more than 2 applications/season.	

¹ The USDA [5] currently has no production statistics for minor use crops listed with <300,000 acres.

IV. Greenhouse-Grown Strawberries

FIFRA 3c(1)(F)(ii) criterion satisfied \rightarrow 3 and 4

"The minor use pesticide plays or will play a significant part in managing pest resistance" **and** "The minor use pesticide plays or will play a significant part in an integrated pest management program."

Minor Use Crop Minor U		Description of Specific	Reason Why Cyflumetofen	
Acreag		Labeled Use Pattern	Satisfies Criterion 3 and 4	
Strawberries	<300,000	Apply Sultan® Miticide at 13.7 fl oz/100 gallons of water (0.18 lb ai). Make application at first sign of spider mite infestation. Consecutive applications not permitted without rotating to a different MOA. No more than 2 apps/season.	Sultan[®] Miticide (cyflumetofen) is efficacious against tetranychid mites and a good IPM fit in greenhouse- grown strawberries. Cyflumetofen offers a novel MOA as a tool to manage resistance to miticides.	

¹ The USDA [5] currently has no production statistics for minor use crops listed with <300,000 acres.

V. Greenhouse-Grown Cucumber

FIFRA 3c(1)(F)(ii) Criterion satisfied \rightarrow 3 and 4

"The minor use pesticide plays or will play a significant part in managing pest resistance" **and** *"The minor use pesticide plays or will play a significant part in an integrated pest management program."*

Minor Use Crop	Minor Use	Description of Specific	Reason Why Cyflumetofen	
	Acreage ¹	Labeled Use Pattern	Satisfies Criterion 3 and 4	
Cucumbers	<300,000	Apply Sultan® Miticide at 13.7 fl oz/100 gallon of water (0.18 lb ai). Make application at first sign of spider mite infestation. Consecutive applications not permitted without rotating to a different MOA. No more than 2 apps/season.	Sultan[®] Miticide (cyflumetofen) is efficacious against tetranychid mites and a good IPM fit in greenhouse- grown cucumber. Cyflumetofen offers a novel MOA as a tool to manage resistance to miticides.	

¹ The USDA [5] currently has no production statistics for minor use crops listed with <300,000 acres.



Spider Mite Pests of Greenhouse-grown Fruiting Vegetables, Cucumbers, and Strawberries

Two-spotted spider mite, (*Tetranychus urticae* Koch) is a major pest of many greenhouse-grown crops and a major cause of economic losses each year. The use of miticides is one of the tactics growers use to control mites in the greenhouses. Usually, it takes more than one spray application per growing season to control mites. Spider mites are notorious for developing resistance to chemicals; therefore, it is recommended for growers to rotate between different products with different MOAs in their management programs to prevent or slow down resistance development to miticides.

Use of biological control agents is another tactic growers rely on to control mites in greenhouses. It is therefore advisable to use miticides safe to beneficial insects and predatory mites to conserve them. Table 2 shows effects of cyflumetofen on different beneficial insects and mites commonly found in most cropping systems.

IPM Compatibility of Sultan® Miticide in Greenhouse Mite Management Programs

Cyflumetofen is registered as Sultan® for greenhouse uses. BASF, in conjunction with The IR-4 Project, developed the use of Sultan on several greenhouse-grown vegetables following a request from stakeholders. On IR-4's Pesticide Clearance Form, stakeholders indicated cyflumetofen was requested based on its suitable IPM for mite control and that it offers a different MOA from existing products to manage resistance to miticides. Mites are known to quickly develop resistance to miticides if proper rotation measure are not in place. Sultan offers quick knockdown to mites, with long residual control, and is compatible in IPM programs using beneficial insects and predatory mites.

VI-XII. Stone Fruits

FIFRA 3c(1)(F)(ii) Criterion satisfied \rightarrow 3 and 4

"The minor use pesticide plays or will play a significant part in managing pest resistance" **and** "The minor use pesticide plays or will play a significant part in an integrated pest management program."

Minor Use Crop	Minor Use Acreage ¹	Description of Specific Labeled Use Pattern	Reason Why Cyflumetofen Satisfies Criterion 3 and 4
Peaches	<300,000		
Cherries, sweet and tart	<300,000	Apply Nealta[®] Miticide at 13.7 fl.oz/A (0.18 lb ai/A) as a foliar	
Plums	<300,000	spray in at least 100 gallons	Nealta [®] Miticide (cyflumetofen) is efficacious against tetranychid mites and a good IPM fit in stone fruits. Cyflumetofen offers a novel MOA as
Plumcots	<300,000	application at first sign of	
Nectarines	<300,000	back-to-back applications. No	a tool to manage resistance to miticides.
Prunes	<300,000	crop season per year.	
Apricots	<300,000		

¹ The USDA [5] currently has no production statistics for minor use crops listed with <300,000 acres.

Mite Pests of Stone Fruits

The main mite pests of stone fruits include Brown mite (*Bryobia rubrioculus*); European red mite (*P. ulmil*); Pacific spider mite (*T. pacificus*); and Two-spotted spider mite (*T. urticae*). These Tetranychid mites damage stone fruit crops starting from early in the season (dormancy) to postharvest. Mites cause damage to trees by removing contents of the leaf cells as they feed leaving behind a mottled appearance on the leaves. Under high mite infestation, Pacific and Two-spotted spider mite damage



can cause leaf stippling which can cause leaves to turns yellow and eventually drop in cherries, peaches, and plum. If defoliation occurs early in the season, it may result in small peach fruits and limbs exposing the fruits to sunburn ([6] UC IPM).

IPM Compatibility of Nealta

Registration of Nealta for use in stone fruits crops was developed in collaboration with The IR-4 Project. The use was requested by stakeholders based on Nealta's key features and strength including: a good IPM fit, a different MOA from the existing products and therefore as tool to manage resistance, and to re-balance IPM as impacted by need to control Spotted wing drosophila in stone fruit crops.

- *Peaches:* In 2021, there were 74,400 acres planted with peaches in the U.S. with California as the leading producer. Other key producers of peaches in the US include Georgia and South Carolina (NASS, 2021).
- *Cherries:* There are two main types of cherries produced in the U.S.: sweet and tart/'sour'. In 2021, there were 84,500 acres planted with sweet cherries and 30,500 acres planted with tart cherries. California, Oregon, and Washington are the main producers of sweet cherries; Michigan has 75% of bearing acres for tart cherries in the U.S. (NASS, 2021).
- *Plums:* In 2021, there were 12,800 acres of bearing plums–all growing in California (NASS, 2021).
- *Plumcot:* Plumcot is an interspecific hybrid of plums and apricot. Plumcot were developed and are mainly grown in California. No statistics were found on U.S. production, but total acre production is believed to be less than 300K acres.
- *Nectarines:* In 2021, there were 13,000 acres with bearing nectarines–all growing in California (NASS, 2021).
- *Prunes:* In 2021, there were 37,000 acres of bearing prunes in the U.S. with most of the production in California (NASS, 2021).
- *Apricots:* In 2021, there were approximately 41,740 acres of apricots planted in the U.S. with nearly 92% of production acreage in California (NASS, 2021).

Section XIII. Hops

FIFRA 3c(1)(F)(ii) Criterion satisfied \rightarrow 3 and 4

"The minor use pesticide plays or will play a significant part in managing pest resistance", **and** "The minor use pesticide plays or will play a significant part in an integrated pest management program."

Minor Use Crop	Minor Use	Description of Specific	Reason Why Cyflumetofen
	Acreage ¹	Labeled Use Pattern	Satisfies Criterion 3 and 4
Hops	<300,000	Apply Nealta® Miticide at 13.7 fl oz/A (0.18 lb ai/A) as a foliar spray in at least 100 gallons spray solution/A. Make application at first sign of spider mite infestation. No back-to-back applications. No more than 2 applications per crop per year.	Nealta[®] Miticide (cyflumetofen) is efficacious against tetranychid mites even, those that have become resistant to other products, like is found in hops. Cyflumetofen offers a novel MOA as a tool to manage resistance to miticides. Cyflumetofen is a good fit in IPM programs.

¹ The USDA [5] currently has no production statistics for minor use crops listed with <300,000 acres.



Mite Pests of Hops

Hops production in the U.S. is mainly in Pacific Northwest states including Washington, Oregon, and Idaho. In 2019, the U.S. had 59,739 acres growing with hops, and 69% of these were in Washington state. Two-spotted spider mite is the predominant mite pest in hops among other Tetranychid mites, such as McDaniel spider mite (*T. mcdanieli*) and Willamette spider mite (*Eotetranychus willamettei*) ([4] Walsh and Barbour 2022). These mites spin webs that they use for various functions (e.g., protection from the rain, natural enemies, or chemical spray droplets; dispersal to look for new hosts). Like in many other crops, mites damage crops by piercing and sucking leaf juices and contents like chlorophyll leaving chlorotic spots on the leaf. High population mite infestations can cause leaf drop due to severe damage. In hops, most damage occurs when mites feed on the hop cone causing them to be dry, brittle, and discolored–they easily shatter which results in yield reduction in both quality and quantity ([4] Walsh and Barbour 2022). Late season mite infestation and feeding damage result in reduced alpha-acid content in the hop cones at harvest. In addition, the presence of mites on harvested cones is a contamination that reduce the quality of the hop cones and can lead to total crop loss or rejection by brewers.

To manage mites on hops, growers, require multiple applications of miticides during the growing season. Resistance to several miticides has been reported in Washington, and growers need a new MOA that is effective in controlling mites. Nealta® Miticide received EPA approval in December 2021 following an IR-4 project to bring an alternative MOA miticide to hops growers ([3] IR-4 Project, 2022). This registration is recognized as bringing a new tool to combat mites and ensure a healthy hops crop for brewers around the world ([3] IR-4 Project, 2022). Other currently registered products that can be used in hops include abamectin, acequinocyl, bifenazate, etaxazole, and hexythiazox.

For hops growers, Nealta brings a different MoA for mite management that is compatible in the IPM and IRM programs for spider mites control. In hops, beneficial arthropods contribute to the control of spider mites and aphids depending on the population densities of pests and prey, environmental conditions, and grower cultural practices.

Benefits of Cyflumetofen

The cited IR-4 Project article highlights the benefits cyflumetofen brings to hop growers including:

- safety to beneficial insects and mites that control damaging mite populations
- a different MOA from other pesticides in the market that show resistance to mite control

Further, Nealta is effective against all mite life stages including eggs, nymphs, and adults. Nealta is compatible with key beneficial insects and mites; therefore, it is a fit in IPM programs to conserve biological control agents in the system.



Summary

Cyflumetofen should be considered by growers for minor crop uses in greenhouse-grown fruiting vegetables, strawberries, and cucumbers, as well as in stone fruit crops and hops because of the need to manage Tetranychid mites. In all minor use crops, multiple MOAs are needed in the application rotation to mitigate the potential for miticide resistance. This makes cyflumetofen a fit in an IPM program because of its unique MOA (i.e., the only registered (IRAC Group 25A product). Cyflumetofen is soft on beneficial arthropods. Cyflumetofen also has excellent activity on Tetranychid mites and is shown to have excellent crop safety.

Therefore, it is BASF's assertion that due to these positive qualities, cyflumetofen meets the **FIFRA 3c(1)(F)(ii)** Criterion 3 and Criterion 4 for extending the exclusive use period of these products.



Citations

- 1. Hu, Jinfeng, Changfang Wang, Jun Wang, Yong You, and Feng Chen. "Monitoring of resistance to spirodiclofen and five other acaricides in Panonychus citri collected from Chinese citrus orchards." Pest Management Xcience 66(9): 1025-1030. 2010.
- Stavrinides, Menelaos C., Pieter Van Nieuwenhuyse, Thomas Van Leeuwen, and Nicholas J. Mills. "Development of acaricide resistance in Pacific spider mite (Tetranychus pacificus) from California vineyards." Experimental and Applied Acarology 50(3): 243-254. 2010.
- 3. U.S. Hop Growers Have New Tool to Manage Two-spotted Spider Mite. <u>www.ir4project.org</u> posted May 26, 2022.
- 4. Walsh, B. D., and J. D. Barbour 2022. Two-spotted Spider Mite. Arthropod and Mollusk Management, Field Guide for Hops. https://www.usahops.org/cabinet/data/6.pdf
- 5. National Agricultural Statistics Service. <u>https://downloads.usda.library.cornell.edu/usda-esmis/files/zs25x846c/4q77gv96p/t722jd76c/ncit0522.pdf</u>
- 6. UC IPM. https://www2.ipm.ucanr.edu/agriculture/peach/