Petition for Tolerance

Fluoxapiprolin
(EPA Reg. No. 264-XXXX)

2-[3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]-1-[4-[4-[5-[2-chloro-6-[(methylsulfonyl)oxy]phenyl]-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-ethanone

For foliar use a fungicide on the following crops:

Brassica head and stem vegetables (Group 5-16)
Bulb vegetables (Group 3-07)
Cucurbit vegetables (Group 9)
Fruiting vegetables (Group 8-10)
Leafy vegetables (Group 4-16)
Leaf petiole vegetables (Subgroup 22B)
Small fruit vine climbing, except fuzzy kiwifruit (Subgroup 13-07F)
Tuberous and corm vegetables (Subgroup 1C)

For rotation to the following crops:

Low growing berry subgroup (Subgroup 13-07G)

January 23, 2023

Bayer CropScience
800 N. Lindbergh Blvd.
St. Louis, MO 63167

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SECTION A

Product Chemistry

CHEMICAL ABSTRACTS NAME

2-[3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]-1-[4-[4-[5-[2-chloro-6-[(methylsulfonyl)oxy]phenyl]-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-ethanone

C.A.S REGISTRY NUMBER

1360819-11-9

IUPAC NAME

2-((5RS)-3-[2-(1-([3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]acetyl)-4-piperidyl)thiazol-4-yl]-4,5-dihydroisoxazol-5-yl)-3-chlorophenyl methanesulfonate

COMMON NAME

Fluoxapiprolin

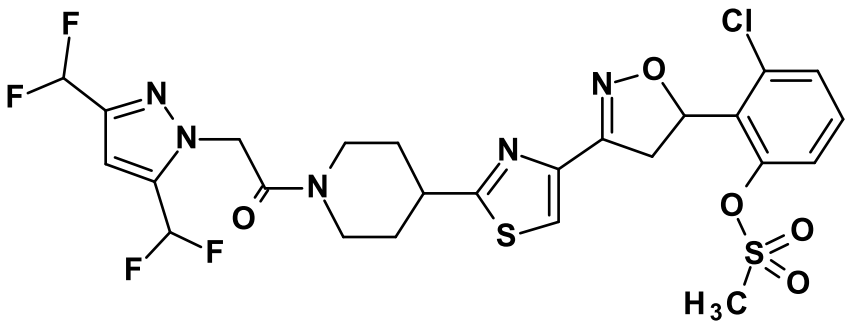
MOLECULAR WEIGHT

650.07

MOLECULAR FORMULA

$C_{25}H_{24}ClF_4N_5O_5S_2$

STRUCTURAL FORMULA



CHEMICAL FAMILY

Piperidinyl-thiazole-isoxazolines

PHYSICO-CHEMICAL PROPERTIES of FLUOXAPIPROLIN

Guideline	Description	Results
830.6302	Color	The substance is light beige
830.6303	Physical State	Solid, the substance is a powder
830.6304	Odor	The substance has an intense odour of solvents (TGAS).
830.6313	Stability to normal and elevated temperatures, metals, and metal ions	Fluoxapiprolin is stable and does not cause corrosion to the polypropylene and polyethylene container materials.
830.6314	Oxidation/ Reduction	Fluoxapiprolin has no oxidising properties.
830.6315	Flammability	Fluoxapiprolin is not flammable.
830.6316	Explodability	Fluoxapiprolin is not explodable.
830.6319	Miscibility	Not required, as the substance is not an emulsifiable liquid.
830.6317	Storage stability	Fluoxapiprolin is stable.
830.6320	Corrosion Characteristics	Fluoxapiprolin does not cause corrosion to the polypropylene and polyethylene container materials.
830.7000	pH	TGAS: The pH of a 1% suspension in distilled water is 5.7 (23°C).
830.7100	Viscosity	Not required as, the substance is not a liquid at room temperature
830.7200	Melting point	143.7 °C (TGAS: technical active substance)
830.7220	Boiling point	Not required as the product is a solid with a high melting point.
830.7300	Density	PAS: D_4^{20} = 1.51 TGAS: D_4^{20} = 1.56
830.7370	Dissociation constants in water	The active substance shows no acidic or basic properties in the range of approximately 1 < pKa < 12.
830.7550	Partition coefficient	pH 4: log P_{ow} 3.4 pH 7: log P_{ow} 3.4 pH 9: log P_{ow} 3.4 at 25°C
830.7840	Water solubility:	Solubility in distilled water: 0.08 mg/L at 20°C (final pH 5.9)
830.7860		
830.7950	Vapor pressure	p (20 °C) = 3.0 x 10^{-5} Pa (by extrapolation) p (25 °C) = 4.5 x 10^{-5} Pa (by extrapolation) p (50 °C) = 2.9 x 10^{-4} Pa (by extrapolation)
830.Supp	Henry's law constant	K = 0.24 Pa•m^3•mol^{-1} at 20°C

Complete product chemistry data on fluoxapiprolin technical are listed in the Data Matrix included in the registration applications accompanying this petition. Bayer CropScience is applying for the registration of one end-use product containing fluoxapiprolin for which tolerances are being requested. Also included in the applicable registration applications are the OECD Tier 2 Summaries and Confidential Statements of Formula (CSFs) for the product which is described below.

Fluoxapiprolin SC 20 fungicide formulation (Xivana) contains 0.17 pounds of the active ingredient fluoxapiprolin per U.S. gallon (20 grams per liter) and is proposed for foliar use in the control or suppression of certain crop diseases in selected fruit and vegetable crops.

SECTION B

Amount, Frequency and Time of Application

The crops to be treated and the rate and frequency of application for domestic use of the fluoxapiprolin end-use product Fluoxapiprolin SC 20 (Xivana) are detailed on the following pages. Complete drafts of proposed labeling for the technical and end-use product accompany the Bayer registration applications.

SPECIFIC CROP DIRECTIONS

CROP USE DIRECTIONS

BRASSICA HEAD and STEM VEGETABLES (Group 5-16)[1]
Crops of Crop Group 5-16 including:

Broccoli; Brussels sprouts; Cabbage; Cabbage Chinese, napa; Cauliflower

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Downy mildew[1] (*Peronospora parasitica*) White rust[1] (*Albugo candida*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A of XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 41.1 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

[[1]Not for use in California [without a supplemental label.]]

BULB VEGETABLES (Group 3-07)[1]
Crops of Crop Group 3-07 including:

Onion, bulb subgroup: Bulb Daylily; Bulb Fritillaria; Bulb Garlic; Bulb Great-Headed Garlic; Bulb Serpent Garlic; Bulb Lily; Bulb Onion; Bulb Chinese Onion; Pearl Onion; Bulb Potato Onion; Bulb Shallot.

Onion, green subgroup: Fresh Leaves Chive; Fresh Leaves Chinese Chive; Elegans Hosta; Leaves Fritillaria; Kurrat; Lady's Leek; Leek; Wild Leek; Beltsville Bunching Onion; Fresh Onion; Green Onion; Macrostem Onion; Tree Onion Tops; Welsh Onion Tops; Fresh Leaves Shallot.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Downy mildew (*Peronospora destructor*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 41.1 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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CUCURBIT VEGETABLES (Group 9)[1]
Crops of Crop Group 9 including:

Melon subgroup: Citron Melon; Muskmelon (hybrids and/or cultivars of Cucumis Melo including True Cantaloupe, Cantaloupe, Casaba, Crenshaw Melon, Golden Pershaw Melon, Honeydew Melon, Honey Balls, Mango Melon, Persian Melon, Pineapple Melon, Santa Claus Melon, Snake Melon); Watermelon.

Squash/Cucumber subgroup: Chayote (Fruit); Chinese Waxgourd; Cucumber; Gherkin; Gourd, Edible; Momordica spp.; Pumpkin; Squash, Summer; Squash, Winter.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Downy mildew[1] (*Pseudoperonospora cubensis*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.
Disease Suppressed	**Application Rate**	**Application Instructions**
Phytophthora blight[1] (*Phytophthora capsici*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 41.1 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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FRUITING VEGETABLES (Group 8-10)[1]
Crops of Crop Group 8-10 including:

Tomato subgroup: Bush Tomato; Cocona; Currant Tomato; Garden Huckleberry; Goji Berry; Groundcherry; Naranjilla; Sunberry; Tomatillo; Tomato; Tree Tomato.

Pepper/Eggplant subgroup: African Eggplant; Bell Pepper; Eggplant; Martynia; Nonbell Pepper; Okra; Pea Eggplant; Pepino; Roselle; Scarlet Eggplant.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Buckeye Rot[1] (*Phytophthora parasitica*) Late blight[1] (*Phytophthora infestans*) Pepper Downy mildew[1] (*Peronospora tabacina*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.
Disease Suppressed	**Application Rate**	**Application Instructions**
Phytophthora blight[1] (*Phytophthora capsici*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 41.1 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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LEAFY VEGETABLES (Group 4-16)[1]
Crops of Crop Group 4-16 including:

Leafy Greens subgroup: Amaranth, Chinese; amaranth, leafy; aster, Indian; blackjack; cat's whiskers; cham-chwi; cham-na-mul; chervil, fresh leaves; chipilin; chrysanthemum, garland; cilantro, fresh leaves; corn salad; cosmos; dandelion, leaves; dang-gwi, leaves; dillweed; dock; dol-nam-mul; ebolo; endive; escarole; fameflower; feather cockscomb; Good King Henry; huauzontle; jute, leaves; lettuce, bitter; lettuce, head; lettuce, leaf; orach; parsley, fresh leaves; plantain, buckhorn; primrose, English; purslane, garden; purslane, winter; radicchio; spinach; spinach, Malabar; spinach, New Zealand; spinach, tanier; Swiss chard; violet, Chinese, leaves; cultivars, varieties, and hybrids of these commodities.

Brassica Leafy Greens subgroup: Arugula; broccoli, Chinese; broccoli raab; cabbage, abyssinian; cabbage, Chinese, bok choy; cabbage, seakale; collards; cress, garden; cress, upland; hanover salad; kale; maca, leaves; mizuna; mustard greens; radish, leaves; rape greens; rocket, wild; shepherd's purse; turnip greens; watercress; cultivars, varieties, and hybrids of these commodities.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate (fl oz/A)	Application Instructions
Downy mildew (*Bremia lactucae*) (*Peronospora farinosa*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 41.1 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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LEAF PETIOLE VEGETABLES (Subgroup 22B)[1]
Crops of CropSubgroup 22B including:

Leaf Petiole Vegetable subgroup: Cardoon; celery; celery, Chinese; fuki; rhubarb; udo; zuiki; cultivars, varieties, and hybrids of these commodities.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Downy mildew (*Peronospora umbellifarum*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **1 day**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [41.1 fluid ounces/Acre (0.054 lb fluoxapiprolin/Acre)]
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- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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SMALL FRUIT VINE CLIMBING - EXCEPT FUZZY KIWIFRUIT (Subgroup 13-07F)[1]
Crops of Crop Group 13-07F including:

Amur River Grape; Gooseberry; Grape; Hardy Kiwifruit; Maypop; Schisandra Berry.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Downy mildew (*Plasmopara viticola*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **14 days**
- Minimum interval between applications: **10 days**
- Minimum application volumes: **25 gallons/Acre** (Ground); **10 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [2 (at 13.7 fl oz/A of XIVANA).]
- Maximum XIVANA allowed per year: [27.4 fluid ounces/Acre (0.036 lb fluoxapiprolin/Acre)]
- [Note to reviewer: the rates and number of applications listed in the above three bullets must be consistent with the rate(s) listed under 'Application Rate' above. The maximum single rate must not exceed 13.7 fl oz/acre and the maximum annual rate must not exceed 27.4 fl oz/acre of XIVANA.]
- Use XIVANA (or any other Group 49 fungicide) for no more than 33% of the total fungicide applications per season. Where the total number of fungicide applications targeting oomycetes is less than 3, make no more than 1 application of XIVANA (or any other Group 49 fungicide).

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TUBEROUS AND CORM VEGETABLES (Subgroup 1C)[1]
Crops of Crop Subgroup 1C including:

Tuberous and corm vegetables subgroup: Arracacha; Arrowroot; Chinese Artichoke; Artichoke, Jerusalem; Canna, Edible; Cassava, Bitter and Sweet; Chayote (Root); Chufa; Dasheen; Ginger; Leren; Potato; Sweet Potato; Tanier; Turmeric; Yam Bean; Yam, True.

Including all cultivars, varieties, and hybrids of these commodities.

Disease Controlled	Application Rate	Application Instructions
Late blight (*Phytophthora infestans*)	10.0 to 13.7 fl oz/A (0.013 to 0.018 lbs fluoxapiprolin/A)	Make no more than 2 sequential applications before rotating to a fungicide with a different mode of action. Tank mix XIVANA with a second fungicide with a different mode of action that is also labeled on the targeted disease.

Restrictions:

- Pre-Harvest Interval (PHI): **7 days**
- Minimum interval between applications: **7 days**
- Minimum application volumes: **10 gallons/Acre** (Ground); **2 gallons/Acre** (Aerial)
- Maximum single application rate: [13.7 fl oz/A XIVANA (0.018 lb/A fluoxapiprolin).]
- Maximum number of applications per year: [3 (at 13.7 fl oz/A of XIVANA) or 4 (at 10.0 fl oz/A of XIVANA).]
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SECTION C

Toxicology

Acute Toxicity

All studies are fully compliant with Good Laboratory Practice (GLP) and tests were conducted in accordance with relevant OECD, EU, and US EPA testing guidelines at the time they were conducted. The acute toxicity of fluoxapiprolin technical ingredient (94.5% purity) was low for all routes evaluated (oral, dermal, and inhalation). The rat acute oral and dermal LD_{50} were >2000 mg/kg bw, with no clinical signs observed in either study. The rat acute inhalation LC_{50} (4-hour) was >2.11 mg/L, with no mortality. Clinical observations showed, labored respiration (slight to severe) and noisy respiration (slight) for all animals, and gasping respiration and activity decreased (slight) was found for 1/5 males, while decreased activity (severe) was noted for 2/5 females. No adverse effects were observed from Day 3 until the conclusion of the study. Fluoxapiprolin technical was not irritating to rabbit skin. In the eye irritation study, conjunctival redness was noted in all three treated animals at the 1hour examination, and this observation was reversed by the 24-hour examination. No corneal effects were observed in any animal. In the mouse local lymph node assay, Fluoxapiprolin technical was shown to have no skin sensitization potential (non-sensitizer). Based on the US EPA classification, the results for the technical grade active ingredient fluoxapiprolin support acute toxicity categories III/IV. The acute toxicity classification of the end use formulation Fluoxapiprolin SC 20 is Toxicity Category III/IV for oral, dermal, and inhalation toxicity and skin and eye irritation. Fluoxapiprolin SC 20 was shown to have sensitization potential in the mouse Local Lymph Node Assay, with an EC3 value between 10% and 25%.

Genotoxicity

Fluoxapiprolin was tested for its genotoxic and mutagenic potential in a battery of *in vitro* or *in vivo* studies covering all required endpoints (gene mutations, chromosomal aberrations, and DNA damage and repair). There was no indication of a genotoxic response in any of the studies conducted with or without metabolic stimulation demonstrating that fluoxapiprolin technical is not considered genotoxic.

Immunotoxicity

The results from guideline 28-day, 90-day and chronic studies in the rat, mouse and dog provide considerable information on potential immunotoxic effects of fluoxapiprolin obtained from hematology, lymphoid organ weights and histopathology performed as elements of general toxicity studies. These results provide no evidence that fluoxapiprolin is toxic to the immune system at any dose or dietary level tested. While these studies do not include a functional assessment of immunosuppression or otherwise satisfy all the requirements of OCSPP 870.7800, the body of information

available with fluoxapiprolin is sufficient to demonstrate the immune system is not a target and further evaluation is not warranted.

Reproductive and Developmental Toxicity

The reproductive and developmental toxicity studies with fluoxapiprolin were conducted between 2015 and 2018 and were in accordance with OECD, EU, US EPA and Japanese MAFF testing guidelines and were fully compliant with GLP. These studies are relevant for the short-term and intermediate-term risk assessments of occupational exposure.

The reproductive No-Observed-Adverse-Effect Level (NOAEL) established in the rat two-generation reproduction study was 3800 ppm (262/289 mg/kg bw/day in males/females, respectively), which was the highest dietary level tested and set based on the kinetically-derived maximum dose (KMD). No adverse effects were observed in any males, females or offspring of either generation.

A dose level of 1000 mg/kg bw/day fluoxapiprolin administered to pregnant Sprague-Dawley rats by oral gavage from gestation days 6 to 20 was considered to be a no observed effect level (NOEL) for maternal, developmental and fetal toxicity. A dose level of 1000 mg/kg bw/day fluoxapiprolin administered to the pregnant New-Zealand white rabbits by oral gavage from gestation days 6 to 28 was considered to be a NOEL for maternal effects and embryo-fetal survival, growth and development.

Subchronic Toxicity

The short-term toxicity studies with fluoxapiprolin were conducted between 2013 and 2018. All subchronic 90-day studies and the rat 28-day dermal study were conducted in accordance with OECD, EU, US EPA and Japanese MAFF testing guidelines and were fully compliant with GLP. The 28-day studies via the oral route (in the rat, mouse and dog) were not performed strictly in compliance with GLP, as they were not subjected to QA inspections, although the same standardized routine operating procedures as applicable for GLP studies were used.

In rats, mice, and dogs, dietary administration of fluoxapiprolin for 28 or 90 days up to approximately the limit dose was not associated with any treatment-related changes for any of the parameters assessed. Therefore, the high dose (equating to a minimum of 882 mg/kg bw/day in males and 895 mg/kg bw/day in females) was considered to be the NOEL for both sexes in the three mammalian species tested (Wistar rat, C57BL6/J mouse, and Beagle dog) following 28 or 90-days of treatment by dietary administration.

Chronic Toxicity

The chronic toxicity and carcinogenicity studies with fluoxapiprolin were conducted between 2016 and 2018 and were in accordance with OECD, EU, US EPA and Japanese MAFF testing guidelines and were fully compliant with GLP.

In rats, dietary administration of fluoxapiprolin for up to 24 months up to a KMD of 288 mg/kg bw/day in males and 374 mg/kg bw/day in females was not associated with any treatment-related changes for any of the parameters assessed and did not induce carcinogenic effects. Therefore, the high dose (288 mg/kg bw/day in males and 374 mg/kg bw/day in females) was considered to be the NOEL for both sexes following 24-months treatment by dietary administration.

In mice, dietary administration of fluoxapiprolin for up to 18 months up to a KMD of 278 mg/kg bw/day in males and 317 mg/kg bw/day in females was not associated with any treatment-related changes for any of the parameters assessed and did not induce carcinogenic effects. Therefore, the high dose tested (equating to 278 mg/kg bw/day in males and 317 mg/kg bw/day in females) was considered to be the NOEL for both sexes following 18-months treatment by dietary administration.

Neurotoxicity

In the absence of neurotoxic effects in the acute neurotoxicity study, a 90-day neurotoxicity study was not conducted. There is no structural relationship to any chemical class which causes delayed neurotoxicity, nor did the repeat-dose studies show any indications of delayed neurotoxicity, and thus a specific study for delayed neurotoxicity of fluoxapiprolin was not conducted.

Animal Metabolism

The adsorption, distribution, metabolism, excretion of fluoxapiprolin has been investigated in several studies. Following oral administration of fluoxapiprolin to rats, blood and plasma levels peaked approximately 2-4 hours in at the low dose and within one hour at the high dose. Plasma concentrations declined to values below 3.4% of the maximum concentration within 72 hours post administration. Absorbed radioactivity was quickly and efficiently eliminated from the bodies of the rats of both sexes.

At 24 hours, majority of the radioactivity was eliminated. The excretion of radioactivity was predominantly fecal. Urinary excretion of radioactivity up to 7.1% of the recovered dose was detected in low dose tests.

Based on the recovered radioactivity detected in bile, urine and bodies without GIT, the absorption rates were calculated in the study with the pyrazole label and amounted to 37.3% for male and 32.5% for female rats within 0 to 48 hours after administration. Within 4 to 48 hours absorption rates were 21.4% in males and 18.9% in females. The most predominant metabolic reaction was the hydroxylation of the phenyl ring and piperidine ring leading to mono-, or -di-hydroxy-phenyl compounds. A further important

metabolic reaction was the hydrolysis of the piperidyl moiety resulting in a 3-OH-propyl side chain which was partly oxidized to a pentanoic acid-group and the carboxylation after deflourination either in Position 3 or in Position 5 of the diflouromethyl moieties in the pyrazole group. Conjugation with glucuronic acid, cysteine, and methyl-sulfinyl acid was also observed. Additional reactions were the piperidine ring opening forming a pyrazole-acetamide or BCS-CS55621-pyrazole-acetamide-COOH (from defluorinated metabolite) and further oxidation to pyrazole-acetic acid, as well as oxidation of the 3-di-fluoromethyl group of the pyrazole ring to carboxylic acid, the hydrolysis and cleavage of the thiazole moiety, and the cleavage between the oxazole moiety and the phenyl ring after oxidation. Defluorination followed by oxidation to 5-carboxylic acid and cleavage between the piperidine moiety and the thiazole ring followed by oxidation led to a piperidine-carboxylic acid was also found. Glucuronidation to BCSCS55621-phenyl-GlcA was observed in low amounts.

In the main ADME studies with the phenyl and pyrazole radiolabel, BCSCS55621-4-OH was the only the metabolite detected >10% of the dose in female rats. Several metabolites were deteced at concentrations <10% to 2% of dose and multiple metabolites were detected below 2% of dose in feces and urine samples of male and female rats. In the pilot ADME study with [acetyl-2-^{14}C]BCS-CS55621, the following major metabolites were identified in samples of urine, feces, plasma, liver, and kidney of male rats: BCS-CS55621-pyrazole-acetamide (plasma and kidney), BCS-CS55621-pyrazole-acetic acid (plasma and kidney), BCS-CS55621-piperidine-carboxylic acid (kidney), BCS-CS55621-4-OH piperidine (liver and kidney) and BCS-CS55621-3-carboxylic acid (liver). In the bioaccumulation study with [pyrazole-4-^{14}C]BCS-CS55621 BCS-CS55621-pyrazole acetamide and BCS-CS55621-piperidine-carboxylic acid were detected as major metabolites in testes of male rats.

Metabolite Toxicology

The major soil metabolite BCS-BP32808 (BCS-CS55621-BDM-pyrazole) was screened for its genotoxic activity and systemic toxicity was evaluated in an acute oral and 28-day rat study. Since BCS-BP32808 was negative in the male Big Blue® Transgenic C57BL/6 mice and in the *in vivo* mouse micronucleus test, it is not of concern for genotoxicity.

The acute oral toxicity study showed that the estimated acute oral median lethal dose (estimated LD_{50}) of BCS-BP32808 corresponded to 175 mg/kg bw in female Crl:WI Wistar rats. The study result triggers the acute oral classification for Category 2 under EPA. Administration of BCS-BP32808 in a 28-day gavage study in the rat elicited non-specific toxic responses or stress-related responses at 5 and 12 mg/kg bw/day, together with reduced motor activity and a suspected non-adverse effect on water balance and possibly liver function. The NOAEL for both sexes in this study was considered to be 2 mg/kg bw/day.

There was no indication of a genotoxic response in any of the studies conducted with or without metabolic stimulation BCS-CC26101 (BCS-CS55621-pyrazole acetic acid; major soil metabolite and crop metabolite), BCS-DC21250 (BCS-CS55621-piperidine; major

soil metabolite) or BCS-CZ38260 (BCS-CS55621-pyrazole-carboxylic acid; major aquatic metabolite). Taking into account the in-silico predictions, as well as read across predictions, there is no concern for bacterial gene mutation potential of BCS-DE61185 (BCS-CS55621-pyrazole-alanine; minor soil metabolite and crop metabolite).

Endocrine Disruption

Fluoxapiprolin did not affect steroidogenesis *in vitro.* In the weanling rat Hershberger assay, Fluoxapiprolin administered up to 900 mg/kg bw/day for 10 days, alone or concurrently with testosterone propionate, had no androgenic or anti-androgenic potential in the immature male rats. BCS-CS55621 induced a very slight delay in preputial separation at the top dose which correlated to a lower mean body weight and a slight decrease in some androgen-dependent tissue weights (not statistically significant) which was also attributable to the lower mean terminal body weight at both dose levels. An *in vivo* uterotrophic assay performed with fluoxapiprolin up to 900 mg/kg/day showed no evidence of estrogenic or anti-estrogenic activity . In addition, the two-generation study, showed no endocrine-mediated treatment-related response.

SECTION D

Residue Data Results

Bayer CropScience is proposing tolerances (Section F) supporting registration of fluoxapiprolin on multiple crops.

The residue chemistry database for fluoxapiprolin is current and complete and adequate to describe the nature and magnitude of residues for use in assessing the human dietary exposure. Residue chemistry data supporting registration of the end use products are listed in the completed EPA Data Matrix form accompanying this petition. A summary of these data follows.

Plant Metabolism:

Primary Crops
The metabolism of fluoxapiprolin (BCS-CS55621) in primary crops is adequately understood to support the proposed tolerances. Plant metabolism studies with fluoxapiprolin (BCS-CS55621) were performed on potato, lettuce, and grapes. Overall parent (BCS-CS55621) is moderately metabolized in primary crops. Unchanged BCS-CS55621 was the main or a major residue in all plants investigated as well as all individual commodities, with the exception of potato tubers which contained no detectable parent BCS-CS55621. The pyrazole ring containing metabolites BCS-CS55621-pyrazole-alanine (BCS-DE61185), BCS-CS55621-pyrazole-acetic acid (BCS-CC26101) and the phenyl ring containing metabolite BCS-CS55621-phenyl-isoxazole acid were the only identified metabolites in human edible commodities (potato tubers, grapes, lettuce head). BCS-DE61185 and BCS-CC26101 were major metabolites in potato tubers. BCS-CS55621-phenyl-isoxazole acid was a minor metabolite in lettuce.

The foliar applied plant metabolism crop studies represent three different crop categories (root, fruit, and leafy vegetable crops). The general metabolic pathways in the primary crop metabolism studies were similar. Generally, parent compound represented the most prominent residue in above ground parts of crops (grapes and lettuce) whereas metabolites that have been formed in soil were be mainly detected in potato tuber. Therefore, it is concluded that the nature of residues in primary crops after foliar application of BCS-CS55621 is sufficiently understood and that no further studies are required.

Rotational Crops
Metabolism studies with fluoxapiprolin in rotational crops were performed in wheat, turnips, and swiss chard using BCS-CS55621 either labeled in the pyrazole or in the phenyl moiety. Parent compound was completely metabolized in all raw agricultural commodities (RACs) in both studies. In the confined rotational crop study with BCS-CS55621 labeled in the pyrazole moiety, up to seven pyrazole derivative metabolites were identified. In the study with BCS-CS55621 labeled in the phenyl moiety, only the

label-specific metabolite BCS-CS55621-phenyl-isoxazole acid was identified accounting for a maximum of 0.01 mg eq/kg in all RACs.

Analytical Method for Data Gathering in Crops

Based on the results of the metabolism studies in primary and rotational crops, an analytical method was developed for all field residue studies that included parent compound and five metabolites. BCS-DE61185 and BCS-CC26101 were identified as metabolites of both primary and rotational crop commodities. BCS-BP32808, BCS-DE72760 and BCSDE72761 were were identified as metabolites of rotational crop commodities.

- Fluoxapiprolin (BCS-CS55621)
- BCS-CS55621-pyrazole-alanine (BCS-DE61185)
- BCS-CS55621-pyrazole-acetic acid (BCS-CC26101)
- BCS-CS55621-BDM-pyrazole (BCS-BP32808)
- BCS-CS55621-pyrazole-methylsulfinyl acid (BCS-DE72760)
- BCS-CS55621-pyrazole-alanine-oxopropanoic acid (BCSDE72761)

Magnitude of the Residues

A full program of magnitude of the residue trials was conducted in the various required regions across the United States and Canada in accordance with guidance for crop field trials from the US EPA and Canada's PMRA to support the requested tolerances. Fluoxapiprolin SC 20 was applied as foliar application. The crop field trials, and their target use patterns are summarized in the table below:

Critical Good Agricultural Practices used in Field Residue Trial

Crop Group	Crop (s)	No. of Trials	Mode of application	Retreatment Interval (Days)	Single Application rate (g a.i./ha)	Total Seasonal Rate (g/ha)	PHI (days)
1C - Tuberous and Corm vegetables	Potato	26	Foliar Broadcast	7	20	60	7
3-07A Onion, Bulb Subgroup	Bulb onion	12	Foliar Broadcast	7	20	60	1
3-07B Onion, Green Subgroup	Green onion	5	Foliar Broadcast	7	20	60	1
4-16 Leafy Vegetable Group	Head Lettuce	13	Foliar Broadcast	7	20	60	1
	Leaf Lettuce	14					
	Spinach	11					
	Mustard Green	8					
5-16 Brassica head and Stem vegetables	Cauliflower	11	Foliar Broadcast	7	20	60	1
	Cabbage	12					
	Broccoli	12					
8-10 Fruiting Vegetable Group	non-bell peppers	12	Foliar Broadcast	7	20	60	1
	Bell Pepper	4					
	Tomato	27					
9 Cucurbit vegetable	Summar Squash	12	Foliar Broadcast	7	20	60	1
	Muskmelon	13					
	Cucumber	11					
13-07F Small fruit vine climbing subgroup, except fuzzy kiwifruit	Grapes	15	Foliar Broadcast	10	20	40	14
22B Leaf petiole vegetable subgroup	Celery	8	Foliar Broadcast	7	20	60	1

The results of the residue trials were consistent with the metabolism studies, with parent BCS-CS55621 comprising most of the residues.

Based on the results of the residue and metabolism studies in primary crops, parent fluoxapiprolin as well as BCS-CS55621-pyrazole-alanine (BCS-DE61185) and BCS-CS55621-pyrazole-acetic acid (BCS-CC26101) were proposed as residue definition for for the risk assessment. However, the most widely observed compound was parent. Therefore, tolerance enforcement is proposed in terms of parent fluoxapiprolin (BCS-CS55621) only in all the crop/ crop group commodities.

Residues in Processed Commodities

Simulated industrial processing studies were conducted on potato,tomato, and grapes. Also, simulated kitchen processing studies (i.e. “residue reduction”) were performed with mustard greens, spinach, cucumber, summer squash, muskmelon, and broccoli. A processed commodity tolerance is proposed for grape, raisin.

Rotational Crop Residues:

Limited rotational crop studies using Fluoxapiprolin SC 20 were performed in wheat, soybean, and turnips planted at three different plant back intervals (PBI) i.e., 30, 120, 365 days. The commodities were analyzed for parent fluoxapiprolin and its metabolites pyrazole-alanine, pyrazole-alanine-oxopropanoic-acid, pyrazole-methylsulfinyl acid, BDM-pyrazole, pyrazole-acetic-acid. A decline in residues in raw agricultural commodities for each crop was observed over the time period of one year. Residues for the parent and relevent metabolites i.e., pyrazole-alanine, pyrazole- acetic acid (residue of concern for primary crops) were less than LOQ at 365-day PBI for all the RACs except turnips. The residues were less than LOQ at the 30-day PBI in all the wheat matrices for all the analytes, as well as the 120- and 365-day PBIs. Therefore, Bayer is proposing 30-day PBI for the all cereal grains (CG 15) and a 12 month PBI for all other crops except root vegetables. Since turnips had residues of BCS-CS55621-pyrazole alanine above the LOQ in both tops and roots at 365-day PBI, Bayer is proposing to have a crop rotation restriction of “do not rotate” for Root vegetables subgroup (CG 1A).

A full rotational crop study for tolerance setting was conducted to measure the magnitude of fluoxapiprolin (BCS-CS55621) and its metabolites in/on strawberry planted as a rotational crop following three broadcast applications of Fluoxapiprolin SC 20 to bare soil at 30-day PBI. The residues observed in this study were less than LOQ for all the analytes except BCS-CS55621-pyrazole alanine, which had maximum residues of 0.012 ppm. Bayer is proposing to use the same residue definition for enforcement as for primary crop.

Livestock Residues:

The metabolism of fluoxapiprolin in livestock has been studied in laying hens and lactating goats using either [phenyl-UL-^{14}C]BCS-CS55621 or [pyrazole-4-^{14}C]BCS-CS55621. The tested species and the radiolabels studied are shown in the table below.

Bayer Submitted Livestock Metabolism Studies

Bayer Report Number	Study Title	Species
M-676631-01-1	[Pyrazole-4-14C]BCS-CS55621 - Metabolism in the laying hen	Hen
M-675801-01-1	[Phenyl-UL-14C]BCS-CS55621 - Metabolism in the laying hen	Hen
M-656179-01-1	[Pyrazole-4-14C]BCS-CS55621 - Metabolism in the lactating goat	Goat
M-656180-01-1	[Phenyl-UL-14C]BCS-CS55621 - Metabolism in the lactating goat	Goat

The total radioactive residues (TRRs) for eggs and edible tissues in six laying hens after 14 consecutive daily dosing with [phenyl-UL-^{14}C]BCS-CS55621 or [pyrazole-4-^{14}C]BCS-CS55621 were very low. An average of 0.12% of the total dose was measured in organ/tissue and 0.10% of the total was measured in eggs. Nearly the entire administered radioactivity was detected in the excreta. This indicates that test compound related radioactivity did not accumulate during the 14 consecutive daily oral dosing with fluoxapiprolin at exaggerated dose rates.

In eggs and fat, parent compound BCS-CS55621 represented the main residue with an amount of up to 0.015 mg eq/kg in eggs and up to 0.016 mg eq/kg in fat. In muscle, BCS-CS55621 was detected as a major component (15.8% of the TRR), accounting for 0.002 mg eq/kg. In liver, parent compound accounted for up to 0.020 mg eq/kg or 8% of the TRR. Chiral analysis of parent compound revealed the unchanged racemic composition of the test item in excreta. For eggs, the chiral ratio of BCS-CS55621 Enantiomer 1 (BCS-CX87605) to BCS-CS55621 Enantiomer 2 (BCS-CX87606) was in the range of 1:1 to 1:2. For muscle, liver and fat, only BCS-CS55621 Enantiomer 2 (BCS-CX87606) was detected.

BCS-CS55621 was metabolized most extensively in liver. Three metabolites were identified in hens. The main metabolic reactions included hydroxylation, cleavage of the piperidine moiety of the parent and cleavage of the ethanoic group of BCS-CS55621-pyrazole-acetic acid.

The TRR-values in milk, organs and tissues in lactating goats after dosing with [phenyl-UL-^{14}C]BCS-CS55621 or [pyrazole-4-^{14}C]BCS-CS55621 were very low compared to the dose level of up to 24 mg a.s./kg feed/day and a dosing period of five days. The highest TRR-value was detected for liver. The elimination of radioactivity was mainly fecal and less than 3% of the dose was eliminated via urine, which was reflected by the low TRR-value for kidney. This excretion behavior was similar to the findings in the ADME studies with rats. The TRR-values in the respective evening and morning milk samples showed a diurnal pattern as they declined slightly prior to the delivery of the next dose for most

days. A continuous increase was observed before a residue plateau-level was reached at day three after the first administration.

In goats, seven metabolites were identified. Chiral analysis of parent compound revealed the unchanged racemic composition of the test item in all analyzed samples (Table 2 and Table 3). Parent compound BCS-CS55621 was the main residue in fat (up to 74.1% of the TRR or 0.009 mg eq/kg). In liver, BCS-CS55621 accounted for up to 10.0% of the TRR and 0.089 mg eq/kg. In milk and kidney, parent compound was detected in low amounts (up to 0.010 mg eq/kg), ranging from 5.7% to 17.6% of the TRR.

Based on the minimal uptake of fluoxapiprolin into animal milk and tissues and the non-quantifiable levels of fluoxapiprolin residues in livestock feed items, there is no reasonable expectation of finite residues of fluoxapiprolin in meat or milk from the currently proposed uses of fluoxapiprolin.

Based on these data, the metabolism studies already conducted are sufficient to describe the likely magnitude of the fluoxapiprolin residue in meat and milk. Therefore, livestock feeding studies are not required.

An analytical method for fluoxapiprolin residue in food of animal origin and biota will be provided to monitor default tolerances in Canada and other international jurisdictions.

SECTION E

Practical Methods for Removing Residues

There is no known method for the effective removal of fluoxapiprolin residues from commodities.

SECTION F

Proposed Tolerances

Tolerances are proposed for the residues of Fluoxapiprolin (2-[3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]-1-[4-[4-[5-[2-chloro-6-[(methylsulfonyl)oxy]phenyl]-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]- ethenone) in/on the following crop and processed commodities. The OECD MRL calculator was used to calculate the tolerances for fluoxapirolin residues in crop commodities.

Commodity / Crop Group	**Proposed Tolerance (ppm)**
Tuberous and Corm vegetables (CG 1C)	0.01
Onion, Bulb Subgroup (CG 3-07A)	0.03
Onion, Green Subgroup (CG 3-07B)	2.0
Head lettuce	0.8
Leafy Vegetable Group (CG 4-16) (except head lettuce)	5.0
Brassica Head and Stem Vegetable Group (CG 5-16)	0.8
Fruiting Vegetable Group (CG 8-10)	0.06
Cucurbit Vegetables Group (CG 9)	0.06
Small fruit vine climbing subgroup, except fuzzy kiwifruit subgroup (CG 13-07F)	0.2
Grape, raisin	0.4
Leaf petiole vegetable subgroup (CG 22B)	1.5

A significant difference was observed in the calculated tolerance for bulb onions and green onions i.e., 0.03 and 2.0 ppm, respectively. Therefore, Bayer proposes separate tolerance for CG 3-07A and CG 3-07B. Similarly, calculated tolerances for head lettuce were significantly lower (>5x difference) than the rest of the CG 4-16 crops (leaf lettuce, spinach, mustard green) i.e., 0.8 and 5.0 ppm, respectively. For head lettuce data from 13 field locations is included in this submission. There is a sufficient number of trials to satisfy the requiment to propose the individual tolerance for head lettuce. Therefore Bayer is proposing individual tolerance for head lettuce to be 0.8 ppm and the rest of CG 4-16 tolerance to be established 5.0 ppm.

Based on the minimal uptake of fluoxapiprolin into animal milk and tissues and the non-quantifiable levels of fluoxapiprolin residues in livestock feed items, there is no reasonable expectation of finite residues of fluoxapiprolin in meat or milk from the currently proposed uses of fluoxapiprolin. Therefore, Bayer believes that no tolerances for food of animal origin are required.

Tolerances are proposed for the indirect/inadvertent residues of Fluoxapiprolin (2-[3,5-bis(difluoromethyl)-1H-pyrazol-1-yl]-1-[4-[4-[5-[2-chloro-6-[(methylsulfonyl)oxy]phenyl]-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]- ethenone) in/on the following rotational crop commodities. The OECD MRL calculator was used to calculate the tolerances for fluoxapirolin residues in crop commodities.

Crop Group	**Proposed Tolerance (ppm)**
Low growing berry subgroup (CG 13-07G)[a]	0.01

SECTION G

Reasonable Grounds in Support of This Petition

The establishment of the proposed tolerances for fluoxapiprolin residues is based on the information summarized below.

Fluoxapiprolin (BCS-CS55621) is a new piperidinyl-thiazole-isoxazoline fungicide from Bayer CropScience (Bayer) which offers robust control of oomycete fungal diseases in a variety of vegetable and vine crops. Fluoxapiprolin is highly active on some of the most damaging oomycete fungi species which cause damaging and difficult-to-control diseases including *Bremia lactucae*, *Plasmopara viticola*, *Pseudoperonospora cubensis*, *Peronospora* spp., and *Phytophthora* spp.

Fluoxapiprolin works through inhibition of oxysterol binding proteins (OSBP) and is classified as a Fungicide Resistance Action Committee (FRAC) Group 49 (OSBPI) fungicide. It is quickly absorbed into plant tissue and is xylem-systemic with translaminar activity and movement upward, but not downward in the plant. Fluoxapiprolin provides protectant, curative and anti-sporulant action, but is most effective when applied as a protectant.

Bayer is applying for the registration of fluoxapiprolin SC (suspension concentrate) 20 liquid product as a foliar use in the following crops/ crop groups leafy vegetables crop group (CG 4-16), brassica head and stem vegetable (CG 5-16), cucurbits (CG 9), fruiting vegetables (CG 8-10), tuberous and corm vegetables subgroup (1C), bulb vegetable (CG 3-07), small fruit vine climbing subgroup, except fuzzy kiwifruit (CG 13-07F) and leaf petiole vegetable subgroup (CG 22B) as primary crops and low growing berry subgroup (CG 13-07G), as rotational crop with 30-day plant back interval.

Fluoxapiprolin Human Safety Profile

The toxicology database for fluoxapiprolin is complete for the purposes of this risk assessment and the characterization of potential human health risks to infants and children. There was no indication of increased sensitivity of the young in any studies, including the reproductive and developmental studies in rats and rabbits; therefore, the special FQPA safety factor may be reduced to 1X and the resultant total uncertainty factor of 100X is adequate. A review of the acute toxicity data for fluoxapiprolin determined that there are no toxicological points of departure for acute exposure and thus no acute dietary assessment is required. For parent fluoxapiprolin, dietary administration of fluoxapiprolin in rats, mice, and dogs for 90 days to approximately the limit dose was not associated with any treatment-related changes for any of the parameters assessed. The chronic point of departure is based on the NOAEL for fluoxapiprolin of 262 mg/kg day in the rat 2-generation study. An uncertainly factor of 100 was used to account for interspecies extrapolation (10x), intra-species variability (10x) and the FQPA safety factor (1x). This resulted in a chronic reference dose (cRfD) and chronic population adjusted dose (cPAD) of 2.62 mg/kg bw/day.

Food exposure estimates were calculated using CARES NG and DEEM-FCID Ver. 4.02 software, with NHANES WWEIA 2005 to 2010 consumption data. Food residues were calculated based upon total residues of parent (BCS-CS55621) and metabolites: BCS-CS55621-pyrazole alanine, and BCS-CS55621-pyrazole acetic acid. This approach represents a worst case for risk assessment since Bayer is proposing enforcement based on parent only.

A drinking water exposure assessment was conducted using USEPA's standard modeling approach and assuming worst case use pattern (e.g. maximum label rates, minimum interval between application). Parent FXN and major soil metabolite were considered residues of concern (ROC). The total exposure from FXN and major soil metabolites were simulated using EPA's formation decline approach due to differences in mobility. The highest potential drinking water exposure value of 3.97 µg/L (acute) was derived from the ground water source of drinking water. A chronic drinking water exposure concentration of 3.11 µg/L was calculated for use in the dietary assessment.

The chronic dietary assessment, including food and water, assumed that 100% of proposed crop uses of fluoxapiprolin are treated. Crop residue values for the dietary assessment included total residue of parent fluoxapiprolin plus the two metabolites BCS DE61185 and BCS-CC26101. No tolerances are required for food of animal origin or rotational crops except and low growing berry subgroup (CG 13-07G). Default processing factors were incorporated. Chronic exposure for food and water only utilizes <0.1% of the cPAD for the general US population and all sub-populations.Summary of dietary (food + drinking water) risk assessment for fluoxapiprolin is shown in the table below.

Chronic point of departure (Rat, 2-generation reproductive (mg kg bw/d))	Uncertainty/FPQA safety Factor	cPAD (mg kg bw/d)	CARES NG and DEEM 4.02 Aggregate Dietary Risk Assessment, Food + Water (General US population and all sub-populations)
262	UF_A = 10X UF_H = 10X FQPA SF = 1x	2.62	<0.1% of the cPAD

UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies), FQPA SF = FQPA Safety Factor

An acute dietary risk assessment was not conducted since no toxicological effects attributable to a single dose were identified from the toxicology studies.

For occupational exposures, all of the MOEs are above the required MOE of 100 showing that there are no unacceptable risks for the proposed uses with baseline

clothing (long-sleeved shirt and long pants, gloves, and shoes plus socks). A 12-hour REI can be established for all uses covered by the Worker Protection Standard (WPS).

The hazard and exposure profile of fluoxapiprolin is well understood and indicates that risks to consumers and workers are acceptable.