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TEMPLATE:

Bayer CropScience

[Insert petition number]

EPA has received a pesticide petition ([insert petition number]) from Bayer CropScience, 800 N. Lindbergh Blvd. St. Louis, MO 63167 requesting, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for 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 or on the raw agricultural commodities in tuberous and Corm vegetables (CG 1C) at 0.01 parts per million (ppm), Onion, Bulb Subgroup (CG 3-07A) at 0.03 ppm, Onion, Green Subgroup (CG 3-07A) at 2.0 ppm, Head lettuce at 0.8 ppm, Leafy Vegetable Group (CG 4-16) (except head lettuce) at 5.0 ppm, Brassica head and Stem vegetables (CG 5-16) at 0.8 ppm, Fruiting Vegetable Group (CG 8-10) at 0.06 ppm, Cucurbit vegetable (CG 9) at 0.06 ppm, Small fruit vine climbing subgroup, except fuzzy kiwifruit (CG 13-07F) at 0.2 ppm, Grape, raisins at 0.4 ppm, and Leaf petiole vegetable subgroup (CG 22B) at 1.5 ppm as primary crops; Low growing berry subgroup (CG 13-07G) at 0.01 ppm in rotational crops. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* The metabolism of fluoxapiprolin (BCS-CS55621) is adequately understood to support the proposed tolerances. Plant metabolism studies were performed on potato, lettuce, and grapes as primary crops. Overall fluoxapiprolin is moderately metabolized in primary crops except for the potato tubers where two

additional metabolites i.e., BCS-CS55621-pyrazole-alanine (BCS DE61185), BCS-CS55621-pyrazole-acetic acid (BCS-CC26101) was observed.
. The metabolic pathways in the primary crop metabolism studies were similar. Unchanged fluoxapiprolin was the main or a major residue in all plants investigated. The pyrazole ring-containing metabolites BCS-CS55621-pyrazole-alanine (BCS DE61185), BCS-CS55621-pyrazole-acetic acid (BCS-CC26101) and phenyl ring-containing metabolite BCS-CS55621-phenyl-isoxazole acid were the only identified metabolites in human edible commodities (potato tubers, grapes, lettuce head).

Metabolism studies with fluoxapiprolin in rotational crops were performed in wheat, turnips, and swiss chard. Fluoxapiprolin was completely metabolized in all commodities. Metabolites included the two pyrazole-containing metabolites from the primary crop studies, plus additional pyrazole-containing metabolites.

Fluoxapiprolin plus the two metabolites BCS-CS55621-pyrazole-alanine and BCS-CS55621-pyrazole-acetic acid are proposed as the residue definition for risk assessment. However, the most widely observed compound in metabolism and residue studies was parent, fluoxapiprolin. Therefore, tolerance enforcement is proposed in terms of parent fluoxapiprolin (BCS-CS55621) only in all the crop/ crop group commodities.

2. *Analytical method.* Tolerances are being proposed solely for parent fluoxapiprolin (BCS-CS55621). The analytical method involves solvent extraction, filtration followed by the addition of isotopically labeled internal standards. Quantitation is by high performance liquid chromatography-electrospray ionization/tandem mass spectrometry (HPLC/MS/MS).

3. *Magnitude of residues.* A full program for magnitude of the residue trials were conducted on head lettuce, leaf lettuce, spinach, mustard green, cauliflower, cabbage, broccoli, summer squash, muskmelon, cucumber, non-bell peppers, bell pepper, tomato, potato, bulb onion, green onion, grapes, and celery 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 limited rotational crop field trials were conducted on soybean, turnips, and wheat; and full rotational crop study for tolerance setting was conducted in strawberries. The results of the field trials support the use of fluoxapiprolin parent as the most appropriate enforcement residue in the harvested raw agricultural commodities. These residue trials satisfy the requirements to support the requested tolerances.

B. Toxicological Profile

1. *Acute toxicity.* All studies are fully compliant with Good Laboratory Practice (GLP) and 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 1-hour 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%.

2. *Genotoxicty.* 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.

3. *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.

4. *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.

5. *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.

6. *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.

After 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.
In the main ADME studies with the phenyl and pyrazole radiolabel, BCS-CS55621-4-OH was the only metabolite at >10% of the dose in female rats. Several metabolites were

detected 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-2-14C]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.

7. *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 a 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).

8. *Endocrine disruption*. Fluoxapiprolin did not affect steroidogenesis *in vitro in* H295R cells. 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 effects.

C. Aggregate Exposure

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

The aggregate dietary exposure (combined food and water) for all US populations and sub-populations was less than 0.1% of the cPAD. The dietary risk assessment was done using median level residues for each crop group and highest potential drinking water exposure value of 3.11 µg/L derived from the ground water source of drinking water.

i. *Food.* Food exposure estimates were calculated using CARES NG and DEEM-FCID Ver. 4.02 software, with NHANES WWEIA 2005 to 2010 consumption data. Estimated Drinking Water Concentration (EDWCs) associated with fluoxapiprolin residue of concern (ROC) use on all crops were calculated using the Pesticide Water Calculator (PWC, version 2.001). The highest potential drinking water exposure from proposed uses were from ground water at 3.97 µg /L. An acute assessment was not needed since there were no toxic effects attributable to a single dose. Therefore, no acute dietary assessment was performed. The chronic dietary assessment assumed that 100% of proposed crops are treated with fluoxapiprolin. Residue values for the dietary assessment were calculated including parent fluoxapiprolin plus the two metabolites BCS DE61185 and BCS-CC26101. A rotational crop tolerance is proposed for the low growing berry subgroup (CG 13-07G). No other rotational crop tolerances are required as Bayer is proposing rotational crop restrictions on the product; or tolerances for food of animal origin, so these commodities were not included. Default processing factors were incorporated. Chronic exposure for food and water only utilizes less than 0.1% of the cPAD for the general US population and all sub-populations.

ii. *Drinking water.* 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 fluoxapiprolin and major soil metabolites BCS-BP32808, BCS-DC21250, and BCS-DA62612 were considered residues of concern (ROC). The total exposure from fluoxapiprolin and the three 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 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. Chronic EDWC was incorporated into exposure assessments using DEEM-

FCID 4.02. Incorporation of the chronic EDWC of 3.11 µg total residues/L into the exposure assessment resulted in chronic aggregate dietary exposure (food and water) of less than 0.1% of the cPAD for the overall U.S. population and sub-populations.

2. *Non-dietary exposure.* There is a potential for non-dietary exposure from the proposed agricultural uses of fluoxapiprolin. An MOE of 100 is adequate to ensure protection of workers and bystanders to fluoxapiprolin from dermal and inhalation exposures. All occupational handler, re-entry worker, and residential bystander exposures are associated with MOEs greater than the target of 100 and are therefore not of concern.

D. Cumulative Effects

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. For this class of chemistry, EPA has not yet conducted a detailed review of common mechanisms to determine whether it is appropriate, or how to include these chemicals in a cumulative risk assessment.

E. Safety Determination

1. *U.S. population.* Risk assessments for fluoxapiprolin (BCS-CS55621) are based on a complete and reliable toxicity data package and conservative assumptions. Chronic aggregate dietary exposure (food and water) utilizes less than 0.1 % of the cPAD for the US Population and sub-populations. No acute aggregate dietary exposure (food and water) was conducted since no acute endpoint was identified from toxicology studies.

2. *Infants and children.* The toxicological and exposure database for fluoxapiprolin (BCS-CS55621) is considered complete. There was no indication of an increased sensitivity of the young in any studies including the reproductive and developmental studies in rats and rabbits. Therefore, the special FQPA can be reduced to 1X and an uncertainty factor of 100 is adequate. Based on conservative assumptions, chronic aggregate dietary exposure (food and water) utilizes less than 0.1% of the cPAD the general US population and all sub-populations. No acute aggregate dietary exposure (food and water) was conducted since no acute endpoint was identified from toxicology studies.

F. International Tolerances: No international tolerances have been established for Fluoxapiprolin yet. Fluoxapiprolin is being reviewed as a joint review in the U.S. and Canada.