UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: January 24, 2005

MEMORANDUM

SUBJECT: Fluoxastrobin: Human Health Risk Assessment for Proposed Uses on Peanuts, Tuberous and Corm Vegetables (Subgroup 1C), Leaf Petiole Vegetables (Subgroup 4B), Fruiting Vegetables (Group 8), Turf, and as a Seed Treatment on Potato (Seed Piece), Peanut and Turf. PC Code: 028869. Petition No: 3F6556. DP Barcodes: D292422, D303256. EPA File Symbol Nos.: 264-TIT (Fluoxastrobin Technical), and 264-TIA (HEC 480 SC Fungicide).

Regulatory Action: Section 3 Registration Action and Tolerance Petition
Risk Assessment Type: Single Chemical Aggregate

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The Office of Pesticide Program's (OPP) Health Effects Division (HED) is tasked with estimating the risk posed to human health from exposure to pesticides. OPP's Registration Division (RD) has asked HED to evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the registration of the new active ingredient fluoxastrobin. Bayer CropScience has requested Section 3 registrations for technical grade fluoxastrobin, as well as fluoxastrobin formulated as HEC 480 SC Fungicide, which is proposed for use on peanuts, tuberous and corm vegetables, leaf petiole vegetables, fruiting vegetables, turf and seed treatment (potato, peanut and turf). In addition to these two Section 3 registrations, Bayer CropScience has simultaneously submitted a petition to propose tolerances for fluoxastrobin on the agricultural commodities associated with the uses proposed on the HEC 480 SC Fungicide label.

This document provides a summary of the findings from the data evaluation and the subsequent assessment of human health risk resulting from the proposed uses of fluoxastrobin. The hazard characterization was conducted by Ghazi Dannan (RAB3); the occupational and residential exposure assessment was performed by Barry O'Keefe (RAB3); chemistry data evaluation and dietary risk assessment were conducted by William Wassell (RAB3); the risk assessment was compiled by Sarah Winfield (RAB3) and the drinking water assessment was provided by Thuy Nguyen of OPP's Environmental Fate and Effects Division (EFED).

Provided revised Sections B (labels) and F (tolerances) with the modifications specified in Section 10.0 of this document are submitted, the residue chemistry and the toxicological databases support the establishment of a conditional registration and permanent tolerances as follows:

Primary crop tolerances for residues of fluoxastrobin and its Z-isomer:

Peanut	0.01	ppm
Peanut, hay	20.0	ppm
Peanut, refined oil	0.03	ppm
Tomato, paste	1.5	ppm
Vegetable, fruiting, group 8	1.0	ppm
Leaf petioles subgroup 4B	4.0	ppm
Vegetable, tuberous and corm, subgroup 1C	0.01	ppm

Rotational crop tolerances, for residues of fluoxastrobin and its Z-isomer:

Alfalfa, forage	0.05	ppm
Alfalfa, hay	0.10	ppm
Cotton, gin byproducts	0.02	ppm
Grain, cereal, forage, fodder and straw, group 16	0.10	ppm
Grass, forage	0.10	ppm
Grass, hay	0.50	ppm
Vegetable, foliage of legume, group 7	0.05	ppm

Livestock commodity tolerances, for residues of fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite:

Cattle, fat	0.10	ppm
Cattle, meat	0.05	ppm
Cattle, meat byproducts	0.10	ppm
Goat, fat	0.10	ppm
Goat, meat	0.05	ppm
Goat, meat byproducts	0.10	ppm
Horse, fat	0.10	ppm
Horse, meat	0.05	ppm
Horse, meat byproducts	0.10	ppm
Milk	0.02	ppm
Milk, fat	0.50	ppm
Sheep, fat	0.10	ppm
Sheep, meat	0.05	ppm
Sheep, meat byproducts	0.10	ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon resolution of the deficiencies specified in Section 10.0.

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1.0 Executive Summary

The HED has evaluated the toxicology, chemistry and exposure databases, and conducted a human health risk assessment for the new pesticidal active ingredient (ai) fluoxastrobin, in response to an application from Bayer CropScience (EPA Company No. 264) to register technical grade fluoxastrobin (94.8% ai, a white crystalline solid), and the fluoxastrobin formulation HEC 480 SC Fungicide (40.3% ai, an off-white liquid). HEC 480 SC Fungicide has been proposed for use as a fungicide on peanuts, tuberous and corm vegetables, leaf petiole vegetables, fruiting vegetables, turf and seed treatment (potato, peanut and turf). In addition to these two Section 3 registrations, Bayer CropScience has simultaneously submitted a petition proposing tolerances for fluoxastrobin on the agricultural commodities associated with the uses proposed on the HEC 480 SC Fungicide label. HED has conducted a human health risk assessment in support of the proposed Section 3 registrations, as well as the tolerance petition.

Use Information/Ingredient Profile

For agricultural crops, HEC 480 SC Fungicide is applied as a broadcast postemergence foliar spray, multiple times (maximum of 4 - 6 times per season), at application rates ranging from 0.12 to 0.18 lb ai/A (pounds ai per acre) with 7- to 14-day application intervals, applied at a maximum seasonal application rate of 0.72 lb ai/A (this maximum application rate includes seed treatment uses); preharvest intervals (PHIs) range from 3 to 14 days. For turf, HEC 480 SC Fungicide is applied a maximum of 4 times per season with a minimum 21-day application interval and a maximum seasonal application rate of 2.2 lb ai/A. While residential postapplication exposure is expected from the proposed turf use, residential handler exposure is not expected (the registrant has communicated the amended label will indicate that turf applications are intended to be made by professional pest control operators only).

The HEC 480 SC Fungicide label points out, that like other strobilurin fungicides, fluoxastrobin does exhibit cross-resistance to other strobilurin Group 11 fungicides; and therefore suggests rotating, alternating or tank-mixing with products having different modes of action and/or limiting the total number of applications per season. Group 11, or QoI fungicides are thus named because they target the same site along the mitochondrial respiratory pathway, disrupting this vital cell function, ultimately preventing fungal spore germination, mycelial growth and the development of infection structures. At this time, it is unclear how the pesticidal mode of action relates to human health, although mitochondrial structure and function are apt to be different between humans and fungi. Nonetheless, the toxicological database provides adequate information to characterize potential hazards/effects.

Hazard Profile

Fluoxastrobin shows low acute toxicity via the oral, dermal, and inhalation routes of exposure; is a moderate eye irritant, and is neither a dermal irritant, nor a sensitizer. Following repeated administration, fluoxastrobin has mild or low toxicity in all tested species other than the dog which displayed adverse liver toxicity at considerably lower doses than those noted for other species. As the most sensitive species, the effects observed in the dog were used as endpoints in the risk assessment. In both the 90-day and one-year oral feeding dog studies, the liver appeared to be the target organ; other target organs include the kidney (dog, mouse and rat), and the

adrenal glands (rat; the effects were not considered endocrine-related).

In the rat and rabbit developmental toxicity studies and the two-generation reproduction rat study, there was no increased susceptibility to prenatal or postnatal exposure to fluoxastrobin and no effects on reproduction. Furthermore, fluoxastrobin is not acutely neurotoxic in rats up to a single high dose of 2000 mg/kg/day, nor did fluoxastrobin show neurotoxic effects different from background levels seen in the control study following repeated dosing in the rat subchronic neurotoxicity study. Therefore, the 1996 Food Quality Protection Act (FQPA) safety factor was reduced to 1X. Results of genotoxicity testing were negative and there were no treatment-related carcinogenicity findings in adequately performed carcinogenicity studies in rats and mice. Henceforth, fluoxastrobin is not likely to be carcinogenic to humans.

No quantitative hazard estimate was selected for the short-term dermal exposure scenario based on lack of systemic or dermal toxicity in the 28-day dermal toxicity study in the rat and the absence of developmental or reproduction toxicity findings. The adverse liver findings (cholestasis) in the 90-day subchronic dog study were used to set endpoints for the intermediate-term dermal, the short- and intermediate-term inhalation, as well as the short- and intermediate-term incidental oral exposure scenarios. The adverse liver findings (cholestasis) in the chronic toxicity dog study were used for setting the quantitative hazard estimate for the long-term dermal and inhalation, as well as the chronic dietary, exposure scenarios (although long-term dermal and inhalation exposures are not expected based on the proposed uses). An acute quantitative hazard estimate was not established because an adverse effect attributable to a single exposure was not identified from the available database (although acute exposure is expected).

Non-Occupational Exposure and Aggregate Risk Assessment

Evaluation of the residue chemistry data, indicated that fluoxastrobin related residues are primarily surface residues (in plants); and that the residues of concern in/on treated food commodities derived from plants (primary and rotational crops) are fluoxastrobin and its Z-isomer; and the residues of concern in/on treated food commodities derived from livestock, are fluoxastrobin, its Z-isomer and its phenoxy-hydroxypyrimidine metabolite. These residues of concern are considered in both tolerance enforcement and dietary risk assessment. The environmental fate and effects database indicated the residues of concern in drinking water are fluoxastrobin and its Z-isomer, which are considered in the drinking water assessment. Although fluoxastrobin can persist in the soil, it degrades via aqueous photolysis, and sorbs onto soil quite strongly, and therefore, it is unlikely to reach or persist in drinking water.

However, there is potential for exposure to residues via the dietary (food + water) and the residential (postapplication exposure from treated turf) pathways. As this is a new chemical, no market basket survey data are available. An unrefined Tier 1 dietary exposure assessment was conducted (assuming tolerance level residues and 100% crop-treated) using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™) and Lifeline™ models. Also, no surface water, groundwater or drinking water monitoring data is available, therefore, conservative estimated drinking water concentrations (EDWCs) were modeled using the Tier 2 surface water model Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS), and the groundwater model

Screening Concentration in Groundwater (SCIGROW).

Hazard and exposure data are required to estimate risk. The hazard (the quantitative hazard estimates from the fluoxastrobin toxicological database) and exposure (the expected exposure scenarios for fluoxastrobin's use pattern) components for the fluoxastrobin risk assessment, resulted in potential risk for the following scenarios (for the relevant population subgroups): the chronic dietary exposure scenario, the intermediate-term dermal scenario, and the short- and intermediate-term incidental-oral scenario. Therefore, chronic and short-/intermediate-term aggregate risk assessments were conducted.

Because all short- and intermediate-term quantitative hazard estimates (via the dermal and incidental oral routes) are based on the same endpoint, a screening level, conservative aggregate risk assessment was conducted, which combined the short-term incidental oral and intermediate-term dermal exposure estimates (*i.e.*, the highest exposure estimates). When chronic dietary exposure (considered background) is combined with these exposure estimates, the resulting aggregate risks for adults and children are below HED's level of concern. The EDWCs for short- and intermediate-term aggregate risk are 28 ppb for surface water and <1 ppb for groundwater. Since the estimated short- and intermediate-term Drinking Water Levels of Comparison (DWLOCs) for adult males, adult females and children were 940 ppb, 820 ppb, and 140 ppb, respectively, and exceed the EDWCs, short- and intermediate-term aggregate risk is not considered to be of concern for fluoxastrobin.

The results of the chronic aggregate assessment also indicate that the combined exposure to fluoxastrobin from food and water is below HED's level of concern for all population subgroups. Dietary exposure from food resulted in a range of estimated exposures representing 6.0% to 25% of the chronic Population Adjusted Dose (cPAD; for all infants [<1 year] and children [1-2 years], respectively). The resulting DWLOCs ranged from 110 ppb to 480 ppb (for children [1-2 years] and adults [20-49 and 50+ years], respectively), and exceed the chronic EDWCs (surface water: 14 ppb, groundwater: <1 ppb); therefore, chronic aggregate risk is not considered to be of concern for fluoxastrobin.

Occupational Exposure and Risk Assessment

Occupational exposure and risk were assessed for the scenarios associated with the proposed uses on the HEC 480 SC label; dermal (handler and postapplication) and inhalation (handler only) exposures were assessed using the Pesticide Handlers Exposure Database (PHED) Version 1.1, HED standard values and default assumptions, the Science Advisory Council for Exposure's (ExpoSAC) Standard Operating Procedures (SOPs), and surrogate data from a study published in the scientific literature measuring handler exposure to the pesticide captan during potato seed treatment and planting. For turf and field crop handler exposure scenarios, the calculated Margins of Exposure (MOEs) are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern. Similarly, for peanut and turf seed treatment handler exposure scenarios, the calculated MOEs are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern. And, for potato seed piece handler exposure scenarios the calculated MOEs for most of the occupational handler exposure scenarios are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern (except for one

scenario involving filling a hopper located outside, however, due to the conservative assumptions used to calculate the exposure estimate, this is not considered to exceed HED's level of concern). Additionally, for both agricultural and non-agricultural occupational postapplication exposure scenarios, the MOEs exceed 100 on the day of treatment (*i.e.*, day 0) and therefore, do not exceed HED's level of concern.

Technical fluoxastrobin has a Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for acute inhalation and primary skin irritation. Therefore, the restricted entry interval (REI) of 12 hours appearing on the proposed fluoxastrobin end use label is acceptable.

Conclusions

HED evaluated Bayer CropScience's petition regarding fluoxastrobin, and determined potential exposure to fluoxastrobin could occur via the dietary (food and drinking water), residential or occupational pathways. HED determined fluoxastrobin is a relatively low toxicity fungicide, and there is reasonable certainty that no harm will result to the general population and to infants and children from aggregate exposure to the proposed uses of fluoxastrobin. Furthermore, based on the occupational assessment included in this document, HED concludes that risks to occupational handlers and postapplication workers from exposure to fluoxastrobin are not cause for concern.

2.0 Ingredient Profile

Fluoxastrobin is a new strobilurin-class fungicidal ai that works by interrupting mitochondrial respiration, thus preventing vital reproductive/infesting activities such as fungal spore germination, mycelial growth and the development of infection structures.

Fluoxastrobin is the accepted common name for the pesticidally active E-isomer of (2-[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy phenyl)-5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime. The Z-isomer of fluoxastrobin is typically present at much lower levels (E:Z ratio of approximately 90:10). Additionally, the Z-isomer of fluoxastrobin is considered to be a metabolite (photo-degradate) of fluoxastrobin. The petitioner has requested that fluoxastrobin (E-isomer only) be designated as the active ingredient.

Fluoxastrobin will be marketed in its technical form (94.8% ai, a white crystalline solid) for use in formulations, and as the formulation HEC 480 SC Fungicide (40.3% ai, an off white soluble concentrate), for use as a fungicide on peanuts, tuberous and corm vegetables, leaf petiole vegetables, fruiting vegetables, turf and seed treatment (potato, peanut and turf).

For agricultural crops, HEC 480 SC Fungicide is applied as a broadcast postemergence foliar spray, multiple times (maximum of 4 - 6 times per season), at application rates ranging from 0.12 to 0.18 lb ai/A with 7- to 14-day application intervals, applied at a maximum seasonal application rate of 0.72 lb ai/A (this maximum application rate includes seed treatment uses); PHIs range from 3 to 14 days. For turf, HEC 480 SC Fungicide is applied a maximum of 4 times per season, at application rates ranging from 0.27 to 0.55 lb ai/A with a minimum 21-day application interval and a maximum seasonal application rate of 2.2 lb ai/A (see Table 2.1 for a more detailed description of the proposed use profile of fluoxastrobin). While residential postapplication exposure is expected from the proposed turf use, residential handler exposure is not expected (the registrant has communicated the amended label will indicate that turf applications are intended to be made by professional pest control operators only).

2.1 Summary of Registered/Proposed Uses

Table 2.1a. Summary of Fluoxastrobin End-Use Products.

Trade Name	File Symbol No.	ai (amount of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
HEC 480 SC Fungicide	264-TIA	40.3%; 4 lb/gal	Suspension concentrate (flowable concentrate; FlC)	Peanut, tuberous and corm vegetables subgroup, leaf petioles subgroup, fruiting vegetables group, seed treatment of potato and peanut	Fungal diseases such as early blight, late blight, leaf spot, leaf rust, and *Rhizoctonia solani*	Draft, dated 1/31/03

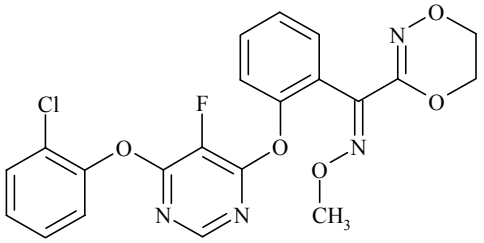
Table 2.1b. Summary of Directions for Use of Fluoxastrobin.

Applic. Timing; Type; and Equip.	Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Peanut					
Postemergence; Broadcast; Ground	0.18 lb ai/A	4	0.72	14	Minimum retreatment interval (RTI) of 14 days. Maximum seasonal application rate includes any seed treatment applications. In areas with up to 4 sprays per year, application should be alternated with at least one application of another effective mode of action fungicide. In areas with 5 or more sprays per year, a maximum of 2 sequential applications may be made, followed by an equal number of another effective mode of action fungicide.
Tuberous and corm vegetables [arracacha, arrowroot, artichoke (Chinese), artichoke (Jerusalem), canna (edible), cassava (bitter, sweet), chayote (root), chufa, dasheen, ginger, leren, potato, sweet potato, tanier, turmeric, and yam (bean, true)]					
Postemergence; Broadcast; Ground or aerial	0.12 lb ai/A	6	0.72	7	Minimum RTI of 7 days; may be applied through irrigation systems. Maximum seasonal application rate includes any seed treatment applications. Each application should be alternated with at least one application of another effective mode of action fungicide.
Leaf petiole vegetables subgroup [cardoon, celery, Chinese celery, celtuce, Florence fennel, rhubarb, and Swiss chard]					
Postemergence; Broadcast; Ground	0.18 lb ai/A	4	0.72	3	Minimum RTI of 7 days. Each application should be alternated with at least one application of another effective mode of action fungicide.
Fruiting vegetables group [eggplant, ground cherry (*physabis* sp.), pepino, pepper (includes: bell pepper, chili pepper, cooking pepper, pimento, sweet pepper), tomatillo, and tomato]					
Postemergence; Broadcast; Ground	0.18 lb ai/A	4	0.72	3	Minimum RTI of 7 days. Each application should be alternated with at least one application of another effective mode of action fungicide.

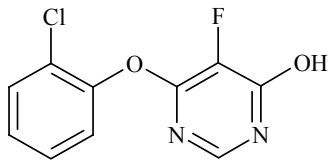
Table 2.1b. Summary of Directions for Use of Fluoxastrobin.					
Applic. Timing; Type; and Equip.	Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Seed treatment [potato (seed piece), peanut]					
Seed treatment; Slurry or mist-type equipment	0.010 lb ai/CWT	Not specified	0.72	Not applicable	Maximum seasonal application rate includes any foliar applications. Treated seed may not be used for food, feed, or oil purposes.
Turf					
Postemergence; Broadcast; Ground	0.27 to 0.55 lb ai/A	4	2.2	Not applicable	Disease Control: Begin applications preventively, and continue as needed on a 21-day interval (minimum interval). To limit the potential for development of disease resistance: Use a maximum of 2 sequential applications of Qol fungicide followed by at least equal number of another effective mode of action fungicide.

2.2 Structure and Nomenclature

Fluoxastrobin is described in Table 2.2a

Table 2.2a. Fluoxastrobin Nomenclature	
Chemical Structure	
Empirical Formula	$C_{21}H_{16}ClFN_4O_5$
Common name	Fluoxastrobin Note: This name was originally approved for a mixture of the E- and Z-isomers (CAS # 193740-76-0) in April 2002. The definition of fluoxastrobin was changed to mean the E-isomer only in January 2003. This change was made based upon a request by the petitioner.
Company experimental name	HEC 5725
IUPAC name	(*E*)-(2-[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy phenyl)-(5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime
CAS name	(1*E*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime
CAS Registry Number	361377-29-9
End-use product/EP	HEC 480 SC Fungicide (EPA File Symbol 264-TIA)
Chemical Class	Strobilurin, methoxyacrylates
Known Impurities of Concern	Fluoxastrobin Z-isomer (also considered metabolite)

The chemical structure of the phenoxy-hydroxypyrimidine metabolite, included in the tolerance expression of livestock commodities, is shown in Table 2.2b.

Table 2.2b. Phenoxy-hydroxypyrimidine metabolite Chemical Structure	
6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol	

2.3 Physical and Chemical Properties

Fluoxastrobin has a low vapor pressure, and therefore, inhalation exposure via the chemical vaporizing is unlikely. The physicochemical properties of fluoxastrobin are described in Table 2.3.

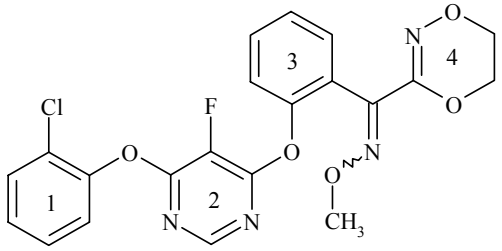
Table 2.3. Physicochemical Properties of Technical Grade Fluoxastrobin.		
Parameter	Value	Reference
Molecular Weight	458.8 amu	
Melting range	103-105 °C	MRID 45865525
pH	6.3 (1% in CIPAC-D water)	MRID 45865520
Density	1.4216 g/cm^3	MRID 45865303
Water solubility	at 20 °C: 0.0019 g/L; 0.0024 g/L at pH 4 0.0023 g/L at pH 7 0.00227 g/L at pH 9	MRIDs 45865520, 45865525
Solvent solubility	at 20 °C: n-heptane 0.05 g/L xylene 38 g/L dichloromethane >250 g/L 2-propanol 6.7 g/L 1-octanol 1.1 g/L polyethylenglycol 400 119 g/L acetone >250 g/L ethyl acetate >250 g/L acetonitrile >250 g/L dimethylsulfoxide >250 g/L	MRIDs 45865520, 45865525
Vapor pressure	5.63x10^{-10} Pa (20 °C) 8.72x10^{-10} Pa (25 °C)	MRID 45865525
Dissociation constant, pK_a	no dissociation constant at pH 4-9	MRID 45865303
Octanol/water partition coefficient, Log(P_{OW})	2.85 (20 °C); P_{OW} = 708	MRID 45865525
UV/visible absorption spectrum	19,358 L/mol · cm at 250 nm	MRID 45865303

3.0 Metabolism Assessment

References: PP#3F6556. *Fluoxastrobin. Petition for the Establishment of Permanent Tolerances for Use on Peanuts, Tuberous and Corm Vegetables Subgroup, Leaf Petiole Vegetables Subgroup, Fruiting Vegetables Group, and Seed Treatment of Peanut and Potato*. William Wassell. 12/XX/04. D289106 and D289107, PC Code 028869.

Ad hoc fluoxastrobin MARC meeting, 9/14/2004.

For metabolism studies submitted in conjunction with this petition, the following numbering scheme was assigned to reference ring-structures in the fluoxastrobin molecule:



3.1 Comparative Metabolic Profile

Fluoxastrobin was extensively metabolized in the rat as evidenced by the extensive metabolite profiles from urine, feces and bile and the relative absence of parent compound (except in the feces of rats given the high dose). The urinary metabolites were primarily the result of cleavage between the second and third rings of the parent compound. Biliary metabolites were primarily products resulting from cleavage of rings 2, 3 and 4, and subsequent hydroxylation, methoxylation, and conjugation with glucuronic acid. HEC5725-E-des-chlorophenyl and HEC5725-des-chlorophenyl-dioxazine-OH were the major metabolites in all excretion matrices.

Some of the rat metabolites seem to be in common with metabolites in studies from lactating goat (*e.g.*, HEC5725-di-OH and its dioxazine-OH, HEC5725-E-des-chlorophenyl and its derived ketone, dioxazine-OH, and glycol, in addition to several dioxazine phenyl two ring metabolites) and laying hen (*e.g.*, several glucuronide conjugates of HEC5725- including mono- and di-OH-GA, and oxime-GA in addition to mono- and bi-ring fragments including dioxazine-oxime, 2-cyanophenol, and salicylic acid).

Fluoxastrobin was not extensively metabolized in tomatoes. In tomatoes, a large majority of the residues remained unchanged parent compound and was primarily on the surface. In all crops except tomatoes, fluoxastrobin was converted to its Z-isomer via sunlight. In tomatoes, conversion to the Z-isomer was not observed. In peanut hay, fluoxastrobin was not extensively metabolized as a large majority of the radioactivity was identified as fluoxastrobin and its Z-isomer. In peanut nutmeat, a majority of the residue was incorporated into natural products. In all of the plant metabolism studies, parent compound was the major residue and metabolites containing all four rings or three rings plus fragments of the dioxazine ring represented the majority of identified metabolites. Only minor cleavage between ring 2 and ring 3 was observed.

Fluoxastrobin was extensively metabolized in rotational crops, as evidenced by the extensive metabolite profiles and relative absence of parent compound. The major metabolic route of fluoxastrobin in rotated crop matrices was hydroxylation, especially at the 4-position of the chlorophenyl moiety to yield HEC5725-E-4-hydroxyphenyl; conjugates of this metabolite were also observed. A second important metabolic route was cleavage of fluoxastrobin to yield HEC5725-E-des-chlorophenyl, which was partly isomerized to the Z-isomer. Cleavage of the ether bridge between the pyrimidine and methoxyiminotolyl rings of the parent compound was a minor metabolic route in rotational crops. Another minor metabolic route was hydroxylation of the parent compound in the dioxazine ring, followed by oxidative cleavage and hydrolysis.

Fluoxastrobin was extensively metabolized in goats and hens, as evidenced by the extensive metabolite profiles and relative absence of parent compound. The exception being goat and poultry fat where a significant portion of the residue was identified as fluoxastrobin. Metabolites consisting of single rings (*e.g.*, 2-chlorophenol) were observed in each of the livestock metabolism studies. One of the main metabolism pathways appears to be cleavage of the ether group in the pyrimidine moiety to form metabolites containing ring 1 and 2 (*e.g.* HEC5725-phenoxy-hydroxypyrimidine) and containing only ring 1 (*e.g.* 2-chlorophenol).

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

For the plant metabolism studies, test substances were labeled in ring 1 (chlorophenyl label), ring 2 (pyrimidine label), or ring 3 (methoxyiminotolyl ring label).

Bayer CropScience has submitted adequate studies investigating the metabolism of fluoxastrobin in three dissimilar crops (wheat, peanuts and tomatoes). Although the petitioner is not proposing use on wheat, the crops selected for the studies are sufficiently representative of the crops for which the petitioner is requesting registration (tuberous and corm vegetables, fruiting vegetables, the leaf petiole subgroup, and peanuts).

The available data from the plant metabolism studies indicate that metabolism of fluoxastrobin is similar in dissimilar crops. In metabolism studies reflecting foliar applications to peanut and tomato, and seed treatment in combination with foliar applications to wheat, fluoxastrobin was found to be a major component of the residue in wheat hay and straw (15-74% TRR [Total Radioactive Residues]), wheat grain (24-70% TRR), peanut hay (60-61% TRR), and tomato (95% TRR). Residues of fluoxastrobin were found in smaller amounts in wheat forage (22-24% TRR), which only received seed treatment application of the test substance because it was harvested before foliar applications were made. Residues of the Z-isomer of fluoxastrobin were found in smaller amounts in wheat hay and straw (1.6-21% TRR), wheat grain (5.6-16% TRR), peanut hay (23-24% TRR), tomato (3.3-3.4% TRR), and wheat forage (0-4.3% TRR). The only metabolite identified in plant commodities from these studies at levels greater than 10% TRR was HEC5725-E-4-OH-Glc-MA (14% TRR in wheat forage). In peanut nutmeat, the radioactivity was found to be associated with natural products.

The petitioner submitted wheat studies reflecting labeling in rings 1, 2, and 3, peanut studies reflecting labeling in rings 2 and 3, and tomato studies reflecting labeling in rings 1 and 3. No

study reflecting labeling in ring 4 was submitted; however, the results of the metabolism studies indicate that ring 4 is likely to undergo ring opening prior to cleavage from the rest of the molecule. Because intact fluoxastrobin was found to comprise ~90% of the TRR in the tomato metabolism studies, a tomato metabolism study reflecting labeling in ring 2 is not needed. Fluoxastrobin was also found to comprise a large portion of the residue in peanut hay; therefore, an additional peanut metabolism study reflecting labeling in ring 1 would not likely result in the identification of any new metabolites.

Brief summaries of the available plant metabolism studies are presented below:

Wheat Metabolism Summary: Bayer CropScience has submitted four studies investigating the metabolism of [methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin, [chlorophenyl-UL-^{14}C]fluoxastrobin, or [pyrimidine-2-^{14}C]fluoxastrobin in spring wheat. In each of these studies, wheat grown from fluoxastrobin treated seeds received two foliar applications of the test substance. Samples of wheat forage, grain and straw were collected at normal maturity.

Fluoxastrobin was found to be a major component of the residue in wheat hay and straw (40-74% TRR) and wheat grain (40-70% TRR). Residues of fluoxastrobin were found in smaller amounts in wheat forage (22-24% TRR), which only received seed treatment application of the test substance because it was harvested before foliar applications were made. Residues of the Z-isomer of fluoxastrobin were found in smaller amounts in wheat hay and straw (14-21% TRR), wheat grain (11-16% TRR) and wheat forage (0-4.3% TRR). The only metabolite identified in plant commodities from these studies at levels greater than 10% TRR was HEC5725-E-4-OH-Glc-MA (14% TRR in wheat forage).

Although the ratio of E:Z-isomer in the fluoxastrobin test substances was 98:2 and the thermodynamic equilibrium for the E:Z ratio is 90:10, the ratio of fluoxastrobin to Z-isomer in wheat matrices was found to range 78:22 to 84:16 in hay, 70:30 to 74:26 in straw, and 78:22 to 82:18 in grain. The petitioner concluded that significant conversion to the Z-isomer via isomerization of the oximether in this study was mainly the result of conversion under sunlight on the wheat foliage.

Based on the results of the submitted wheat metabolism studies, the petitioner proposed that fluoxastrobin is metabolized in wheat via the following, or combinations of the following, reactions: (i) isomerization of the oximether to form the Z-isomer of fluoxastrobin; (ii) hydroxylation of the chlorophenyl ring to monohydroxy isomers; (iii) oxidative ring opening and degradation of the dioxazine ring; (iv) cleavage of the oximether; (v) cleavage of the parent molecule to form HEC5725-2-chlorophenol and HEC5725-des-chlorophenyl, and, to a lesser extent, HEC5725-E-des-pyrimidine; (vi) nucleophilic substitution of the chlorophenol ring by glutathione, followed by stepwise degradation of the HEC5725-des-chlorophenyl-glutathione to HEC5725-des-chlorophenyl-thio; and (vii) conjugation of hydroxyl and thiol groups to glucosyl, glucosyl-malonyl, glucosyl-sulfate, and malonyl conjugates. The petitioner stated that cleavage of the ether bridge of the pyrimidine moiety to form HEC5725-phenoxy hydroxypyrimidine and HEC5725-E-des-pyrimidine occurred much less than elimination of HEC5725-2-chlorophenol.

Peanut Metabolism Summary: Bayer CropScience has submitted studies investigating the metabolism of [methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin and [pyrimidine-2-

^{14}C]fluoxastrobin in peanut. Three foliar applications were made to peanuts at 0.233-0.244 lb ai/A/application for a total application rate of 0.717 lb ai/A (1x the proposed maximum seasonal rate). Peanut hay and nutmeat were harvested 14 days after the last foliar application and dried in the greenhouse for 4 days prior to collection.

In metabolism studies reflecting foliar applications to peanut, fluoxastrobin was found to be a major component of the residue in peanut hay (60-61% TRR). Residues of the Z-isomer of fluoxastrobin were found in smaller amounts in peanut hay (23-24% TRR). In peanut nutmeat, the radioactivity was found to be associated with natural products.

Although the ratio of E:Z-isomer in the fluoxastrobin test substances was ~98:2 and the thermodynamic equilibrium for the E:Z ratio in fluoxastrobin is between 95:5 and 90:10, the ratio of fluoxastrobin to Z-isomer in peanut hay was ~70:30 in both studies. As for wheat, the petitioner concluded that significant conversion to the Z-isomer via isomerization of the oximether in this study was mainly the result of conversion under sunlight on the foliage.

Excluding the assimilation of $^{14}CO_2$ from the soil into natural products in the nutmeat, the petitioner proposed that fluoxastrobin is metabolized in peanuts via the following, or combinations of the following, reactions: (i) isomerization of the oximether to form the Z-isomer of fluoxastrobin; (ii) oxidative ring opening and degradation of the dioxazine ring; (iii) cleavage of the oximether to form HEC5725-ketone; (iv) nucleophilic substitution of the chlorophenyl ring by glutathione, followed by stepwise degradation of the HEC5725-des-chlorophenyl-glutathione; (v) cleavage of the parent molecule to form HEC5725-des-pyrimidine or HEC5725-phenoxy-hydroxypyrimidine, and, to a lesser extent, HEC5725-des-chlorophenyl; (vi) conjugation of hydroxyl and thiol groups to glucosyl and glucosyl-malonyl conjugates; and (vii) hydroxylation of the chlorophenyl ring (minor reaction; only observed in the ring-1 label study).

Tomato Metabolism Summary: Bayer CropScience has submitted studies investigating the metabolism of [methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin and [chlorophenyl-UL-^{14}C]fluoxastrobin in tomato. Three foliar applications were made to tomatoes at ~0.128 lb ai/A/application, for a total nominal application rate of 0.385 lb ai/A (0.5x the proposed maximum seasonal rate). Mature tomatoes were harvested 3 days after the last application.

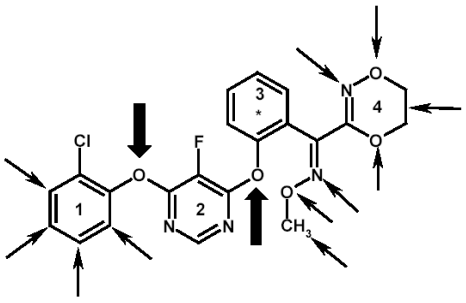
In metabolism studies reflecting foliar applications to tomato, fluoxastrobin was found to be a major component of the residue in tomato (95% TRR). Residues of the Z-isomer of fluoxastrobin were found in smaller amounts in tomato (3.3-3.4% TRR).

The ratio of fluoxastrobin to its Z-isomer was essentially unchanged during the metabolism study. The ratio of E:Z-isomer in the test substance was ~98:2, and the ratio of E:Z-isomer identified in tomato was ~97:3.

Fluoxastrobin was not extensively metabolized in tomatoes; residues remained primarily on the surface. Based on the results of this study, the petitioner proposed that fluoxastrobin is metabolized in tomato via hydrolysis or cleavage of the parent molecule to form the dioxazinyl-phenylketone, amide, and ketone metabolites.

3.2.2 Description of Livestock Metabolism

The petitioner has submitted two goat metabolism and two hen metabolism studies reflecting labeling in rings 1 and 3. For each of the livestock metabolism studies, the petitioner provided the following schematic of the positions in the parent molecule involved in the metabolic reactions. The petitioner noted that the ring 2 and ring 3 systems were not attacked.



As for plants, no study reflecting labeling in ring 4 was submitted; the results of the metabolism studies indicate that ring 4 is likely to undergo ring opening prior to cleavage from the rest of the molecule. However, unlike plants, no livestock metabolism study reflecting labeling in ring 2 was submitted. Metabolism of fluoxastrobin was found to be more extensive in livestock, and metabolites consisting of single rings (*e.g.*, 2-chlorophenol and 2-cyanophenol) were observed in each of the livestock metabolism studies.

The submitted goat and hen metabolism studies are adequate to satisfy data requirements and to delineate the qualitative nature of the residue in livestock. Brief summaries of the available livestock metabolism studies are presented below:

Goat Metabolism: Bayer CropScience has submitted studies investigating the metabolism of [methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin and [chlorophenyl-UL-^{14}C]fluoxastrobin in lactating goats. The test substance was administered orally to a single goat at 180 ppm (methoxyiminotolyl label) or 265 ppm (chlorophenyl label) in the diet once per day for three consecutive days; the dose levels represent exaggeration rates of 15x and 22x, respectively.

Fluoxastrobin and its Z-isomer were found to be major residues in goat fat (12-46% TRR) but were found in smaller quantities in milk, goat muscle, liver, and kidney (0.31-6.8% TRR). Metabolites identified at >10% TRR in goat commodities were HEC5725-phenoxy-hydroxypyrimidine (milk at 11% TRR, eggs at 25% TRR, goat muscle at 53% TRR, goat kidney at 25% TRR, goat fat at 29% TRR), HEC5725-2-cyanophenol-SA (milk at 23% TRR and goat kidney at 15%), HEC5725-dioxazinyl-alcohol-derivative (goat liver at 16% TRR), HEC5725-di-OH-diene-pyrimidine-OH (milk at 21% TRR), and HEC5725-hydroxyphenyl (goat liver at 11% TRR and goat fat at 13% TRR).

Based on the results of the goat metabolism studies, the petitioner proposed that fluoxastrobin is metabolized in goats via: (i) hydroxylation of the chlorophenyl ring to mono- and dihydroxy isomers; (ii) bis hydroxylation and reduction of the chlorophenyl ring to dihydroxy dien E-

isomers; (iii) hydroxylation of the dioxazine ring followed by oxidative ring opening and further degradation of the dioxazine ring; (iv) oxidative demethylation of the oximether group and cleavage of this group to the ketone and alcohol metabolites; (v) cleavage of the ether group in the pyrimidine moiety to HEC5725-2-chlorophenol and HEC5725-des-chlorophenyl or to HEC5725-phenoxy-hydroxy-pyrimidine and HEC5725-des-pyrimidine; (vi) bis hydroxylation and reduction of the chlorophenyl ring of HEC5725-phenoxy-hydroxypyrimidine to dihydroxy dien E-isomers; and (vii) conjugation of the hydroxyl groups to glucuronic acid and sulfate compounds.

Poultry Metabolism: Bayer CropScience has submitted studies investigating the metabolism of [chlorophenyl-UL-^{14}C]fluoxastrobin or [methoxyiminotolyl-UL-^{14}C]fluoxastrobin in laying hens. The test substance was administered orally to six hens at 187 ppm or 198 ppm in the diet once per day for three consecutive days; the dose levels represent exaggeration rates of 75,000x and 79,000x, respectively.

Fluoxastrobin and its Z-isomer were found to be major residues in hen eggs, fat, and muscle (11-48% TRR) but were found in smaller quantities in hen liver (0.31-6.8% TRR). Metabolites identified at >10% TRR in hen commodities were HEC5725-phenoxy-hydroxypyrimidine (eggs at 25% TRR, hen liver at 21% TRR, hen muscle at 35% TRR, and hen fat at 21% TRR), HEC5725-2-chlorophenol (up to 23% TRR in eggs and up to 12% TRR in liver), and HEC5725-salicylic acid (eggs at 12% TRR).

Based on the results of the studies, the petitioner proposed that fluoxastrobin is metabolized in hens via: (i) hydroxylation of the chlorophenyl ring to mono- and dihydroxy isomers; (ii) hydroxylation of the dioxazine ring followed by oxidative ring opening and further degradation of the dioxazine ring; (iii) oxidative demethylation of the oximether group and cleavage of this group to the ketone and alcohol metabolites; (iv) cleavage of the ether group in the pyrimidine moiety to HEC5725-2-chlorophenol or HEC5725-phenoxyhydroxy-pyrimidine and methoxyiminotolyl-dioxazine ring and methoxyiminotolyl ring metabolites; and (v) conjugation of the hydroxyl groups to glucuronic acid and sulfate conjugates. The metabolism leads finally to the formation of HEC5725-2-chlorophenol, its sulfate conjugate, salicylic acid, 2-OH-mandelic acid, and HEC5725-ketocarboxylic acid.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

The submitted confined rotational crop studies are adequate to satisfy data requirements and to delineate the nature of the residue in rotated crop commodities.

Bayer CropScience has submitted confined rotational crop studies with [pyrimidine-2-^{14}C]fluoxastrobin, [methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin, or [chlorophenyl-UL-^{14}C]fluoxastrobin in rotated crops. The radiolabeled test substance was applied to bare sandy loam soil in planting containers at 0.75 lb ai/A (1x the proposed maximum seasonal rate for annual crops) in two studies and at 0.61 lb ai/A (0.85x). Rotational Swiss chard, turnip, and spring wheat were planted 30, 157-175, and 301-328 days after treatment (DAT).

Pyrimidine Label Study: Total identified residues ranged 8.2-83.5% TRR in rotated crop

commodities, except for turnip roots from the 301-day PBI, which were not analyzed because of low TRR. Fluoxastrobin was the major identified residue in all 30-DAT rotated crop commodities, except wheat grain. Fluoxastrobin was identified at 10.9-26.8% TRR in 30-DAT Swiss chard and turnip tops and roots, at 20.1-49.4% TRR in 30-DAT wheat forage, hay, and straw, and at 3.7% TRR in wheat grain; the Z-isomer of fluoxastrobin was identified at 0.7-2.1% TRR (<0.001-0.05 ppm) in these 30-DAT matrices. In 157-DAT commodities, fluoxastrobin was the major identified residue in wheat forage, hay, and straw at 22.8-43.8% TRR; fluoxastrobin was identified at 4.0%, 8.8%, and 0.7% in turnip tops, turnip roots, and wheat grain and was not identified in Swiss chard. The Z-isomer of fluoxastrobin was identified at 1.9-3.3% TRR in 157-DAT wheat hay and straw. In 301-day rotational crops, fluoxastrobin was not detected in wheat grain and was present at <10% TRR in all remaining matrices: 0.5% TRR in Swiss chard, 0.9% TRR, in turnip tops, and 5.3-6.9% TRR in wheat forage, hay, and straw. The Z-isomer was identified at 0.3-1.0% TRR in 301-DAT turnip tops and wheat hay and straw.

HEC5725-E-des-chlorophenyl was the major identified residue in 157-DAT Swiss chard, turnip tops, and turnip roots (17.5-25.3% TRR) and in 301-DAT Swiss chard, turnip tops, and wheat forage, hay, and straw (13.5-22.4% TRR). HEC5725-E-des-chlorophenyl was identified in 30-DAT rotational crops at 3.8-9.0% TRR in Swiss chard and turnip matrices, at 6.8-10.6% TRR in wheat hay and straw, and at 0.9-1.0% TRR in wheat forage and grain. In 157-DAT wheat matrices, HEC5725-E-des-chlorophenyl was identified at 8.3-11.2% TRR in hay and straw and at 1.2-3.4% TRR in forage and grain. The following metabolites were also identified at ≥10% TRR in rotational crop commodities: HEC5725-E-4-OH-Glc-MA in 30-DAT wheat hay (19.4% TRR); HEC5725-E-4-hydroxyphenyl in 30-DAT wheat straw (18.6% TRR); HEC5725-des-chlorophenyl-keto-dioxazine in 301-DAT Swiss chard and wheat forage (10.1-12.4% TRR); and des-chlorophenyl-dioxazine-OH in 301-DAT wheat forage, hay, and straw (10.0-13.5% TRR). Numerous minor metabolites were identified at <10% TRR in rotated crop matrices.

The majority of the radioactivity in wheat grain was characterized in the diastase hydrolysate as glucose, believed to be derived from starch. Glucose was also identified at low levels in the aqueous phase of wheat straw. The petitioner stated that incorporation of radioactivity into natural products probably resulted from the mineralization of the pyrimidine ring of fluoxastrobin in soil.

Methoxyiminotolyl-ring Label Study: Total identified residues ranged 13.4-81.7% TRR in rotated crop commodities, except turnip roots from the 162- and 314-day PBIs which were not analyzed because of low TRR. The major residue in all rotated crop commodities except wheat grain was fluoxastrobin; fluoxastrobin was not detected in grain from any PBI. In 30-DAT rotational crops, fluoxastrobin was present at 14.0-47.5% TRR; levels were lowest in Swiss chard and highest in turnip root and wheat forage and hay. The Z-isomer of fluoxastrobin was identified at 1.2-2.8% TRR (<0.001-0.02 ppm) in turnip roots, wheat forage, and wheat straw. In 162-DAT rotational crops, fluoxastrobin was identified at 9.2-10.1% TRR in Swiss chard and turnip top and at 23.9-48.9% TRR in wheat forage, hay, and straw; the Z-isomer was identified at 0.7-2.3% TRR (<0.001-0.03 ppm) in Swiss chard and wheat forage, hay, and straw. In 314-DAT rotational crops, fluoxastrobin was identified at 0.6% TRR in Swiss chard, 10.0% TRR in turnip top, and 15.8-19.5% TRR in wheat forage, hay, and straw. The Z-isomer was identified at 0.9-2.4% TRR in wheat hay and straw.

The following metabolites were identified at ≥10% TRR in rotational crop commodities: HEC5725-des-chlorophenyl-dioxazine-OH in 30- and 162-DAT Swiss chard (11.0-11.5% TRR) and 314-DAT wheat forage (13.2% TRR); HEC5725-E-des-pyrimidine in 30-DAT turnip tops (12.4% TRR); HEC5725-E-4-OH-Glc in 30- and 162-DAT wheat hay (15.9-20.5% TRR) and straw (10.0-16.0% TRR); HEC5725-E-hydroxyphenyl in 30-DAT wheat straw (17.7% TRR); HEC5725-E-des chlorophenyl in 314-DAT Swiss chard (13.1% TRR) and wheat hay (11.8% TRR); and HEC5725-des-chlorophenyl-keto-dioxazine in 314-DAT wheat forage (11.9% TRR). Numerous minor metabolites were also identified at <10% TRR in rotational crop matrices. The majority of the radioactivity in wheat grain was characterized as being hydrolyzable by diastase.

Chlorophenyl Label Study: Total identified residues ranged 20.8-90.1% TRR in rotated crop commodities, except for turnip roots from the 328-day PBI, which were not analyzed because of low TRR. The major identified residue in all rotated crop commodities was fluoxastrobin. Fluoxastrobin was identified at 29.5-36.0% TRR in 30-DAT Swiss chard and turnip tops and roots, and was identified at 39.2-44.0% TRR in 30-DAT wheat forage, hay, and straw, and at 64.8% TRR in grain; the majority of fluoxastrobin in wheat grain from all PBIs was identified after diastase hydrolysis. The Z-isomer was identified at 0.6-5.6% TRR (<0.001-0.13 ppm) in 30-DAT crops. In 175-DAT rotational crops, fluoxastrobin was identified at 25.5%, 19.3%, and 42.8% TRR in Swiss chard and turnip tops and roots, respectively, and was identified at 67.6-73.4% TRR in wheat forage and grain and at 30.3-31.4% TRR in hay and straw; the Z-isomer was identified at 0.2-5.3% TRR (<0.01-0.06 ppm) in Swiss chard and wheat hay, straw, and grain. In 328-DAT rotational crops, fluoxastrobin was identified at 12.6% TRR in Swiss chard and was identified at 62.8-64.5% TRR in wheat forage and grain, and at 21.2-30.5% TRR in wheat hay and straw; the Z-isomer was identified at 2.5-5.0% TRR (≤0.01 ppm) in wheat forage, hay, and straw.

The following metabolites were also identified at ≥10% TRR: HEC5725-2-chlorophenol in 175-DAT Swiss chard (18.0% TRR), turnip tops (26.4% TRR), turnip roots (10.3% TRR), wheat forage (11.9% TRR), and wheat hay (24.0% TRR), and in 175- and 328-DAT wheat straw (10.8-14.1% TRR); HEC5725-OH-CA-Glc in 30- and 328-DAT Swiss chard (12.4-14.1% TRR); HEC5725-E-4-OH-Glc in 328-DAT wheat hay and straw (12.5-13.6% TRR); HEC5725-E-4-OH-Glc-MA in 30- and 175-DAT turnip roots (12.6-14.9% TRR), and 30- and 328-DAT wheat hay (10.6-13.5% TRR); and HEC5725-E-4-hydroxyphenyl in 30-, 175-, and 328-DAT wheat straw (10.2-12.3% TRR). Numerous minor metabolites were identified at <10% TRR in rotational crop matrices.

The metabolite patterns did not vary significantly in rotated crop matrices at the 30-, 175-, and 328-day PBIs. The majority of the metabolites observed in wheat matrices and turnip roots consisted of HEC5725-E-4-hydroxyphenyl and its glucoside and glucoside malonic acid conjugates, which accounted for totals of 8.9% TRR (grain) to 20.5% TRR (forage). In Swiss chard and turnip tops, the majority of the metabolites consisted of HEC5725-2-chlorophenol and its glucoside, which accounted for totals of 10.3% TRR in Swiss chard and 5.9% TRR in turnip tops.

The ratio of fluoxastrobin to its Z-isomer in the test substances was 97:3 (ring-2 label) or 98:2 (ring-1 and ring-3 labels), and the thermodynamic equilibrium for the E:Z ratio in fluoxastrobin is 90:10. The ratio of E:Z-isomer in fluoxastrobin identified in rotational crop matrices ranged

98:2 (ring-1 wheat hay, second PBI) to 74:26 (ring-2 wheat grain, first PBI). The petitioner attributed the greater conversion to the Z-isomer in wheat straw to the influence of sunlight, but noted that the lower levels of Z-isomer observed in the rotational crop studies compared to the wheat primary crop metabolism studies were probably due to protection of the test substance from light due to soil incorporation.

Based on the submitted studies, the major metabolic route of fluoxastrobin in rotated crop matrices was hydroxylation, especially at the 4-position of the chlorophenyl moiety to yield HEC5725-E-4-hydroxyphenyl; glucose and glucose malonic acid conjugates of this metabolite were also observed. A second important metabolic route was cleavage of fluoxastrobin to yield HEC5725-E-des-chlorophenyl, which was partly isomerized to the Z-isomer. HEC5725-E-des-chlorophenyl was further metabolized by hydroxylation to HEC5725-des-chlorophenyl-dioxazine-OH and HEC5725-2-chlorophenol, which was conjugated with glucose. HEC5725-des-chlorophenyl-dioxazine-OH was partly cleaved to form HEC5725-des-chlorophenyl-glycol, which was oxidized to HEC5725-des-chlorophenyl-CA. HEC5725-des-chlorophenyl-dioxazine-OH was also oxidized to HEC5725-des-chlorophenyl-keto-dioxazine which cleaved to form HEC5725-des-chlorophenyl-CA. A minor portion of HEC5725-E-des-chlorophenyl was conjugated with glutathione and conjugated with glucose to form HEC5725-des-chlorophenyl-S-Glc in wheat straw. Cleavage of the ether bridge between the pyrimidine and methoxyiminotolyl rings of the parent compound was a minor metabolic route in rotational crops, yielding HEC5725-E-des-pyrimidine and HEC5725-OH-phenoxy-amino-PMD. Another minor metabolic route was hydroxylation of the parent compound in the dioxazine ring, followed by oxidative cleavage and hydrolysis to form HEC5725-amide, HEC5725-carboxylic acid, HEC5725-CA-glycol ester, and HEC5725-OH-CA-Glc.

The petitioner submitted confined rotational crop studies reflecting labeling in rings 1, 2, and 3. No study reflecting labeling in ring 4 was submitted; however, as for primary crops, the results of the metabolism studies indicate that ring 4 is likely to undergo ring opening prior to cleavage from the rest of the molecule. The studies indicate that the metabolism of fluoxastrobin in rotational crops is similar to that in primary crops.

The submitted confined rotational crop studies indicate the potential for quantifiable residues of fluoxastrobin in rotated crop commodities. The only metabolite identified in the confined rotational crop studies that was not identified in the primary crop metabolism studies was HEC5725-des-chlorophenyl-keto-dioxazine, which was found at levels >10% TRR in 301-DAT Swiss chard and wheat forage (ring-2 label study) and 314-DAT wheat forage (ring-3 label study). HEC5725-des-chlorophenyl-keto-dioxazine was formed from HEC5725-des-chlorophenyl-dioxazine-OH, a metabolite which was found in two primary wheat metabolism studies. Based upon the submitted studies, HED concludes the residues of concern for rotational crops for risk assessment and tolerance setting purposes are fluoxastrobin and its Z-isomer.

3.3 Environmental Degradation

The environmental fate data provide sufficient information to determine whether the environmental degradation of fluoxastrobin poses a human health hazard via drinking water, even though the submitted aerobic and anaerobic aquatic metabolism studies were deemed unacceptable by EFED. The data indicate that the proposed use of fluoxastrobin as a foliar spray

on agricultural crops could potentially lead to fluoxastrobin in drinking water. Although foliar interception may reduce the amount of fluoxastrobin available for runoff, it is believed that this chemical could reach surface waters through spray drift, penetration of the canopy to the soil surface at application, and foliar washoff followed by runoff.

Based on laboratory studies, fluoxastrobin could persist for several months to several years in soil (depending on the soil type); and under field conditions, fluoxastrobin was shown to persist for over a year, although it did not seem to leach underground. Also, there were two soil metabolites (HEC5725-E-des-chlorophenyl [HEC 7155] and HEC5725-carboxylic acid [HEC 7180]) and one water metabolite (HEC5725-oxazepine) identified.

However, despite fluoxastrobin's potential to persist in soil, it has low mobility (relatively high Koc-ads values [420-1580 mL/g]), and degrades via aqueous photolysis; furthermore, only one metabolite was detected in field studies (the soil metabolite HEC5725-E-des-chlorophenyl), and it was detected at a low percentage of the application rate. Subsequently, it is very unlikely that any degradate / metabolite of fluoxastrobin will persist in the environment for any extended period of time to reach surface water and/or leach into groundwater at any considerable amount.

3.4 Toxicity Profile of Major Metabolites and Degradates

All metabolites that contain the ether bridge (between the phenyl and pyrimidinyl rings) may share similar toxicity to the parent based on their structural similarity to the parent.

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

3.5.1 Tabular Summary

Table 3.5. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary and Rotational Crops	Fluoxastrobin and its Z-isomer	Fluoxastrobin and its Z-isomer
Livestock	Ruminant and Poultry	Fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol]	Fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol]
Drinking Water		Fluoxastrobin and its Z-isomer	Not Applicable

3.5.2 Rationale for Inclusion of Metabolites and Degradates

The metabolic profile of fluoxastrobin is extensive and comprehensive. The metabolites

identified at significant levels in metabolism studies on representative livestock, primary and rotational crops were also identified in rat metabolism studies; therefore, their potential toxic effects are assumed to have been taken into account in the toxicity studies. Fluoxastrobin was extensively metabolized in livestock and the phenoxy-hydroxypyrimidine metabolite (which was identified at significant levels) was included in the tolerance expression. The potential toxic effects of this metabolite are assumed to have been taken into account in the toxicity studies since it was also identified in the rat metabolism studies.

Primary Crops: Plant metabolism studies using wheat, peanuts, and tomatoes indicate that fluoxastrobin and its Z-isomer are the only major residues identified (>10% TRR with the exception of one other metabolite (HEC5725-E-4-OH-Glc-MA) which was only detected in a livestock feed item (wheat forage). The analytical method proposed for enforcement of tolerances for residues in/on plant commodities determines combined residues of fluoxastrobin and its Z-isomer and does not determine the analytes individually.

Rotational Crops: The petitioner has proposed 30-day plant back intervals and/or tolerances for residues in rotational crops based upon a 30-day plant back interval. For the 30-day plant back interval, fluoxastrobin was the major residue identified, with only a few exceptions in Swiss chard (12-30% TRR), turnip tops (11-33% TRR), turnip roots (27-48% TRR), wheat forage (33-49% TRR), wheat hay (33-40% TRR), and wheat straw (20-44% TRR). Fluoxastrobin was identified at varying amounts in 30-day wheat grain (0-65% TRR). The Z-isomer of fluoxastrobin was identified in Swiss chard (0-3.1% TRR), turnip tops (0-2.3% TRR), turnip roots (2.1-2.8% TRR), wheat forage (1.2-2.8% TRR), wheat hay (0-4.3% TRR), wheat straw (0-5.6% TRR), and wheat grain (0-1.3% TRR). No other residues were identified in all crops. The analytical method proposed for enforcement of tolerances for residues in/on plant commodities determines combined residues of fluoxastrobin and its Z-isomer and does not determine the analytes individually.

Livestock: Livestock metabolism studies using lactating goats and laying hens indicate that residues of fluoxastrobin and its phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol] are present at significant levels in all ruminant and hen tissues. The phenoxy-hydroxypyrimidine does not contain the ether bridge (between the phenyl and pyrimidinyl rings) and may be less toxic than the fluoxastrobin. However, the phenoxy-hydroxypyrimidine metabolite residue levels in tissues may act a surrogate for other residues (such as HEC5725-di-OH-diene-pyrimidine-OH and HEC5725-di-OH-diene) which are not determined by the proposed enforcement method for livestock commodities. The analytical method proposed for enforcement of tolerances for residues in/on livestock commodities determines residues of fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite. Residues of fluoxastrobin and its Z-isomer are determined as combined residues and not individually.

Water: Residues of fluoxastrobin and its Z-isomer are expected to be persistent in the environment. Two major soil metabolites (HEC5725-E-des-chlorophenyl and HEC5725-carboxylic acid) were identified in laboratory studies. However, HEC5725-carboxylic acid was not detected in the field studies and HEC5725-E-des-chlorophenyl was detected at minor levels (<10% of applied radioactivity). The Z-isomer of fluoxastrobin was detected in all of the field studies.

4.0 Hazard Characterization/Assessment

Reference: HED/RAB3 fluoxastrobin hazard meetings, October and November 2004.

4.1. Hazard and Dose-Response Characterization

4.1.1. Database Summary

4.1.1.1. Studies available and considered

Available toxicity studies include a complete acute battery of tests (acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, acute eye irritation, acute dermal irritation and dermal sensitization), subchronic (90-day) feeding studies in the rat, mouse and dog, a subchronic dermal toxicity study in the rat, chronic studies (including a combined chronic feeding/carcinogenicity study in the rat, a carcinogenicity study [feeding] in the mouse and a chronic oral study [capsule] in the dog), developmental toxicity studies in both the rat and rabbit and a two-generation reproduction study in the rat, acute and subchronic screening neurotoxicity studies in the rat and a complete mutagenicity battery (*in vitro* bacterial reverse gene mutation, *in vitro* mammalian forward gene mutation, *in vitro* mammalian chromosome aberrations in Chinese hamster lung (V79) cells and a mouse *in vivo* mammalian cytogenetics - micronucleus assay). In addition, there is a subacute immunotoxicity study in mice. There were no key data available from the general literature, including human clinical or exposure data at this time.

4.1.1.2. Mode of action, metabolism, toxicokinetic data

Fluoxastrobin is considered a novel strobilurin analog (other strobilurin fungicides include azoxystrobin, dimoxystrobin, kresoxim-methyl, metominostrobin, orysastrobin, picoxystrobin, pyraclostrobin, and trifloxystrobin).

The biochemical mode of action of strobilurins consists of interaction with the ubiquinone binding site of the mitochondrial bc1 complex (complex III) in fungal cells, thereby preventing the oxidation of ubihydroquinone and the transfer of electrons to cytochrome c. Interrupting the electron transport chain in this way prevents oxidative phosphorylation, thus causing a severe reduction in the availability of ATP, the main energy currency of the cell. The shortage of energy has a very wide range of biochemical consequences, such as the breakdown of essential membrane potentials and concentration gradients and the inhibition of nucleic acid and protein biosynthesis. Fungal spore germination, mycelial growth and the development of infection structures are thus prevented.

Fluoxastrobin appears to have mainly foliar activity with only limited translocation within the plant.

Following an 8-hour dermal application in a male monkey, absorption was negligible (1.16% preliminary, 2.16% main). The normalized absorption value for the main study was 2.31%.

Absorption, distribution, and metabolism were fully characterized in several rat metabolism

studies using each of the three ^{14}C-radiolabeled rings in fluoxastrobin. Following a single oral low or high dose, absorption was almost complete at a low dose with peak plasma concentrations being attained within 0.5 to 8 hours depending on the dose and label position. Fecal excretion was the major route of elimination (75-91% within 48 hours) while renal excretion was a secondary route (11-20%). Elimination of the radioactivity via expired air was inconsequential (<0.1%) thereby confirming stability of the label. In high-dose groups, much of the fecal radioactivity (43-54% of administered dose) was attributed to parent compound (due to saturated absorption). Bile duct cannulation experiments at a low dose revealed that nearly 100% of the fecal radioactivity was contributed by the bile in the form of hydroxylated, methylated, and conjugated products. Tissue/carcass burdens accounted for about 1% of the administered radioactivity at 48 hours post dose. Most of this radioactivity was associated with the liver (~0.2-0.4%) and gastrointestinal tract (~0.4%).

Fluoxastrobin was extensively metabolized as evidenced by the extensive metabolite profiles from urine, feces and bile and the relative absence of parent compound (except in the feces of rats given the high dose). The urinary metabolites were primarily the result of cleavage between the second and third rings of the parent compound. Biliary metabolites were primarily products resulting from cleavage of rings 2, 3 and 4, and subsequent hydroxylation, methoxylation, and conjugation with glucuronic acid. HEC5725-E-des-chlorophenyl and HEC5725-des-chlorophenyl-dioxazine-OH were the major metabolites in all excretion matrices.

4.1.1.3. Sufficiency of studies/data

The submitted studies are of good quality and provide sufficient information to determine whether fluoxastrobin poses a human health hazard. The only data deficiency that exists is the requirement for additional information on the mouse subacute immunotoxicity study (for potential upgrade). However, this study is not required for risk assessment.

4.1.2. Toxicological Effects

Fluoxastrobin has a low order of acute toxicity based on its classification in Toxicity Category III (LD_{50} > 2000 mg/kg) via the oral and dermal routes, and Toxicity Category IV by the inhalation route of exposure. Fluoxastrobin is a moderate eye irritant (Toxicity Category III), but is neither a dermal irritant nor a sensitizer.

Fluoxastrobin seems to have a mild or low toxicity following repeated administration in all tested species other than the dog. In both the 90-day and one-year oral feeding dog studies, there was liver toxicity in the form of cholestasis as evidenced by hepatocytomegaly and cytoplasmic granular changes associated with increased liver weight and increased serum liver alkaline phospatase (ALP). In addition, several phase I and phase II liver drug metabolizing enzymes were induced. Other toxicity in dogs included body weight loss or reduced gain, decreased food efficiency, and effects on kidneys including increased relative weight in females and degeneration of proximal tubular epithelium in males. The no observed adverse effect level (NOAEL) of 1.5 mg/kg/day in the one year dog study was used for setting the chronic RfD.

The liver also seemed to be a target organ in other studies but the toxicological relevance of liver findings in species other than the dog is questionable. For instance, among the changes were

increased liver weight in the mouse and rat with hypertrophy and cytoplasmic changes in the mouse. However, there were no increases in any of the serum liver enzymes including ALP.

In the 90-day oral toxicity study in rats, the urinary system in males was a target organ as evidenced by increased kidney weight and histopathology findings in kidneys, urinary bladder, and urethra including the presence of calculi in the urethra and kidneys. In another rat study, there were markedly increased urinary pH in males in addition to increased urinary calcium excretion in the form of calcium oxalate crystals. Kidney changes were also seen in a 90-day mouse feeding study with increased kidney weights and tubular hypertrophy in females. Following 90-day administration in dogs, there was degeneration of the proximal tubular epithelium in males.

The adrenal glands seem to be another target organ in males of the 90-day rat study where vacuolation was seen in the zona fasciculate of the adrenal cortex. In another 30-day rat feeding study, adrenal cortical cytomegaly with fine vacuolization was seen in all high dose males and the responses were comparable between the groups treated with the pure fluoxastrobin E- or a 2:1 E/Z-isomers. The adrenal changes are not likely to be endocrine related effects.

In the rat and rabbit developmental toxicity studies and the two-generation reproduction rat study, there was no increased susceptibility to prenatal or postnatal exposure to fluoxastrobin and no effects on reproduction.

Fluoxastrobin is not acutely neurotoxic in rats up to a single high dose of 2000 mg/kg/day or by repeated dietary feeding in the rat subchronic neurotoxicity screening study where the top dose was nearly half the limit dose of 1000 mg/kg/day. Other studies in rats including the subchronic, chronic toxicity/carcinogenicity, two-generation reproduction, and developmental toxicity were tested to or above the limit dose with no indication of clinical signs, histopathology or other signs of toxicity that could be attributed to neurotoxicity. Also, in both the 90-day and one-year dog studies, neurologic examinations, including mental status/behavior, gait characteristics, postural status and reactions, and spinal/cranial reflexes, were carried out and were found within normal limits.

Fluoxastrobin is not immunotoxic based on repeated dosing studies in rats and mice. In the 90-day oral toxicity rat study, there was no difference between the control and treated animals in spleen cell count, macrophage activities after PMA stimulation and plaque-forming cell assay after challenge with sheep erythrocytes. Slight decreases were noted in IgG concentration in the high dose males but not females. A subacute immunotoxicity study in mice found no changes in B-cell activated or T-cell mediated IgM responses to SRBC.

Fluoxastrobin and major metabolites were negative in a battery of genotoxicity tests.

The carcinogenic potential of fluoxastrobin was adequately tested in rats and mice of both sexes. There was no evidence of carcinogenicity in rats or mice.

4.1.3. Dose-response

The 90-day subchronic oral and the chronic toxicity studies in dogs were the primary studies

used for the dose-response assessment. The dog is the most sensitive species noted from testing with fluoxastrobin, with the effects noted in these studies occurring at considerably lower doses than those noted for the rat. No systemic or dermal irritation was noted in the 21-day dermal toxicity study in the rat; therefore no endpoint was selected for short-term dermal risk assessment. For the intermediate-term dermal exposure scenario, the 90-day dog study was selected. The 90-day dog study was also selected for both the short- and intermediate-term inhalation and incidental oral exposure scenarios. The one-year dog study was chosen for the chronic RfD and long-term dermal and inhalation risk assessments. No acute RfD was calculated as no relevant endpoint was noted in the available database (this included the acute neurotoxicity screening study in rats as well as the developmental and reproduction studies). All the endpoints selected were noted after multiple exposures to fluoxastrobin (dose-response/endpoint selection were HED RAB3-based decisions, made in October and November 2004)

Table 4.1a Acute Toxicity Profile - Fluoxastrobin

Guideline No.	Study Type	MRID	Results	Toxicity Category
870.1100	Acute oral - rat	45865612	LD_{50}>2000 mg/kg	III
870.1200	Acute dermal - rat	45865613	LD_{50}>2000 mg/kg	III
870.1300	Acute inhalation - rat	45865618	LC_{50} = 4.9 mg/L	IV
870.2400	Acute eye irritation - rabbit	45865620	moderate irritant	III
870.2500	Acute dermal irritation - rabbit	45865622	not an irritant	IV
870.2600	Skin sensitization - guinea pig	45865624	not a sensitizer	-

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fluoxastrobin

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity (rats)	45865627 (1998); /acceptable/guideline / M: 0, 125, 1000 or 8000 ppm (0, 8.7, 70.4 or 580.0 mg/kg/day) F: 0, 250, 2000 or 16000 ppm (0, 21.5, 162.9 or 1416.1 mg/kg/day)	NOAEL = M: 70.4 mg/kg/day; F: 162.9 mg/kg/day LOAEL = M: 580.0 mg/kg/day based on reduced body weight gain and food intake, vacuolation in the zona fasciculate of the adrenal cortex, calculi in the urethra and kidney, and histological lesions in kidney, urinary bladder, and urethra. LOAEL = F: 1416.1 mg/kg/day based on increased liver weight (by 20%).
870.3100 90-Day oral toxicity (mice)	45865626 (1998) /acceptable/non-guideline / 0, 450, 1800 or 7000 ppm M: 0, 81.1, 313.4 or 1303.7 mg/kg bw/day F: 0, 135.1, 539.2 or 2256.9 mg/kg/day	NOAEL/LOAEL were not assigned. There was dose related increase of liver weight in both sexes and in kidney weight in females, in addition to other effects whose toxicological relevance was considered uncertain. Among these effects were increased hepatocellular hypertrophy with cytoplasmic changes in the high-dose males and minimal to moderate kidney tubular hypertrophy in mid- and high-dose females.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fluoxastrobin		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3150 90-Day oral toxicity (dogs)	45865629 (2001); 45865628 (2001); 45865722 (2000) / acceptable/guideline / 4 beagle dogs/sex/dose (MRID 45865629): 0, 25, 50, 100, 800 or 2500 ppm M: 0, 0.7, 1.4, 3.0, 24.8 or 76.0 mg/kg/day F: 0, 0.7, 1.5, 3.0, 24.2 or 75.0 mg/kg/day	NOAEL = M/F: 3.0 mg/kg/day (100 ppm) LOAEL = M/F 24.8/24.2 mg/kg/day (800 ppm) based on dose-related reductions in net body weight gain and food efficiency in addition to toxicity findings in the liver in both sexes (cholestasis) and in kidneys (increased relative weights in females and degeneration of the proximal tubular epithelium in males).
870.3200 28-Day dermal toxicity (rats)	45865630 (2000) / acceptable/guideline / 0, 100, 300 or 1000 mg/kg bw/day (6 hours/day, 5 days/week for the first three weeks; 7 days/week for the fourth week)	NOAEL = 1000 mg/kg/day (the limit dose, for both systemic and dermal) LOAEL not identified.
870.3700a Prenatal developmental (rats)	45865631 (1997) / acceptable/guideline 0, 100, 300 or 1000 mg/kg bw/day	**Maternal** NOAEL ≥ 1000 mg/kg bw/day (limit dose) LOAEL not identified. **Developmental** NOAEL ≥ 1000 mg/kg bw/day LOAEL not identified.
870.3700b Prenatal developmental (rabbits)	45865632 (1999) / acceptable/guideline / 22 naturally mated female Himalayan rabbits/group by gavage: 0, 25, 100, 400 mg/kg/day	**Materna**l NOAEL = 100 mg/kg/day LOAEL = 400 mg/kg/day based on cold ears, transient body weight loss, and decreased food consumption. **Developmenta**l NOAEL ≥ 400 mg/kg/day LOAEL not identified.
870.3800 Reproduction and fertility effects (rats)	45865633 (2001); 45865634 (2001) / acceptable/guideline / 0, 100, 1000 or 10000 ppm M: 0, 6.3, 70.0 or 665.0 mg/kg bw/day F: 0, 7.8, 84.7 or 825.4 mg/kg bw/day	**Parental Systemic** NOAEL = M/F 70.0/84.7 mg/kg/day LOAEL = M/F 665.0/825.4 g/kg/day based on decreased premating body weight gain of the P-generation males and females and decreased premating absolute body weight of the F_1 males and females. **Reproductive** NOAEL = M/F > 665.0/825.4 mg/kg/day LOAEL not identified. **Offspring** NOAEL = M/F 70.0/84.7 mg/kg/day LOAEL = M/F 665.0/825.4 mg/kg/day based on decreased body weights, delayed preputial separation, and incomplete ossification in the F_1 and/or F_2 males and females.
870.4100b Chronic toxicity (dogs)	45865701 (2002); 45865722 (2000) / acceptable/guideline / 4 beagle dogs/sex/dose: 0, 25, 50, 250 or 1200 ppm M: 0, 0.8, 1.7, 8.1 or 34.9 mg/kg bw/day F: 0, 0.7, 1.5, 7.7 or 37.4 mg/kg/day	NOAEL = M/F:1.7/1.5 mg/kg/day LOAEL = M/F:8.1/7.7 mg/kg/day based on body weight reductions and hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis.
870.4200b Carcinogenicity (mice)	45865702 (2001) / acceptable/guideline / 0, 100, 700 or 4200 ppm M: 0, 18.5, 135.4 or 775.6 mg/kg bw/day F: 0, 29.5, 204.0 or 1265.1 mg/kg bw/day	NOAEL = M/F: 775.6/1265.1 mg/kg bw/day LOAEL not identified. **No evidence of carcinogenicity**.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fluoxastrobin		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300 Combined chronic toxicity/ carcinogenicity (rats)	45865703 (2001) / acceptable/guideline / M: 0, 40, 100, 1000 or 5000 ppm (0, 2.1, 5.2, 53.0 and 271.9 mg/kg/day) F: 0, 100, 500, 2500 or 12500 ppm (0, 6.9, 35.2, 181.3 and 1083.2 mg/kg/day)	NOAEL = M/F: 53.0/181.3 mg/kg/day LOAEL = M/F: 271.9/1083.2 mg/kg/day based on decreased body weight, body weight gain, and food efficiency in both sexes, decreased spleen weight in males, and microscopic lesions in the uterus of females. At the doses tested, there was a treatment-related increase in incidences of uterine adenocarcinoma and thyroid follicular cell adenoma in 12500 ppm group female rats compared with control incidences. **The increased tumor incidences were addressed and resolved following an *ad hoc* senior CARC member meeting as explained under section 4.4.10.**
870.6200a Acute neurotoxicity screening battery (rats)	45865712 (2001) / acceptable/guideline / 12 rats/sex: 0, 200, 500 or 2000 mg/kg bw	NOAEL (neurotoxic) ≥ 2000 mg/kg (limit dose) LOAEL not identified.
870.6200b Subchronic neurotoxicity screening battery (rats)	45865713 (2002) / acceptable/guideline / 12 rats/sex: 0, 200, 1000, 7500 ppm M: 0, 12.7, 59.5 or 473.9 mg/day F: 0, 15.1, 71.7 or 582.4 mg/kg/day	NOAEL (systemic and neurotoxic) = M/F: 473.9/582.4 mg/kg/day LOAEL not identified.
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation	45865704 (1996) / acceptable/guideline / plate incorporation: 16, 50, 158, 500, 1581 and 5000 ug/plate; following preincubation: 10, 32, 100, 316, 1000 and 3162 ug/plate	negative (considered non-mutagenic in *Salmonella typhimurium* cultures treated up to cytotoxic/precipitating levels)
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation	45865705 (1998) / acceptable/guideline / plate incorporation and following preincubation: 16, 50, 158, 500, 1581 and 5000 ug/plate **Test substance: HEC 5725N (E:Z = 90:10%)**	negative (considered non-mutagenic in this *Salmonella typhimurium*/microsome test)
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation	45865706 (2000) / unacceptable/guideline / plate incorporation: 16, 50, 158, 500, 1581 and 5000 ug/plate; following preincubation: 100, 200, 400, 800, 1600 and 3200 ug/plate **Test substance: HEC 5725-phenoxy-hydroxy-pyrimidine**	negative (considered non-mutagenic in this *Salmonella typhimurium*/mammalian activation gene mutation assay)
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation	45865707 (2001) / acceptable/guideline / plate incorporation: 16, 50, 158, 500, 1581 and 5000 ug/plate; following preincubation: 5, 16, 50, 158, 500 and 1581 ug/plate **Test substance: HEC 5725-phenoxy-hydroxy-pyrimidine**	negative (considered non-mutagenic in this *Salmonella typhimurium*/mammalian activation gene mutation assay)

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fluoxastrobin		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation	45865708 (2001) / unacceptable/guideline / 16 to 5000 ug/plate (6 concentrations) **Test substance: HEC 5725-dihydroxy-pyrimidine**	negative (considered non-mutagenic in this *Salmonella typhimurium*/mammalian activation gene mutation assay)
Gene Mutation 870.5300 *In vitro* mammalian forward gene mutation	45865709 (1997) / acceptable/guideline / gene mutation assay: 1 to 200 ug/mL; preliminary cytotoxicity: 6.25 to 800 ug/mL (8 concentrations)	negative (considered non-mutagenic in the *in vitro* forward mutation V79-HPRT test)
Gene Mutation 870.5375 *In vitro* mammalian chromosome aberrations in Chinese hamster lung (V79) cells	45865710 (1996) / acceptable/guideline / initial doses: 0, 20, 40, 80, 160, and 320 ug/mL; in repeat assays: 0, 80, 160 and 320 ug/mL	negative (considered to be negative for clastogenicity in this *in vitro* mammalian cell test)
Cytogenics 870.5395 *In vivo* mammalian cytogenetics - micronucleus assay (mouse)	45865711 (1999) / acceptable/guideline / 75, 150 and 300 mg/kg/day intraperitoneally	negative (considered non-clastogenic, as indicated by no increases in micronuclei in bone marrow)
870.7485 Metabolism and pharmaco-kinetics (rat)	45865714/45865716/45865717/45865718 (2001) Acceptable/Guideline	Absorption, distribution, and metabolism were fully characterized in several rat metabolism studies using each of the three 14C-radiolabelled rings in fluoxastrobin. Absorption was almost complete following a single oral low dose. Peak plasma concentrations were attained within 0.5 to 8 hours depending on the dose and label position. Fecal excretion was the major route of elimination while renal excretion was a secondary route and elimination via expired air was negligible. Within 48 hours of dosing, most of the radioactivity was recovered in urine and feces. Fluoxastrobin was extensively metabolized as evidenced by the extensive metabolite profiles from urine, feces and bile and the relative absence of parent compound (except in the feces of rats given the high dose).
870.7600 Dermal penetration (monkey)	45911501/45911502 (2003) Acceptable/NonGuideline	Following an 8-hour dermal application in a male monkey, absorption was negligible (1.16% preliminary, 2.16% main). The normalized absorption value for the main study was 2.31%.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fluoxastrobin		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7800 Immunotoxicity - Mouse (Subacute Feeding Study)	45865726 (2001) Unacceptable/guideline 0, 450, 1800, or 7000 ppm (equivalent to 0, 106.8, 367.3, and 1534.4 mg/kg/day for males and 0, 157.3, 659.6, and 2383.3 mg/kg/day for females)	No clinical signs of toxicity or mortality were found and no treatment-related effects were found on body weight, food intake, or B-cell activated, T-cell mediated IgM response to SRBC. However, the study is considered unacceptable because of uncertainty in dietary test material intake, failure to report spleen weight of each mouse at necropsy, and failure of the laboratory to demonstrate its capability in performing this type of assay.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Database

The database for evaluating *in utero* or postnatal susceptibility is adequate and includes developmental toxicity studies in both rats and rabbits and a two-generation reproduction study in the rat.

4.2.2 Evidence of Neurotoxicity

Fluoxastrobin is not acutely neurotoxic in rats up to a single high dose of 2000 mg/kg/day or by repeated dietary feeding in the rat subchronic neurotoxicity screening study where the top dose was nearly half the limit dose of 1000 mg/kg/day. Other studies in rats including the subchronic, chronic toxicity/carcinogenicity, two-generation reproduction, and developmental toxicity were tested to or above the limit dose with no indication of clinical signs, histopathology or other signs of toxicity that could be attributed to neurotoxicity. In addition, both the 90-day and one-year dog studies included neurologic evaluations for potential neurotoxic effects, such as peripheral and cranial reflex tests, task performance tests, gait, and behavioral observations. There were no treatment-related neurotoxicity findings in dogs.

Acute Neurotoxicity - Rats [OPPTS 870.6200a (§81-8)] OECD 424.
EPA MRID 45865712.

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 45865712), four groups of fasted, 9 week old Charles River Wistar rats (12/sex/group) were given a single oral dose of HEC 5725 (94.1-94.6% a.i., mixed batch # 06261/ 0008) in 0.5% methylcellulose/ 0.4% Tween 80 in deionized water at doses of 0, 200, 500, or 2000 mg/kg bw with a dosing volume of 10 ml/kg and observed for 15 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 12 animals/sex/group before treatment and at Days 0, 7, and 14. At study termination, 6 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 6 animals/sex of the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Plasma concentrations of HEC 5725 following oral exposure to 100 mg/kg were used to determine that plasma concentration peaked between 3 and 8 hours. The following

observations and measurements were included in the study: clinical observations, mortality checks, body weight, automated measurements of activity (figure-eight maze), a functional observation battery, brain weight, and a gross necropsy. Skeletal muscle, peripheral nerves, eyes (with optic nerves), and tissues from the central nervous system were examined microscopically for lesions.

There were no treatment related effects on mortality, clinical signs, body weight, brain weight or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no treatment-related effects.

Based on the results of this acute oral neurotoxicity study, the neurotoxic lowest observed adverse effect level (LOAEL) for HEC 5725 in male and female rats was not identified and the no observed adverse effect level (NOAEL) is ≥2000 mg/kg (limit dose).

This neurotoxicity study is classified as **Acceptable/ Guideline** and does satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

Subchronic Neurotoxicity - Rats [OPPTS 870.6200b (§82-7)].
EPA MRID 45865713.

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 45865713), Technical Grade HEC 5725 (94.5-94.9% a.i., Batch # 06261/0008) was administered to 12 Wistar Hanover Crl: WI[Glx/BRL/Han]IGS BR rats/sex at dietary concentrations of 0, 200, 1000, or 7500 ppm for 13 weeks. Time-weighted average doses were 0, 12.7, 59.5, or 473.9 mg/kg/day, respectively, for males and 0, 15.1, 71.7, or 582.4 mg/kg/day, respectively, for females. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed on all animals pre-test and at weeks 4, 8, and 13. At study termination, 6 animals/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, control and high-dose rats were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

All animals survived to scheduled sacrifice. There were no treatment-related clinical signs of toxicity, or effects on body weight, food consumption, or gross or microscopic pathology. FOB findings and motor activity were similar between the treated and control groups.

The increased incidence of axonal degeneration of the thoracic spinal cord among the high dose males and females (5/6 vs. 2/6 in control males, and 3/6 vs. 0/6 in control females) was not considered an adverse treatment related finding based on the following. Firstly, the severity scores were minimal (1.0, 1.5, 1.3, and 0, respectively). Secondly, when lesions are combined from all levels of the spinal cord, the overall degeneration was similar among the high-dose and controls (6 vs. 4 in males and 4 vs. 4 in females). The mid- and low dose animals were not evaluated. Thirdly, upon HED's request, the Registrant provided data on spinal cord nerve degeneration in control animals of both sexes from another subchronic neurotoxicity study using Spiromesifin (PC Code 024875, CAS # 283594-90-1, MRID 45819607). The control incidences of degeneration in thoracic spinal cord (3/6 and 4/6 in male and female controls, respectively and severity of 1.0 in both) and in all levels of the spinal cord (5/6 and 5/6) were comparable to the

findings in the current study. Therefore, the apparently increased incidences of thoracic spinal cord degeneration in the high dose Fluoxastrobin male and female groups are within other control incidences and are not considered treatment related adverse findings.

Animals of both sexes could have tolerated a higher dose. However, based on findings in another subchronic study in rats, selecting the top dose in males was justified due to a significant loss in body weight in addition to histopathology findings in adrenal cortex and urinary system at a comparable dose (MRID 45865627). On the other hand, at more than twice the high dose in the current study, females in the other study had minimal or no adverse effects. Nonetheless, testing at a higher dose is unlikely to unravel adverse neurotoxicity findings since there were no indications or signs of neurotoxicity at half the limit dose in the current study or even at higher doses of Fluoxastrobin in other repeat dosing studies.

As explained in more detail under positive control (Section I.C.6), method validation of motor activity testing and verification of personnel qualifications to perform FOB in rats are adequately documented in two separate relatively recent studies (MRIDs 45464601 and 45464602).

Based on lack of treatment related adverse findings in this study, the systemic and neurotoxicity NOAEL for HEC 5725 in rats is ≥7500 ppm (473.9 and 582.4 mg/kg/day for males and females, respectively) and the LOAEL was not identified.

The study is classified as **Acceptable/Guideline** and does satisfy the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

4.2.3 Developmental Toxicity Studies

Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.
EPA MRID 45865631.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID# 45865631), HEC 5725 (Fluoxastrobin; 98.9%, batch #NLL 6112-8) was administered to 25 mated female Wistar [HanIbm: WIST (SPF)] rats/group by gavage in bi-distilled water with 4% carboxymethylcellulose sodium salt at dose levels of 0, 100, 300, or 1000 mg/kg bw/day on gestation days (GD) 6 through 20, inclusive. On GD 21, surviving females were sacrificed and necropsied and liver weight was recorded. All live fetuses were weighed, sexed, and examined for external alterations. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination. A subset of 10 dams/group was used to evaluate selected clinical chemistry parameters; to determine the cytochrome P-450 content and – and O- demethylase activities in liver tissue; and for liver histopathology.

There were no treatment-related effects on survival, clinical signs, body weight, food consumption, cesarean parameters, or gross pathology. There were no treatment-related effects on the cytochrome P-450 content or – and O- demethylase activities in liver tissue, and there were no treatment-related effects on serum triglyceride, albumin, and total protein concentration, or on aspartate aminotransferase and alanine aminotransferase activities. At 1000 mg/kg bw/day, there were treatment-related slight increases in the mean absolute liver weight and mean relative (to

corrected body weight) liver weight (respectively 111% and 110% of controls; $p<0.01$), although the mean absolute liver weight fell within the historical control range (12.39 g. vs. 10.32-12.90 g.). The increased liver weight may be related to a dose- and treatment-related increase in the incidence of minimal lymphoid cell foci in the high-dose group (noted in 4/10, 6/10, 6/10, and 9/10 control, low-, mid-, and high-dose animals, respectively); however, neither effect was considered toxicologically significant or adverse.

The maternal toxicity LOAEL for fluoxastrobin in Wistar rats is not identified, and the maternal toxicity NOAEL is greater than or equal to 1000 mg/kg bw/day (limit dose).

There were no treatment-related increases in fetal deaths/resorptions, and the fetal sex ratio was not affected by treatment. The mean fetal weight of the treated groups was similar to that of controls, and there was no adverse effect on fetal ossification rates. There were no reported external, visceral, or skeletal malformations or anomalies. Variations were observed in a total of 2/22, 1/24, 1/23, and 1/21 litters from the control, low-, mid-, and high-dose groups, respectively.

The developmental toxicity LOAEL for fluoxastrobin in Wistar rats is not identified, and the developmental toxicity NOAEL is greater than or equal to 1000 mg/kg bw/day.

The developmental toxicity study in the rat is classified **Acceptable/Guideline**. Although there was no evidence of maternal toxicity at the highest dose level tested, the 1000 mg/kg bw/day limit dose was attained; this study therefore **does satisfy** the guideline requirement for a developmental toxicity study [OPPTS 870.3700a; OECD 414] in the rat.

Prenatal Developmental Toxicity Study - Rabbit [OPPTS 870.3700b (§83-3b) OECD 414].
EPA MRID 45865632.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45865632), HEC 5725 (94.5% a.i., batch # 06261/0008) was administered to 22 naturally mated female Himalayan rabbits/group by gavage at dose levels of 0, 25, 100, or 400 mg/kg bw/day from gestation days (GD) 6 through 28, inclusive. On GD 29, all surviving does were sacrificed and examined grossly. Each placenta was weighed. Each fetus was weighed and examined for external abnormalities and sex determination. All fetuses were examined viscerally by fresh dissection, with a transverse section through the brain in made in about 50% of the fetuses, followed by evisceration. The eviscerated carcasses were processed for skeletal examination, including cartilage and skeletal staining.

All animals survived to scheduled sacrifice and gross necropsy was unremarkable. An increased incidence of soft feces in high-dose animals and dose-related incidences of light colored feces were indicative of excretion of the test article. Other clinical signs were limited to three high-dose animals with cold ears on several occasions. No significant differences in body weight and body weight change values occurred between the treated and control groups throughout the study. The high-dose group lost slightly more weight than the controls during GDs 6-9 (-43.9 g vs -25.8 g for the controls), but overall weight gain during the treatment interval was comparable to the controls. Food consumption by the mid- and high-dose groups was 85% and 65%, respectively, of the control group level during GDs 6-9, food efficiency was also decreased during this period. No other differences in mean food consumption were observed between the treated groups and

the control group during the study.

Therefore, the maternal toxicity LOAEL for HEC 5725 in Himalayan rabbits is 400 mg/kg/day based on cold ears, transient body weight loss, and decreased food consumption and efficiency and the maternal toxicity NOAEL is 100 mg/kg/day.

No statistically significant differences were noted between the treated and control groups for numbers of corpora lutea, implantations, live fetuses, or resorptions, gravid uterine weight, fetal sex ratios, and pre- or post-implantation losses. Fetal body weight was similar between the treated and control groups. The number of fetuses (litters) examined for external, visceral, and malformations/variations in the control, low-, mid-, and high-dose groups was 161 (22), 140 (20), 138 (20), and 141 (21), respectively. No treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus.

Therefore, the developmental toxicity NOAEL for HEC 5725 in Himalayan rabbits is greater than or equal to 400 mg/kg/day and the developmental toxicity LOAEL is not identified.

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and does satisfy the guideline requirements for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

4.2.4 Reproductive Toxicity Study

Reproduction and Fertility Effects Study – Rat [OPPTS 870.3800 (§83-4) OECD 416].
EPA MRID 45865634/45865723/45865633.

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 45865634 and 45865723) HEC 5725 (94.5% a.i., batch/lot # 06261/0008) was administered to 30 Wistar rats/sex/dose in the diet at dose levels of 0, 100, 1000 or 10,000 ppm. Premating doses for the P-generation parental animals were 6.3, 70.0, or 665.0 g/kg bw/day for males and 7.8, 84.7, or 825.4 mg/kg bw/day for females. One litter was produced for each generation. Parental animals of both generations were administered test or control diets for 10 weeks prior to mating, and throughout mating, gestation, and lactation. Dietary concentrations were selected on the basis of a preliminary study (MRID 45865633).

Parental toxicity was limited to decreases in body weight gain of the P-generation males and females and decreases in absolute body weights of the F_1 males and females at 10,000 ppm. There were no significant changes in absolute body weight of the P males, but the overall body weight gain (from day 0 to day 70) was decreased by 14.8%, in comparison to controls, suggesting a cumulative effect of treatment. Decreases in the body weight of the P females were statistically, but not biologically, significant at 10,000 ppm ($p<0.05$ or $p<0.01$, decreases of <10%) and occurred late in premating (days 56-70); however, the overall body weight gain was decreased by 17.1%. The effect on body weight was statistically and biologically significant throughout premating for the F_1 males ($p<0.01$; decreases of 12.6-15.4%). For the F_1 females, the decreases in body weight were statistically significant throughout premating, but biologically significant only at day 0 of premating ($p<0.01$, decreases of 5.8-13.1%).

Changes in absolute organ weight were observed at 10,000 ppm, mainly for the pituitary and ovaries of the P females; the brain of the F_1 females; the liver, uterus, and thymus of both generations of females; and the brain and thymus of the F_1 males. Relative (to body weight) organ weights were also affected in some organs. The changes in organ weight were statistically significant ($p \leq 0.05$) but are not considered biologically relevant since necropsy revealed no macroscopic or microscopic correlates.

The parental systemic toxicity NOAEL for male and female rats is 1000 ppm (70.0 mg/kg/day for males, 84.7 mg/kg/day for females). The parental systemic toxicity LOAEL of HEC 5725 in male and female rats is 10,000 ppm (665.0 g/kg/day for males, 825.4 mg/kg/day for females), based on decreased premating body weight gain of the P-generation males and females and decreased premating absolute body weight of the F_1 males and females.

Statistically and biologically significant decreases in body weight were observed at 10,000 ppm in the F_1 male and female pups from day 7 to day 21 of lactation ($p<0.01$, decreases of 11.6-26.0%), in the F_2 male pups from day 14 to day 21 ($p<0.01$, decreases of 15.6-21.2%), and in the F_2 female pups from day 7 to day 21 ($p<0.05$ or $p<0.01$, decreases of 10.9-23.3%). There was a statistically significant delay in preputial separation of the 10,000 ppm F_1 pups and incomplete ossification in the femurs of F_1 pups at 10,000 ppm, effects that were probably secondary to reduced pup growth. There were no treatment-related effects on viability, and litter size, and no clinical signs were observed during lactation. Treatment-related effects were not observed at 100 or 1000 ppm.

The offspring systemic/developmental toxicity NOAEL for male and female pups is 1000 ppm (70.0 mg/kg/day for males, 84.7 mg/kg/day for females). The offspring systemic/developmental toxicity LOAEL of HEC 5725 in male and female rats is 10,000 ppm (665.0 mg/kg/day for males, 825.4 mg/kg/day for females), based on decreased body weights, delayed preputial separation, and incomplete ossification in the F_1 and/or F_2 males and females.

Mating performance and fertility of males and females of the P and F_1 parental generations were not affected by treatment with HEC 5725 nor were estrous cyclicity of females and sperm measures in males.

The reproductive toxicity NOAEL for HEC 5725 in rats is greater than 10,000 ppm (665.0 mg/kg/day for males and 825.4 mg/kg/day for females) and the reproductive toxicity LOAEL is not identified.

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rats. The age at the start of premating should be clarified for the parental F_1 males and females.

4.2.5 Additional Information from Literature Sources

The European Dossier (Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC Draft: August 2003) provided additional

information on fluoxastrobin. The general conclusions of the EU Dossier are in agreement with HED's conclusions.

4.2.6 Pre- and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

The toxicity database for fluoxastrobin included acceptable developmental toxicity studies in both rats and rabbits as well as a two-generation reproduction toxicity study in rats. The data provide no indication of increased susceptibility of rats or rabbits to *in utero* exposure to fluoxastrobin.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

There are no concerns or residual uncertainties for pre- and/or post-natal toxicity following exposure to fluoxastrobin.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

No studies in the fluoxastrobin database show evidence of neurotoxicity at the dose levels tested (some studies exceeded the limit dose).

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

There are no concerns or residual uncertainties for pre- and/or postnatal toxicity following exposure to fluoxastrobin, and additionally, fluoxastrobin is not considered neurotoxic (based on results from the acute and subchronic neurotoxicity studies).

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49 years

No acute toxicity endpoint was identified. There was no endpoint noted in the database from a single dose exposure that could be used for risk assessment. This included the acute neurotoxicity (tested to the limit dose) and developmental studies as well as the other short- and long-term studies.

4.4.2 Acute Reference Dose (aRfD) - General Population

No acute toxicity endpoint was identified. There was no endpoint noted in the database from a single dose exposure that could be used for risk assessment. This included the acute neurotoxicity (tested to the limit dose) and developmental toxicity studies as well as the other short- and long-term studies.

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: 870.4100b Chronic Toxicity - dog

MRID No.: 45865701/45865722

Executive Summary: In a chronic toxicity study (MRID 45865701), HEC 5725 (94.1% - 94.7% a.i., batch # 06261/0008) was administered in the diet to 4 beagle dogs/sex/dose at dose levels of 0, 25, 50, 250 or 1200 ppm (equivalent to 0, 0.8, 1.7, 8.1 or 34.9 mg/kg bw/day for males and 0, 0.7, 1.5, 7.7 or 37.4 mg/kg/day for females) for 391-394 days. In addition to the required parameters, neurological examinations were conducted on all animals pre-treatment and just prior to study termination. Electrocardiogram (ECG) assessments were performed after three months of treatment.

All animals survived to study termination and there were no clinical signs of toxicity. No neurological, ophthalmological or ECG findings of toxicological significance were observed.

Mean terminal body weights were decreased in females at 250 ppm and 1200 ppm (89% and 83% of the control, respectively), and in the 1200 ppm males (86% of control). Overall (days 0-385) body weight gain was decreased in high-dose males (80% of control) and females (58% of control) at 1200 ppm, and in the 250 ppm females (74% of control). Mean food consumption was statistically decreased in high-dose males for the first 5 study days, and for 30 of the first 36 days of treatment, high-dose males had the lowest food consumption values of all groups. The decreases in food consumption in high-dose females was less pronounced, with the lowest values for 20 of the first 36 days of treatment. However, the high variability of food consumption and food efficiencies among all groups throughout the study precluded a reliable interpretation of the data.

Increased serum ALT (alanine aminotransferase), GGT (Gamma glutamyl transferase), and ALK (alkaline phosphatase) in high-dose males was often statistically significant throughout the study. In the high-dose male group, ALT activity was increased on days 178 and 386 at 214% and 200% of the control, respectively, and ALK activity was increased on days 87, 178, and 386 at 190%, 236% and 276% of the control. Males of the 250 ppm dose group also had significantly increased ALK on the same days at 157%, 177%, and 195% of the control (all $p \leq 0.05$). For the same three periods, ALK activity was increased in the mid-dose females (142%, 163%, and 320% of control; all $p \leq 0.05$), and in the high-dose females (253%, 350%, and 344% of the control; all $p \leq 0.05$). Absolute hepatic weights were mildly increased in the 250 ppm and high-dose males (118% and 121% of control, respectively); relative (to body weight) hepatic weights in males were dose-related, and statistically significant at 250 ppm and 1200 ppm (112% and 142% of control weight, respectively). Increases in absolute and relative liver weights were statistically significant in the high-dose females (114% and 135% of the control weights, respectively), but a dose response was absent. Some of the changes are indicative of a toxic effect on the liver. Of particular significance are increased ALK and changes in hepatocytes presented as hepatocyte enlargement (hepatocytomegaly) and homogenous granularity of the cytoplasm all of which are consistent with cholestasis (obstruction of bile flow) as supported by similar findings in the 90-day dog study (MRID 45865629). The liver findings in this study are considered adverse in both sexes of the 250 ppm and 1200 ppm dose groups.

Degeneration of the kidney was noted in one male each in the 25 ppm, 250 ppm, 1200 ppm and control groups, and the greatest and sometimes statistically significant decreases in serum total protein and albumin were measured throughout the study in high-dose males and females. The degeneration in the high-dose male was of moderate severity and involved cellular enlargement with nuclear pyknosis and occasional mitotic figures. The degeneration observed in the lower dose males was less severe, with fewer pyknotic nuclei in the tubules. Histopathological changes observed in the high-dose male were reported as clearly differentiated from findings in the other groups. Pigmentation was noted in the renal cortex of males from all groups, and high-dose males were the most often affected. Renal pigmentation was observed in one female each from the 25 ppm, 50 ppm, and 250 ppm groups, and in three high-dose females. The renal findings and, possibly, the decreased serum levels of albumin and total protein, indicate an effect of the test compound on the kidney, which was adverse in the affected high-dose male.

Hyperplasia of the parathyroid's reserve cells was noted in two 250 ppm males (minimal severity) and in one 1200 ppm male (mild or slight). Although serum calcium levels were consistently lowest in the high-dose groups, the decreases were minimal (94-98% of the control). Thus, it is unclear whether the parathyroid gland was adversely affected. Alternatively, the decreases in serum calcium may have been related to a mild effect on renal function.

Dose and Endpoint for Establishing cRfD: 1.5 mg/kg/day (NOAEL for females) with a LOAEL of 7.7 mg/kg/day (females) based on body weight reductions and liver toxicity (cholestasis) in both sexes.

Uncertainty Factor: 100 (10X for intraspecies variation, 10X for interspecies extrapolation)

Comments about Study/Endpoint/Uncertainty Factor: Fluoxastrobin seems to have a mild or low toxicity following repeated administration in all tested species other than the dog. The dog appears to be the most sensitive species.

$$\textbf{Chronic RfD} = \frac{1.5 \text{ mg/kg/day}}{100 \text{ (UF)}} = \textbf{0. 015 mg/kg/day}$$

4.4.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: 870.3150 90-Day Oral Toxicity - Dog

MRID No.: 45865629/4586528/45865722

Executive Summary: Two subchronic studies were submitted – a "low dose" study and a "main" study:

In the main 90-day oral toxicity study **(MRID 45865629)**, HEC 5725 (fluoxastrobin, 94.1-94.6% a.i., batch # 06261/0008) was administered for 95-98 days to four Beagle dogs/sex/dose in the diet at dose levels of 0, 100, 800 or 2500 ppm (reduced from 3000 ppm after 8 days) (equivalent to 0, 3.0, 24.8 or 76.0 mg/kg bw/day in males, and 0, 3.0, 24.2 or 75.0 mg/kg bw/day in females).

In addition to routine guideline requirements, this study evaluated potential cardiac and neurologic effects before treatment initiation, and just before termination; none were identified.

All animals survived to study termination. There were no clinical observations, ophthalmology findings, or compound related ECG or BP changes. Neurologic examinations including mental status/behavior, gait characteristics, postural status and reactions, and spinal/cranial reflexes, thoracic auscultation and rectal body temperatures were within normal limits.

At the initial high dose of 3000 ppm, all males and females lost weight during the first week of treatment due to severely reduced food consumption. After day 8, the dose was reduced to 2500 ppm, and mean food consumption in high-dose males and females improved and approached or exceeded control intakes by Day 29. Although total food consumption values in treated groups were comparable with those of the controls, days 0-91 body weight gains were decreased in a dose-related manner in males (low to high: 82%, 65%, and 60% of control, respectively) and in the 800- and 2500-ppm females (54% and 42% of control, respectively). Overall food efficiencies were decreased in a dose-related manner in males (61-80% of control) and in the mid- and high-dose females (57% & 47% of the control, respectively), indicating an adverse effect of the compound.

There were several adverse liver findings at the mid- and high-doses. Alkaline phosphatase (ALK) activity, a marker of biliary epithelial cells and canalicular hepatocyte membranes, was increased (often at statistically significant levels) in both sexes throughout treatment at the 800- and 2500-ppm doses (males: 147-309% of control, females: 122-341% of control). Cholesterol levels were decreased according to dose throughout the study and at statistically significant levels in the mid- and high-dose male groups (63-89% of control) and in the high-dose female group (68-75% of control). There were also large dose-dependent increases in cytochrome P-450 (P-450) and phase I activities of, N– and O-demethylase, 7-ethoxycoumarin deethylase (ECOD), aldrin epoxidase (ALD), in addition to phase II UDP-glucuronosyltransferase (UDP-GT and GLU-T), epoxide hydroxylase (EH), and glutathione-S-transferase (GS-T), demonstrating the induction of phase I and II enzyme reactions. Absolute and relative (to body) liver weights were increased according to dose in the 800- and 2500-ppm males, and in high-dose females. Hepatocytomegaly was observed in 3 of 4 mid-dose males and females, and in all high-dose animals; the cytoplasm was also characterized by foamy eosinophilic alteration. These microscopic changes are likely due to cholestasis (obstruction of bile flow) as supported by the large increases in serum alkaline phosphatase and decreases in cholesterol. These liver findings are considered adverse in both sexes of the 800 and 2500 ppm dose groups.

There were other dose-related increases in liver microsomal P-450 (CYP2B1 and CYP3A4) activities including testosterone hydroxylation at 6β, 16a, 16β, and 2β in males and females; the increased activities may have been related to the dose-related but statistically insignificant increases in absolute and relative epididymal weights (115-155% of control). Conversion of testosterone to androstenedione was also increased in the high dose females at 177% of the control, again suggesting an induction of P-450 (CYP2B1).

The compound had an adverse effect on kidneys as indicated by slightly increased (113-120 % of controls) mean absolute and relative kidney weights in the high dose males and in relative kidney weights of mid- and high-dose females in addition to findings of degeneration in proximal tubular

epithelium in one mid-dose and three high-dose males. Serum albumin was significantly decreased in all high-dose groups throughout the study, and total serum protein was significantly reduced ($p \leq 0.05$) at all time points in high-dose females. A mild, dose-related hypocalcemia was noted in treated groups that may have been related to the kidney effects.

There were increases (non-significant) in TSH in high-dose males (104-200% of the control) and in mid- and high-dose females (133-250% of control). Changes in TSH were accompanied by minor reductions in T_3 in the high-dose males and females (71-78% of control values) which were statistically significant only in females at day 29; however, T_4 values had little or no change. Reduced T_3 levels are very likely due to increased phase II liver microsomal glucuronidation activities (GLU-T and UDP-GT) resulting in a concomitant rise in TSH to offset enhanced glucoronidation and excretion of T_3. There were no treatment related effects on thyroid weights or histopathology. Cumulatively, these results indicate that HEC 5725 indirectly affected the dog thyroid function, namely T_3 and TSH, and that these effects are not likely due to thyroid endocrine disruption.

In another 90-day oral toxicity study **(MRID 45865628)** which was conducted after the main study, HEC 5725 (fluoxastrobin, 94.1-94.7% a.i., batch # 06261/0008) was administered to four Beagle dogs/sex/dose in the diet at dose levels of 0, 25 or 50 ppm (equivalent to 0, 0.7 or 1.4 mg/kg bw/day in males and 0, 0.7 or 1.5 mg/kg bw/day in females). In addition to the guideline requirements, this study included a neurologic evaluation for potential effects, such as peripheral and cranial reflex tests, task performance tests, gait, and behavioral observations.

No compound-related effects were observed in the low-dose study for any of the parameters tested.

Considering both studies together: The LOAEL for fluoxastrobin (HEC 5725) is 800 ppm (24.8 mg/kg/day for males and 24.2 mg/kg/day for females), based on dose-related reductions in body weight, weight gain, food consumption/efficiency, and liver toxicity (cholestasis) in both sexes in addition to kidney findings (increased relative weights in females and degeneration of the proximal tubular epithelium in males). The NOAEL is 100 ppm (equivalent to 3.0 mg/kg/day) for both sexes.

When considered together, the two 90-day oral toxicity studies in the dog (MRIDs 45865629 & 45865628) are **Acceptable/Guideline** (OPPTS 870.3150; OECD 409).

Comments about Study/Endpoint: The dog is the most sensitive species for this compound and the time frame for the endpoint supports the exposure scenario.

Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: 870.3150 90-Day Oral Toxicity - Dog

MRID No.: 45865629/4586528/45865722

Executive Summary: See incidental oral exposure - short-term above

Dose and Endpoint for Risk Assessment: 3.0 mg/kg/day (NOAEL in both sexes) with a LOAEL of 24.2 mg/kg/day based on dose-related reductions in body weight, weight gain, food consumption/efficiency, and liver toxicity (cholestasis) in both sexes in addition to kidney findings (increased relative weights in females and degeneration of the proximal tubular epithelium in males).

Comments about Study/Endpoint: The dog is the most sensitive species for this compound and the time frame for the endpoint supports the exposure scenario.

4.4.5 Dermal Absorption

A preliminary study (MRID 45911501) was conducted in which a single 20 µCi (200 µg) dose of [^{14}C]HEC 5725 (lot no. 12250/39, purity >99%) was administered intravenously or dermally (EC 100 formulation) to one male rhesus monkey. The intravenous dose served as a reference for 100% bioavailability. For the main study (MRID 45911502) a single 15 µCi (150 µg) dose of [^{14}C]HEC 5725 (lot no. 12250/39, purity >99%) was administered dermally (EC 100 formulation) to five male rhesus monkeys. The dermal application was for eight hours. Excreta were monitored for up to 192 hours (intravenous dose) or 120 hours (dermal application).

There were no significant adverse effects that could be attributed to the test article. One monkey vomited and another (both in the dermal exposure group; main study) exhibited soft stools at 4 hours post-application. Actual doses were 195 µg (i.v.), 172 µg (preliminary dermal), and 148µg (main dermal). These doses correspond to 60.9 µg/kg, 7.17 µg/cm^2, and 6.12 µg/cm^2; only 2.5, 14, and 1% from nominal, respectively. Radioactivity mass balances for the respective test groups were acceptable at 94.0, 102.0, and 93.4%. Following intravenous administration, 52.99% of the administered radioactivity was excreted via the urine, 19.91% via feces, and an additional 21.1% was recovered from cage debris/rinses over the 192-hour experimental period. Approximately 93% of excretion in the urine occurred by 48 hours. Fecal excretion of the radiolabeled compound following intravenous administration, although significant (19.91%), was approximately 37.6% of that for urine. Following the 8-hour dermal application, the majority of radioactivity was associated with the dermal swabs and the extracts of those swabs (~84.3-88.4% of applied radioactivity). Only 2.7-12.9% of the radioactivity was associated with the cover material affirming the investigators' contention that most of the applied dose was available for absorption and not bound to the appliance materials.

The results of the preliminary study clearly showed that following intravenous administration allowing for 100% bioavailability, HEC 5725 is rapidly and nearly totally excreted in the urine and feces within 48 hours. Following an 8-hour dermal application in a male monkey, absorption was negligible (1.16% preliminary, 2.16% main). The normalized absorption value for the main study was **2.31%**. However, for risk assessment purposes, HED/RAB3 set the dermal absorption value at 2.3%

4.4.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

Dermal Exposure: Short-Term (1- 30 days) Exposure

Study Selected: none

MRID No.: none

Executive Summary: none

Dose and Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: There was no systemic or localized hazard noted in a 28-day dermal toxicity study in the rat and there are no developmental or reproductive toxicity concerns, therefore this risk assessment is not necessary.

Dermal Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: 870.3150 90-Day Oral Toxicity - Dog

MRID No.: 45865629/4586528/45865722

Executive Summary: See incidental oral - short-term above (Sec. 4.4.4)

Dose and Endpoint for Risk Assessment: 3.0 mg/kg/day (NOAEL in both sexes) with a LOAEL of 24.2 mg/kg/day based on dose-related reductions in body weight, weight gain, food consumption/efficiency, and liver toxicity (cholestasis) in both sexes in addition to kidney findings (increased relative weights in females and degeneration of the proximal tubular epithelium in males).

Comments about Study/Endpoint: The dog is the most sensitive species for this compound and the time frame for the endpoint (90-days) supports the exposure scenario. Although the 28-day dermal toxicity study in the rat at the limit dose showed no systemic toxicity, HED decided to use a conservative endpoint for longer than 1-month exposure.

Dermal Exposure Long-Term (> 6 Months)

Study Selected: 870.4100b Chronic Toxicity - dog

MRID No.: 45865701/45865722

Executive Summary: See chronic reference dose above (Sec. 4.4.3)

Dose and Endpoint for Risk Assessment: 1.5 mg/kg/day (NOAEL for females) with a LOAEL of 7.7 mg/kg/day (females) based on body weight reductions and hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis in both sexes.

Comments about Study/Endpoint/Uncertainty Factor: Fluoxastrobin seems to have a mild or low toxicity following repeated administration in all tested species other than the dog. The dog appears to be the most sensitive species.

4.4.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Inhalation Exposure: Short-Term (1- 30 days)

Study Selected: 870.3150 90-Day Oral Toxicity - Dog

MRID No.: 45865629/4586528/45865722

Executive Summary: See incidental oral - short-term above (Sec. 4.4.4)

Dose and Endpoint for Risk Assessment: 3.0 mg/kg/day (NOAEL in both sexes) with a LOAEL of 24.2 mg/kg/day based on dose-related reductions in body weight, weight gain, food consumption/efficiency, and liver toxicity (cholestasis) in both sexes in addition to kidney findings (increased relative weights in females and degeneration of the proximal tubular epithelium in males).

Comments about Study/Endpoint: The dog is the most sensitive species for this compound and the time frame for the endpoint supports the exposure scenario. There are physical/chemical properties of this compound which preclude toxicity testing by the inhalation route and the acute inhalation toxicity was determined Toxicity Category IV.

Inhalation Exposure: Intermediate-Term (1- 6 Months)

Study Selected: 870.3150 90-Day Oral Toxicity - Dog

MRID No.: 45865629/4586528/45865722

Executive Summary: See incidental oral - short-term above (Sec. 4.4.4)

Dose and Endpoint for Risk Assessment: 3.0 mg/kg/day (NOAEL in both sexes) with a LOAEL of 24.2 mg/kg/day based on dose-related reductions in body weight, weight gain, food consumption/efficiency, and liver toxicity (cholestasis) in both sexes in addition to kidney findings (increased relative weights in females and degeneration of the proximal tubular epithelium in males).

Comments about Study/Endpoint: The dog is the most sensitive species for this compound and the time frame for the endpoint supports the exposure scenario.

Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: 870.4100b Chronic Toxicity - dog

MRID No.: 45865701/45865722

Executive Summary: See chronic reference dose above (Sec. 4.4.3)

Dose and Endpoint for Risk Assessment: 1.5 mg/kg/day (NOAEL for females) with a LOAEL of 7.7 mg/kg/day based on body weight reductions and hepatocytomegaly and cytoplasmic changes

associated with increased serum liver alkaline phosphatase indicative of cholestasis.

Comments about Study/Endpoint/Uncertainty Factor: Fluoxastrobin seems to have a mild or low toxicity following repeated administration in all tested species other than the dog. The dog appears to be the most sensitive species.

4.4.8 Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	N/A	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal	N/A	100	100
Inhalation	100	100	100

For Occupational exposure: This is based on the conventional uncertainty factor of 100X (10X for intraspecies variation and 10X for interspecies extrapolation)**.**

For Residential exposure: This is based on the conventional uncertainty factor of 100X (10X for intraspecies variation and 10X for interspecies extrapolation).

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: For short-term aggregate exposure risk assessment the oral and inhalation routes; and for intermediate-, and long-term aggregate exposure risk assessments, the oral, dermal (oral equivalent) and inhalation routes can be combined because of the common toxicity endpoints (reduced body weight and liver toxicity) via these routes.

4.4.10 Classification of Carcinogenic Potential

Based on the October 25, 2004 HED *ad hoc* senior CARC member meeting (attended by Bill Burnam, Karl Baetcke, Stephen Dapson, Vicki Dellarco, Paula Deschamp, Jessica Kidwell, Jess

Rowland, Louis Scarano, and Sarah Winfield), it was decided that fluoxastrobin did not warrant a CARC meeting and no additional statistical analyses were needed for the increased incidence of uterine adenocarcinomas or the thyroid follicular cell adenomas seen in female Wistar rats in the combined chronic toxicity/carcinogenicity study in rats (MRID 45865703). It was concluded that there was no carcinogenic concern for fluoxastrobin based on the following.

The incidence of uterine adenocarcinomas in the study was 3/50 (6%), 1/49 (2%), 2/50 (4%), 5/50 (10%), and 10/49 (20%) at 0, 100, 500, 2500, and 12,500 ppm, respectively, with a statistically significant increase (trend and pair-wise) in the incidence of uterine adenocarcinomas in female rats at 12,500 ppm, a dose considered to be adequate and not excessive. Since the incidence of uterine adenocarcinomas (20%) at the high dose was within the historical control range of 0-24% for the testing laboratory, this tumor was not considered to be treatment-related. [The highest control incidence (24%) was in a study conducted almost in parallel (February 1999-February 2001) with the present study.] In addition, a slight increase (trend only) in the incidence of accompanying uterine focal glandular hyperplasia was seen in the females at 12,500 ppm (incidences with increasing dose were 1/50 (2%), 1/49 (2%), 2/50 (4%), 1/50 (2%), 6/49 (12%)). However, the incidence of hyperplasia (12%) was only slightly above the available historical control data for the testing laboratory for Wistar rats (RITA database: 0-10%, with a mean of 1.6%). Furthermore, all glandular hyperplasias were rated as minimal or slight.

There was an increased incidence (trend only) of thyroid follicular cell adenomas (3/60 (5%)) in the 12,500 ppm females, compared to none in the controls or the 100- 2500 ppm dose groups. The incidence of thyroid adenomas in historical controls for Bayer AG in-house studies ranged from 0-2% for studies for Wistar rats and the Hsd:Cpd:WU substrain. The Charles River historical control database for Wistar rats (March, 2003), however, showed thyroid follicular cell adenomas with a mean of 3.5% and range of 0-9% for 10 studies. Given the lack of a statistically significant pair-wise increase (trend only) in thyroid follicular cell adenomas (with no carcinomas seen), and consideration of a more comprehensive historical control database, it was concluded that the increase in thyroid follicular cell adenomas was not treatment-related.

Therefore, it was concluded that there was no evidence of carcinogenicity for fluoxastrobin. This was based on a lack of treatment-related tumors in rats or mice, no mutagenicity concern, and negative SAR. Other members of this strobilurin class of fungicides (azoxystrobin and trifloxystrobin) have not been shown to be carcinogenic (one chemical, pyraclostrobin needs additional data). The only member of this class with evidence of carcinogenicity is kresoxim-methyl (classified as a likely carcinogen, causes liver tumors).

Studies Supporting Carcinogenic Classification:

Combined chronic toxicity/carcinogenicity (diet) - rat OPPTS 870.4300/§83-5/OECD 453

EPA MRID 45865703.

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 45865703), HEC 5725 (Fluoxastrobin, 94.3-94.6% a.i., mixed batch # 06261/0008) was administered to groups of 50 male and 50 female Wistar [Hsd Cpd:WU] rats at dietary concentrations of 0, 40, 100, 1000, or 5000 ppm for males and 0, 100, 500, 2500, or 12500 ppm

for females for up to 2 years. Additionally, groups of 10 males and 10 females were treated similarly for 1 year for interim evaluations. The weight normalized doses were 0, 2.1, 5.2, 53.0, and 271.9 mg/kg/day, respectively, for males and 0, 6.9, 35.2, 181.3, and 1083.2 mg/kg/day, respectively, for females.

No treatment-related effects occurred on survival rates, hematologic parameters, the eyes, neurological parameters of the FOB, or organ weights in either sex. The only treatment-related clinical signs were transient vaginal bleeding observed after week 61 in females at 12500 ppm. Male rats in the 5000 ppm group and female rats in the 12500 ppm group weighed significantly less than controls throughout most of the study, with the magnitude of the deficit increasing with time. The high-dose males weighed 10% less and the high-dose females weighed 18% less than controls at study termination. Initially (weeks 0-1), both sexes at their respective high-dose levels displayed a significant decrease in body-weight gain (males 18%/females 24% less than control), and body-weight gain for the weeks 1-13 interval was 14% (males) and 21% (females) less than control for these two groups. The high-dose females did not gain weight during the second year of the study, while the high-dose males displayed a negative body-weight gain (-17 grams) for the weeks 53-105 interval that was comparable to that of the control (-17 grams). The high-dose males gained 13% less than controls over the entire study, while the high-dose females gained 32% less than controls over the entire study. Females at the 2500 ppm dose level gained 10% less than controls overall. Food consumption per animal was similar in treated and control rats, but food consumption per kg body weight was significantly increased at almost all or all weekly intervals in both sexes, ranging up to 21% for males and 44% for females. Food efficiency for the entire study, however, was slightly decreased by 10% (1.93 vs 2.14) for males at 5000 ppm and markedly decreased by 40% (0.81 vs 1.34) for females at 12500 ppm and by 13% for females at 2500 ppm. Females at the 2500 ppm (9% less) and 12500 ppm (21% less) dose levels consumed less water overall than the control females.

Treatment-related decreases in liver enzyme activities (AST, ALT, AP) were observed throughout the study, with a dose response evident, mainly in females. Although the toxicological significance of the finding is not known, similar observations were made in four subchronic oral toxicity studies also, demonstrating an effect on the liver. Decreased triglycerides were observed throughout the study in females at the high-dose level, although statistical significance was not attained. A dose-related increase in cholesterol was observed in females at weeks 27, 54, and 79, and the levels remained elevated at week 105, but there was no dose-response at that time. At their respective high-dose levels, both sexes displayed decreased urinary phosphorus levels (males throughout the study; females through week 79). An increase in urine pH was demonstrated in high-dose males during the first year and in females throughout the study (mainly at 2500 ppm and 12500 ppm), although statistical significance was not attained. In the high-dose females, a statistically-significant decrease in bone calcium (in ashes from femur [15% less] and in femur [19% less]) was observed compared to the control after 2 years of treatment. A similar but not statistically-significant decrease in bone calcium (17% less and 18% less, respectively) was observed in the high-dose males after 2 years. In males, there was a significant increase in bone potassium at the two highest dose levels (in ashes from bone [107-108%]) compared to the control.

The effects on absolute and/or relative weights of several organs in male and female rats were attributed to the decrease in terminal body weight. Males at the 5000 ppm dose level displayed

decreased absolute and relative spleen weights. The incidence of glandular hyperplasia in the uterus was marginally increased in females at 12500 ppm (6/49 vs 1/50 in control). Females at the high-dose level displayed an increased incidence of myeloid hyperplasia in the bone marrow, and females at the two highest dose levels displayed a dose-related increase in basophilic hypertrophic focus in the salivary glands. Mineralization of the testes was observed only in treated males, with the high-dose males displaying the highest incidence. The incidence and severity of mastocytosis in mesenteric lymph nodes were significantly increased at their respective high-dose levels in males (31/49 vs 14/48 for controls, severity: 1.7 vs 1.3 for controls) and females (45/48 vs 30/49; severity: 2.0 vs 1.3 for controls). The statistically significant increases in incidences of other microscopic lesions in male and female rats at 5000/12500 ppm were considered incidental increases in spontaneous, age-related, lesions.

At the doses tested, the incidence of uterine adenocarcinoma was increased in female rats; the incidence was 3/50 (6%), 1/49 (2%), 2/50 (4%), 5/50 (10%), and 10/49 (20%) at 0, 100, 500, 2500, and 12500 ppm, respectively. The incidence in historical controls ranged from 0-14%. In addition, the incidence of thyroid follicular cell adenoma in female rats was 1/10 for the interim sacrifice group and 2/49 for the main study compared with no neoplasms in the control or 100, 500, and 2500 ppm interim or main study. The incidence of thyroid follicular cell adenoma was not statistically significant compared with concurrent controls, but it is considered a rare tumor occurring in only 0-2% of historical controls. The increased incidences of uterine adenocarcinoma and thyroid follicular cell adenoma are considered treatment related. The increased incidences in uterine adenocarcinoma and thyroid follicular cell adenoma suggest that HEC 5725 is a potential endocrine disrupter. Dosing was considered adequate based on 10% decreases in body weights in males at 5000 ppm and a >10% decrease in body weight in female rats.

The LOAELs for HEC 5725 in the rat are 5000 ppm for males (271.9 mg/kg/day) and 12500 ppm for females (1083.2 mg/kg/day) based on decreased body weight, body weight gain, and food efficiency in both sexes, decreased spleen weight in males, and microscopic lesions in the uterus of females. The corresponding NOAELs are 1000 ppm (53.0 mg/kg/day) for males and 2500 ppm (181.3 mg/kg/day) for females.

At the doses tested in this study, HEC 5725 has carcinogenic activity based on increased incidences of uterine adenocarcinoma and thyroid follicular cell adenoma in 12500 ppm group female rats compared with control incidences.

This chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline**, and it satisfies the guideline requirement for a chronic toxicity/carcinogenicity study [OPPTS 870.4300); OECD 453] in the rat.

Discussion of Tumor Incidence Findings in Rats: The increased tumor incidences were addressed and resolved as explained earlier under section 4.4.10.

Carcinogenicity feeding - mouse [OPPTS 870.4200b (§83-2(b))]; OECD 451.

EPA MRID 45865702/45865723.

EXECUTIVE SUMMARY: In a 78-week oral carcinogenicity study (2001, MRID 45865702), HEC 5725 (fluoxastrobin, 94.3-94.6% a.i., Batch # 06261/0008) was administered to a total of 50 Crl: CD-1 (ICR)BR mice/sex/dose in the diet at concentrations of 0, 100, 700, or 4200 ppm (equivalent to 0, 19, 135, or 776 mg/kg bw/day for males and 0, 30, 204 or 1265 mg/kg bw/day for females).

There were no significant treatment-related effects on mortality. A significant increase in pallor appearance in females at 4200 ppm (12/50 vs. 2/50 in controls). Body weights were slightly decreased in males at 700 and 4200 ppm (~2% - 7%), and were significantly decreased at 4200 ppm sporadically during the first year of treatment. Slightly decreased body weights were also seen in high-dose females (~3%), but the differences were significant only at week 66, and the decrease in weight gain was not dose related. No treatment related effects on food intake were noted.

Significant dose-related *decreases* were seen in plasma alanine aminotransferase (ALT) in males ↓52 to 69%) in the high dose group and in females in the mid (↓39 to 57%) and high (↓69% to 83%) and aspartate aminotransferase (AST) in the high dose group males (↓19-28%) and in the mid (↓28-31%) and high (↓29% to 43%) in females. The decreased enzyme activities were dose-related, but such *decreases* in activity are not recognized as toxic responses. In the high dose group, the absolute and relative (to body weight) liver weights were significantly increased by 16% and 20% in males and 20% and 22% in females, respectively, and the relative liver weight was increased by 8% in males at 700 ppm. Increased incidences of liver hepatocyte hypertrophy (38%) and periportal/centrilobular eosinophilic cytoplasmic changes (36%) compared to the control (0%) were seen in females at 4200 ppm. The increases in liver weight and hepatic pathology were considered adaptive and not adverse. **The LOAEL for fluoxastrobin mice is not identified. The NOAEL is ≥4200 ppm for males and females (776 mg/kg/day for males and 1265 mg/kg/day for females).**

Treatment of CD-1 mice with a dietary levels of up to 4200 ppm fluoxastrobin for 78 weeks did not result in a significant increase in neoplasms. The high dose is considered adequate for carcinogenicity assessment based on the liver weight increases since the high dose in females of 1265 mg/kg/day is in excess of the limit dose and the high dose of 776 mg/kg/day in males is considered acceptably close to the limit dose.

This study was considered **Acceptable/Guideline**, and satisfies the guideline requirement for a carcinogenicity study in mice (OPPTS 870.4200/ OECD 451).

Table 4.4, below, summarizes the toxicological doses and endpoints for fluoxastrobin for use in human risk assessments.

Table 4.4. Summary of Toxicological Doses and Endpoints for Fluoxastrobin for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49) Acute Dietary (general population)	none	N/A	There was no indication of an adverse effect attributable to a single dose. An aRfD was not established.
Chronic Dietary (all populations)	NOAEL=1.5mg/kg/day UF = 100X Chronic RfD=0.015 mg/kg/day cPAD= 0.015 mg/kg/day	1X	Chronic toxicity in the dog LOAEL = M/F:8.1/7.7 mg/kg/day based on body weight reductions and hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis.
Incidental Oral Short-Term (1 - 30 days) and Intermediate-Term (1 - 6 months)	NOAEL=3.0 mg/kg/day UF = 100X	Residential LOC for MOE = 100	90-day subchronic dog LOAEL = M/F 24.8/24.2 mg/kg/day (800 ppm) based on dose-related reductions in net body weight gain and food efficiency in addition to toxicity findings in the liver (cholestasis) in both sexes, and kidneys (increased relative weights in females and degeneration of the proximal tubular epithelium in males).
Dermal Short-Term (1 - 30 days)	Not applicable	None	None: There were no systemic or dermal toxicity findings in a 28-dermal toxicity study in the rat up to the limit dose (1000 mg/kg/day) and there were no developmental or neurotoxicity concerns raised in other studies.
Dermal Intermediate-Term (1 - 6 months)	NOAEL=3.0 mg/kg/day UF = 100X dermal absorption rate=2.3%	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day subchronic dog LOAEL = M/F 24.8/24.2 mg/kg/day (800 ppm) based on dose-related reductions in net body weight gain and food efficiency in addition to toxicity findings in the liver (cholestasis) in both sexes, and kidneys (increased relative weights in females and degeneration of the proximal tubular epithelium in males).

Table 4.4. Summary of Toxicological Doses and Endpoints for Fluoxastrobin for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Long-Term (> 6 months)	NOAEL=1.5 mg/kg/day UF = 100X dermal absorption rate=2.3%	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Chronic toxicity in the dog LOAEL = M/F:8.1/7.7 mg/kg/day based on body weight reductions and hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis.
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1 - 6 months)	NOAEL=3.0 mg/kg/day UF = 100X	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day subchronic dog LOAEL = M/F 24.8/24.2 mg/kg/day (800 ppm) based on dose-related reductions in net body weight gain and food efficiency in addition to toxicity findings in the liver (cholestasis) in both sexes, and kidneys (increased relative weights in females and degeneration of the proximal tubular epithelium in males).
Inhalation Long-Term (> 6 months)	NOAEL=1.5 mg/kg/day UF = 100X	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Chronic toxicity in the dog LOAEL = M/F:8.1/7.7 mg/kg/day based on body weight reductions and hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis.
Cancer (oral, dermal, inhalation)	**Classification:** Not likely to be carcinogenic to humans.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the hazard data, HED recommended the special FQPA SF be reduced to 1X because there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The fluoxastrobin risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- The dietary food exposure assessment utilizes proposed tolerance level or higher residues and 100% crop treated information for all commodities. By using these screening-level assessments, chronic exposures/risks will not be underestimated.

- The dietary drinking water assessment (Tier 1 and 2 estimates) utilizes values generated

by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

- The residential exposure assessment utilizes activity-specific transfer coefficients and turf transferable residues (TTR), as well as maximum application rates for the postapplication scenario. The refined residential assessment is based on reliable data and is unlikely to underestimate exposure/risk.

4.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on fluoxastrobin, there was no estrogen, androgen, and/or thyroid mediated toxicity. As discussed earlier, the findings of increased incidences in uterine adenocarcinoma and thyroid follicular cell adenoma in the rat chronic toxicity/carcinogenicity study were determined to be unrelated to treatment (refer to section 4.4.10). These observations, which were found within random occurrence in this strain of rats, are not treatment-related and, henceforth, are not indicative of possible endocrine disruption. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fluoxastrobin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

Because fluoxastrobin is a new active ingredient, and as such has never been registered, HED has no public health data (incident data or other) for this pesticide. Also, it is not expected that it or any of its metabolites would be monitored by National Health and Nutrition Examination Survey (NHANES) or the Agricultural Health Study (AHS).

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

Reference: PP#3F6556. *Fluoxastrobin. Petition for the Establishment of Permanent Tolerances for Use on Peanuts, Tuberous and Corm Vegetables Subgroup, Leaf Petiole Vegetables Subgroup, Fruiting Vegetables Group, and Seed Treatment of Peanut and Potato*. William Wassell. 12/XX/04. D289106 and D289107, PC Code 028869.

6.1.1 Residue Profile

Nature of the Residue - Plants and Livestock: The nature of the residue in plants and livestock is adequately understood based on acceptable metabolism studies conducted on lactating goats, laying hens, wheat, peanut, tomato, and confined rotational crops. The submitted metabolism studies indicate that fluoxastrobin and its Z-isomer are the major residues in primary and rotated crops, and that fluoxastrobin, its Z-isomer and its phenoxy-hydroxypyrimidine metabolite are the major residues in goats and hens. Following multiple foliar applications, detectable combined residues of fluoxastrobin and its Z-isomer are likely to be present in/or tomato, pepper, and trimmed celery at up to 0.6 ppm. Residues on peanut hay are likely to be much higher (up to 17 ppm), but non-detectable (<0.01 ppm) in peanut nutmeats and tuberous and corm vegetables. The residue of concern in/on primary and rotated plant commodities for tolerance setting and risk assessment purposes are fluoxastrobin and its Z-isomer. The residues of concern for livestock for tolerance setting and risk assessment purposes are fluoxastrobin, its Z-isomer, and the phenoxy-hydroxypyrimidine. Based upon the results of the poultry metabolism study, HED concludes that the proposed uses fall under 40 CFR § 180.6(a)(3) for poultry commodities (*i.e.*, there is no reasonable expectation of finite residues in poultry commodities).

Residue Analytical Methods - Plants: Two LC/MS/MS methods for the enforcement of tolerances for residues of fluoxastrobin and its Z-isomer in plant commodities have been proposed: LC/MS/MS Method No. 00604, entitled "Analytical Determination of Residues of the Fungicide HEC 5725 In/On Cereals, Cereal Processed Products and Vegetables by HPLC-MS/MS" and LC/MS/MS Method No. 00649, entitled "Analytical Method 00649 for the Determination of Residues of HEC 5725 In/On Matrices of Plant Origin by HPLC-MS/MS."

Adequate method recovery and radiovalidation data were submitted and the reported /validated limit of quantification (LOQ) for combined residues of fluoxastrobin and its Z-isomer was 0.01 ppm in all the commodities tested. The proposed enforcement Method No. 00604 has been forwarded to ACB for petition method validation (PMV). Pending completion of the PMV and submission of additional information, the proposed enforcement Method No. 00604 is adequate for the enforcement of tolerances in conjunction with a conditional registration. Modification of the method as per the PMV should be made a condition of the registration of fluoxastrobin.

Residue Analytical Methods - Livestock: A LC/MS/MS method, Bayer Method No. 00691, Modification 001, is proposed for the enforcement of tolerances for combined residues of fluoxastrobin, its Z-isomer, and the phenoxy-hydroxypyrimidine metabolite in livestock commodities.

Adequate method validation and radiovalidation data have been submitted for Method No. 00691. The validated LOQ was 0.01 ppm for each analyte in all cattle matrices except cream, and 0.02 ppm for each analyte in cream. The reported LOD was 0.0025 ppm for each analyte in all matrices. Pending submission of additional information and a modified method, the analytical method data are classified as scientifically acceptable. The method has been forwarded to ACB for PMV. Modification of the method as per the PMV should be made a condition of the registration for fluoxastrobin

Multiresidue Methods: Based on the results of testing through FDA Multi-Residue Method Test guidelines in PAM Vol. I (dated 1/94), HED concludes the multiresidue methods are not adequate for enforcement of the proposed tolerances.

Crop Field Trial Data: The submitted crop field trial data (summarized in Table 6.1.1a) support the following tolerances for the combined residues of fluoxastrobin and it Z-isomer: peanut at 0.01 ppm; peanut hay at 20.0 ppm; fruiting vegetable, group 8, at 1.0 ppm; leaf petioles, subgroup 4B, at 4.0 ppm; and tuberous and corm vegetable, subgroup 1C, at 0.01 ppm.

Table 6.1.1a. Summary of Residues from the Crop Field Trials with Fluoxastrobin.

Crop Matrix	Total Applic. Rate (lb ai/A)	PHI[1] (days)	Combined Residues of Fluoxastrobin and its Z-isomer (ppm)						
			n[2]	Min.	Max.	HAFT[3]	Median	Mean	Std. Dev.[4]
Leaf Petioles Subgroup 4B (proposed use = 0.72 lb ai/A total application rate, 3-day PHI)									
Celery, untrimmed	0.71-0.85	3-4	16	0.641	3.26	3.1	2.23	2.09	0.82
Celery, trimmed	0.71-0.85	3-4	14	0.017	0.465	0.407	0.198	0.201	0.155
Fruiting Vegetable Group 8 (proposed use = 0.72 lb ai/A total application rate, 3-day PHI)									
Pepper (4 lb/gal FlC)	0.71-0.75	2-4	18	0.0447	0.535	0.482	0.119	0.185	0.151
Pepper (50% WP)	0.72-0.73	3	6	0.0985	0.376	0.375	0.156	0.214	0.126
Tomato (4 lb/gal FlC)	0.71-0.73	2-4	24	0.0639	0.636	0.455	0.188	0.203	0.119
Tomato (50% WP)	0.72-0.74	3	6	0.0253	0.233	0.215	0.126	0.125	0.082
Peanut (proposed use = 0.72 lb ai/A total application rate, 14-day PHI)									
Peanut, hay	0.72-0.74	13-15	24	1.28	16.86	14.56	4.33	5.29	4
Peanut, nutmeat	0.72-0.74	13-15	24	<0.01	<0.01	<0.01	0.005	0.005	0
Tuberous and Corm Vegetable Subgroup 1C (proposed use = 0.72 lb ai/A total application rate, 7-day PHI)									
Potato, tubers (4 lb/gal FlC)	0.70-0.74	6-8	54	<0.01	0.0104	0.01	0.005	0.005	0.001
Potato, tubers (50% WP)	0.71-0.72	6-7	6	<0.01	0.0135	0.01	0.005	0.007	0.0034

[1] PBI = plant back interval.
[2] n = number of samples.
[3] HAFT = highest average field trial residue.
[4] Std. Dev. = standard deviation.

Conclusions. Provided the petitioner submits additional information pertaining to a summary of the weather conditions for the growing season for each trial, stating whether conditions were normal or whether any unusual conditions were observed, and supporting information and confirmatory raw data to support the storage stability study, the submitted field trial residue data are adequate to satisfy data requirements.

Processed Food/Feed: The processing data indicate that combined residues of fluoxastrobin and its Z-isomer concentrate 8.0X in peanut refined oil, 1.3X in potato wet peel, and 2.4X in tomato paste. Because the calculated processing factor for peanut refined oil exceed the theoretical factor, the theoretical processing factor, 2.8X, will be used to determine the need for tolerances for peanut oil. Based on a processing factor of 2.8X for refined peanut oil and a HAFT residue of

0.01 ppm for peanut, the expected residues in peanut refined oil following treatment at 1X would be 0.03 ppm. Because the residues are greater than the proposed tolerance of 0.01 ppm for peanut nutmeat, a tolerance for residues in peanut refined oil is needed; a tolerance for residues of fluoxastrobin and its Z-isomer at 0.03 ppm in/on refined peanut oil is appropriate.

Based on a processing factor of 1.3X for potato wet peel and a HAFT residue of 0.01 ppm for potato, the expected residues in potato wet peel following treatment at 1x would be 0.013 ppm. Because the expected residues do not significantly exceed the proposed tolerance of 0.01 ppm for potato (tuberous and corm vegetable), a tolerance for residues in/on potato wet peel is not needed.

Based on a processing factor of 2.4X for tomato paste and a HAFT residue of 0.455 ppm for tomato, the expected residues in tomato paste following treatment at 1x would be 1.09 ppm. Because the residues are greater than the proposed tolerance of 1.0 ppm for tomato, a tolerance for residues in/on tomato paste is needed; a tolerance for residues of fluoxastrobin and its Z-isomer at 1.5 ppm in/on tomato paste is appropriate.

Field Accumulation in Rotational Crops:

Limited rotational crop study: Bayer CropScience has submitted a limited field rotational crop study on the representative crops mustard greens (leafy vegetable), turnips (root vegetable), and wheat (cereal grain).

At the 1-month PBI, combined residues of fluoxastrobin and its Z-isomer were below the method LOQ (<0.01 ppm) in mustard greens and turnip tops and roots, <0.01-0.0658 ppm in wheat grain, 0.0117-0.1140 ppm in wheat forage, 0.0305-0.1210 ppm in wheat hay, and 0.0117-0.0551 ppm in wheat straw.

At the 4-month PBI, combined residues of fluoxastrobin and its Z-isomer were below the method LOQ (<0.01 ppm) in wheat grain, <0.01-0.0829 ppm in wheat forage, <0.01-0.0522 ppm in wheat hay, and <0.01-0.0218 ppm in wheat straw.

At the 8-month PBI, combined residues of fluoxastrobin and its Z-isomer were below the method LOQ (<0.01 ppm) in wheat grain, <0.01-0.0120 ppm in wheat forage, <0.01-0.0105 ppm in wheat hay, and <0.01-0.0105 ppm in wheat straw. Because combined residues of fluoxastrobin and its Z-isomer were below the method LOQ (<0.01 ppm) in all samples of rotated mustard greens and turnip tops and roots from the 1-month PBI, samples of these commodities from the 4-, 8-, and 12-month PBIs were not analyzed. Similarly, because combined residues of fluoxastrobin and its Z-isomer were at or below the method LOQ (≤0.01 ppm) in all samples of rotated wheat commodities from the 8-month PBI, samples of rotated wheat commodities from the 12-month PBI were not analyzed.

Conclusions. Provided the petitioner submits the information summarized below, the limited field rotational crop residue data are classified as scientifically acceptable. For each rotational crop trial from which samples were analyzed, the petitioner must provide soil characteristics data as well as a summary of the weather conditions for the growing season, stating whether conditions were normal or whether any unusual conditions were observed. In addition, supporting information and confirmatory raw data to support the storage stability study must be

submitted.

Extensive field rotational crop studies: Based on the results of the limited rotational crop study, the petitioner conducted extensive field rotational crop studies reflecting a 1-month plant back interval on alfalfa, cereal grains, cotton, grass, and legume vegetables. A summary of the results of these studies is presented in Table 6.1.1b.

Table 6.1.1b. Summary of Residues from the Extensive Field Rotational Crop Trials with Fluoxastrobin.

Rotated Crop Matrix	Total Applic. Rate (lb ai/A)	PBI[1] (days)	Combined Residues of Fluoxastrobin and its Z-isomer (ppm)						
			n[2]	Min.	Max.	HAFT[3]	Median	Mean	Std. Dev.[4]
Alfalfa									
Alfalfa, forage	0.71-0.74	26-32	24	<0.01	0.034	0.032	0.005	0.008	0.008
Alfalfa, hay	0.71-0.74	26-32	24	<0.01	0.055	0.053	0.005	0.012	0.016
Cereal Grain, Crop Group 15									
Corn, K+CWHR	0.71-0.74	27-31	18	<0.01	0.016	0.013	0.005	0.006	0.003
Corn, grain	0.71-0.72	27-31	30	<0.01	<0.01	<0.01	0.005	0.005	0
Rice, grain	0.71-0.75	27-37	23	<0.01	<0.01	<0.01	0.005	0.005	0
Sorghum, grain	0.71-0.73	28-39	18	<0.01	<0.01	<0.01	0.005	0.005	0
Wheat, grain	0.54; 0.68-0.73	27-34	30	<0.01	<0.01	<0.01	0.005	0.005	0
Forage, Fodder, and Straw of Cereal Grain, Crop Group 16									
Corn, forage	0.71-0.74	27-31	38	<0.01	0.038	0.036	0.005	0.008	0.007
Corn, stover	0.71-0.74	27-31	38	<0.01	0.094	0.093	0.009	0.015	0.02
Rice, straw	0.71-0.75	27-37	24	<0.01	<0.01	<0.01	0.005	0.005	0.001
Sorghum, forage	0.71-0.73	28-39	18	<0.01	<0.01	<0.01	0.005	0.005	0.001
Sorghum, stover	0.71-0.73	28-39	18	<0.01	0.013	0.012	0.005	0.006	0.002
Wheat, forage	0.54; 0.68-0.73	27-34	30	<0.01	0.084	0.083	0.01	0.017	0.019
Wheat, hay	0.54; 0.68-0.73	27-34	30	<0.01	0.078	0.069	0.02	0.023	0.018
Wheat, straw	0.54; 0.68-0.73	27-34	30	<0.01	0.063	0.061	0.02	0.024	0.018
Cotton									
Cottonseed	0.67-0.73	27-47	24	<0.01	<0.01	<0.01	0.005	0.005	0
Cotton gin byproducts	0.67-0.73	28-31	12	<0.01	0.012	0.011	0.005	0.006	0.002
Grass, Crop Group 17									
Grass, forage	0.71-0.76	26-31	24	<0.01	0.066	0.063	0.014	0.017	0.016
Grass, hay	0.71-0.76	26-31	24	<0.01	0.328	0.322	0.015	0.046	0.087
Legume Vegetable, Crop Group 6									
Succulent edible-podded beans	0.72-0.74	28-32	12	<0.01	<0.01	<0.01	0.005	0.005	0
Succulent shelled beans	0.72-0.73	28-30	12	<0.01	<0.01	<0.01	0.007	0.007	0
Dried shelled beans	0.72-0.73	28-31	18	<0.01	<0.01	<0.01	0.005	0.005	0

Table 6.1.1b. Summary of Residues from the Extensive Field Rotational Crop Trials with Fluoxastrobin.									
Rotated Crop Matrix	Total Applic. Rate (lb ai/A)	PBI[1] (days)	Combined Residues of Fluoxastrobin and its Z-isomer (ppm)						
			n[2]	Min.	Max.	HAFT[3]	Median	Mean	Std. Dev.[4]
Succulent edible-podded peas	0.72-0.75	28	6	<0.01	<0.01	<0.01	0.007	0.007	0
Succulent shelled peas	0.72-0.74	26-30	12	<0.01	<0.01	<0.01	0.005	0.005	0
Dried shelled pea	0.70-0.73	27-31	10	<0.01	<0.01	<0.01	0.005	0.005	0
Soybean seed	0.71-0.72	28-33	30	<0.01	<0.01	<0.01	0.005	0.005	0
Foliage of Legume Vegetable, Crop Group 7									
Cowpea, forage	0.71-0.72	29-30	6	<0.01	0.03	0.03	0.006	0.013	0.012
Cowpea, hay	0.71-0.72	29-30	6	<0.01	<0.01	<0.01	0.008	0.008	0
Field pea, forage	0.72-0.73	28-31	6	<0.01	<0.01	<0.01	0.005	0.005	0
Field pea, hay	0.72-0.73	28-31	6	<0.01	<0.01	<0.01	0.005	0.005	0
Soybean, forage	0.71-0.72	28-33	30	<0.01	0.046	0.045	0.005	0.009	0.01
Soybean, hay	0.71-0.72	28-33	30	<0.01	0.029	0.026	0.009	0.013	0.008

[1] PBI = plant back interval.
[2] n = number of samples.
[3] HAFT = highest average field trial residue.
[4] Std. Dev. = standard deviation.

Conclusions. Provided the information below is submitted, the submitted extensive field rotational crop residue data are adequate to satisfy data requirements. For each rotational crop trial, the petitioner must provide soil characteristics data as well as a summary of the weather conditions for the growing season, stating whether conditions were normal or whether any unusual conditions were observed. The petitioner must also provide an explanation for grass forage and hay samples from the Stilwell, KS trial which appear to have been harvested over one year (410-481 days) following planting of the grass crop.

The petitioner has proposed the following rotational crop restrictions: 0-day plant back interval for any crop listed on the label; 30-day plant back interval for root and tuber vegetables (*e.g.*, carrot, potato, radish, sugarbeet, turnip), bulb vegetables (*e.g.*, onion and garlic), leafy vegetables (*e.g.*, celery, lettuce, spinach), *Brassica* vegetables (*e.g.*, broccoli, cauliflower, cabbage, mustard greens), alfalfa, cotton, legume vegetables (dry and succulent peas and beans), cereal grains, and forage grasses; 365-day plant back interval for all other crops.

The limited field rotational crop data, which indicated no quantifiable residues of fluoxastrobin and its Z-isomer in mustard greens and turnip roots and tops at a 30-day PBI, are adequate to support the proposed 30-day PBI for root and tuber vegetables, bulb vegetables, leafy vegetables, and *Brassica* vegetables, pending submission of the required additional information. The extensive field rotational crop data are adequate to support the proposed 30-day PBI for alfalfa, cotton, cereal grains, forage grasses, and legume vegetables, pending submission of the required additional information. The extensive field rotational crop data indicate that the following tolerances for the combined residues of fluoxastrobin and its Z-isomer in/on rotated crops are appropriate: alfalfa forage at 0.05 ppm; alfalfa hay at 0.10 ppm; cotton gin byproducts at 0.02

ppm; forage, fodder and straw of cereal grain, group 16, at 0.10 ppm; grass forage at 0.10 ppm; grass hay at 0.50 ppm; and foliage of legume vegetable, group 7, at 0.05 ppm. The data indicate that a tolerance for residues in/on legume vegetables, crop group 6, is not needed.

Waiver Requests:

Rotated Corn: In support of waiver requests for data pertaining to processing studies for rotated corn, cotton, rice, soybean, and wheat, Bayer CropScience has submitted studies depicting the magnitude of the residues in rotated corn grain, cotton seed, rice grain, soybean, and wheat grain following application to the soil at an exaggerated rate. In the study, the crops were planted approximately 34 days after a single spray application made to bare soil at 3.6 lb ai/A; the application rate corresponded to 5x the proposed seasonal application rate. Corn grain, undelinted cottonseed, rice grain, soybean seed, and wheat grain were harvested at maturity, and because application was made to bare soil and thus prior to the formation of grain heads, aspirated grain fractions were not generated or collected. Combined residues of fluoxastrobin and its Z-isomer were nondetectable (<0.003 ppm) in rotated corn grain, cotton seed, rice grain, soybean, and wheat grain; therefore, the grain or seed samples were not further processed.

Conclusions: Provided the petitioner submits the information summarized below, the data from the exaggerated rate corn, cotton, rice, soybean and wheat rotational crop field trials are classified as scientifically acceptable. The petitioner must provide soil characteristics data for the study.

Pending submission of the outstanding confirmatory data, HED concludes that waivers of data requirements pertaining to corn, cotton, rice, soybean, and wheat processed commodities are appropriate because combined residues of fluoxastrobin and its Z-isomer were nondetectable in rotated corn grain, undelinted cotton seed, rice grain, soybean seed, and wheat grain following soil treatment at an exaggerated rate (5x the proposed seasonal application rate). Additionally, HED concludes that a waiver of data requirements pertaining to aspirated grain fractions of corn, soybean and wheat is appropriate as fluoxastrobin will not be applied to wheat after the formation of the seed head.

Meat, Milk, Poultry, and Eggs: A cattle feeding study data indicate that tolerances are needed for secondary residues of fluoxastrobin in cattle, goat, horse, and sheep commodities. The maximum theoretical dietary burden of fluoxastrobin to beef cattle, dairy cattle, and swine are 6.72 ppm, 12.32 ppm, and 0.009 ppm, respectively. The dosing levels are equivalent to 0.8x, 4.2x, and 13.5x the maximum theoretical dietary burden to beef cattle, 0.45x, 2.3x, and 7.4x the maximum theoretical dietary burden to dairy cattle, and 620x, 3200x, and 10000x the maximum theoretical dietary burden to swine. Combined residues of fluoxastrobin, Z-isomer, and phenoxy-hydroxypyrimidine were generally found to have a linear relationship with the dosing level in liver, muscle, fat, and kidney. Combined residues of fluoxastrobin, Z-isomer, and phenoxy-hydroxypyrimidine in milk appeared to plateau by the second week of dosing (study day 12). The maximum combined residues of fluoxastrobin, its Z-isomer, and phenoxy-hydroxypyrimidine in milk and tissues are listed in the Table 6.1.1c below.

Matrix	Table 6.1.1c Maximum Combined Residues of Fluoxastrobin, its Z-isomer, and Phenoxy-hydroxypyrimidine by Feeding Level (ppm).		
	5.55 ppm (0.45x)	28.49 ppm (2.3x)	90.67 ppm (7.4x)
Milk	<0.02 [1]	<0.02 [1]	<0.0427
Skim milk	--	--	<0.02 [1]
Cream	--	--	<0.2009 [1]
Liver	<0.0233	0.1037	0.2666
Kidney	0.0527	0.2097	0.599
Muscle	<0.02	0.0514	0.0845
Fat	<0.0235	0.1578	0.2361

[1] Samples from study day 28 were the only samples analyzed.

Tolerances for residues of fluoxastrobin, its Z-isomer, and the phenoxy-hydroxypyrimidine metabolite (HEC 7154) should be set at the combined LOQs (0.02 ppm) for residues in milk, and at 0.10 ppm, 0.05 ppm, and 0.10 ppm for residues in fat, meat, and meat byproducts, respectively, of cattle, goats, horses, and sheep. The available data indicate that a tolerance is needed for residues in milk fat; based on the maximum residues in milk (0.02 ppm) and an assumed 25X concentration factor, a tolerance of 0.5 ppm would be appropriate.

Based on residue levels in milk and tissues from the lowest dosing level in the cattle feeding study, and the fact that the lowest dosing level represents 620X the maximum theoretical dietary burden to swine, HED concludes that tolerances for residues in hog commodities are not needed.

International Harmonization

There are currently no Mexican, Canadian, nor CODEX maximum residue limits established for fluoxastrobin. Thus, harmonization is not an issue for this petition.

6.1.2 Chronic Dietary Exposure and Risk

Reference: *Fluoxastrobin: Chronic Dietary Exposure Assessments for the Section 3 Use on Peanuts, Tuberous and Corm Vegetables Subgroup, Leaf Petiole Vegetables Subgroup, Fruiting Vegetables Group, and Seed Treatment of Peanut and Potato*. William Wassell. 11/XX/04. D290107, PC Code 028869.

Dietary risk incorporates both exposure and toxicity data for a given pesticide. Although there is potential for acute and chronic dietary exposure, the toxicological database for fluoxastrobin identified no adverse effect attributable to a single dose, therefore an acute dietary exposure assessment was not performed. Furthermore, fluoxastrobin was determined unlikely to be carcinogenic to humans, and therefore a cancer dietary assessment was not conducted. Subsequently, only a Tier 1 chronic dietary exposure assessment was conducted, which assumed tolerance level residues and 100% crop treated.

The fluoxastrobin chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.0) and the Lifeline™ model (Version 2.0). Both models incorporate consumption data from

USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days.

For DEEM-FCID™, Version 2.0, foods "as consumed" (*e.g.*, apple pie) are linked to EPA-defined food commodities (*e.g.* apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, adults 20-49 years old, females 13-49 years old, and adults 50+ years old. For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (*e.g.*, orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For Lifeline™, a recipe file is used to relate raw agricultural commodities (RACs) to foods "as-eaten." Lifeline™ converts the RAC residues into food residues by randomly selecting a RAC residue value from the "user defined" residue distribution (created from the residue, percent crop treated, and processing factors data), and calculating a net residue for that food based on the ingredients' mass contribution to that food item. For example, 'apple pie' will have a residue distribution based on the residues provided for apples (adjusted by the appropriate processing factors and percent crop treated), as well as the residues for each of the other ingredients in the apple pie recipe for which there may be tolerances. Lifeline™ calculates dietary exposure from 'apple pie' based on the amount eaten, and the residue drawn from the 'apple pie' residue distribution for that eating occasion. Lifeline™ then models the individual's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ groups CSFII diaries based on the respondents' age and the season during which the food diary was recorded. Dietary exposure estimates were reported for the same population subgroups as reported for DEEM-FCID™, in order to facilitate comparison.

The results of both the DEEM-FCID™ and Lifeline™ dietary exposure assessments are then used to calculate dietary risk, which is expressed as a percentage of a maximum acceptable dose (*i.e.*, the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the Reference Dose (RfD) divided by the special FQPA Safety Factor. For non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD. The results of the fluoxastrobin dietary risk assessment are presented below in Table 6.1.2.

Table 6.1.2. Results of Chronic Dietary Exposure and Risk Estimates for Fluoxastrobin.					
Population Subgroup	**cPAD, mg/kg/day**	**DEEM-FCID**		**Lifeline**	
		Exposure, mg/kg/day	**% cPAD**	**Exposure, mg/kg/day**	**% cPAD**
U.S. Population	0.015	0.0015	10%	0.0014	9.5%
All infants (< 1 yr)	0.015	0.00091	6.0%	0.00085	5.6%
Children 1-2 yrs	0.015	**0.0037**	25%	**0.0033**	22%
Children 3-5 yrs	0.015	0.0031	20%	0.0027	18%
Children 6-12 yrs	0.015	0.0021	14%	0.0018	12%
Youth 13-19 yrs	0.015	0.0014	9.2%	0.0013	8.4%
Adults 20-49 yrs	0.015	0.0013	8.7%	0.0013	8.6%
Adults 50+ yrs	0.015	0.0013	8.7%	0.0013	8.5%
Females 13-49 yrs	0.015	0.0012	8.3%	0.0014	9.6%

* cPAD = chronic PAD, is reported to 2 significant figures, and %cPAD = (Exposure ÷ cPAD) x 100%.
**The values for the population with the highest risk for each type of risk assessment are bolded.

6.2 Water Exposure/Risk Pathway

Reference: *Revised Drinking Water Assessment for the Section 3 Registration of the New Chemical Fluoxastrobin (HEC5725) for Uses on Peanut , Potato and Tuber Vegetables, Leaf Petioles subgroup, Fruiting Vegetables, and Turf; and Seed Treatments for Potato, Peanut and Turf*. Thuy Nguyen. 11/23/2004. D289104 S3NC, PC Code 028869.

The proposed use of fluoxastrobin as a foliar spray on agricultural crops could potentially lead to fluoxastrobin in drinking water. Even though foliar interception may reduce the amount of fluoxastrobin available for runoff, it is believed that this chemical could reach surface waters through spray drift, penetration of the canopy to the soil surface at application, and foliar washoff followed by runoff.

Based on laboratory studies with fluoxastrobin technical (which contains mainly fluoxastrobin [*i.e.*, the E-isomer], but also the Z-isomer), fluoxastrobin and its Z-isomer could persist for several months to several years in soil (depending on the soil type); and under field conditions, fluoxastrobin and its Z-isomer were shown to persist for over a year, although it did not seem to leach underground. Also, there were two soil metabolites (HEC5725-E-des-chlorophenyl [HEC 7155] and HEC5725-carboxylic acid [HEC 7180]) and one water metabolite (HEC5725-oxazepine) identified.

However, despite the potential of fluoxastrobin technical to persist in soil, it has low mobility (relatively high Koc-ads values [420-1580 mL/g]), and degrades via aqueous photolysis; furthermore, only one metabolite was detected in field studies (the soil metabolite HEC5725-E-des-chlorophenyl), and it was detected at a low percentage of the application rate. Subsequently, it is very unlikely that any degradate/metabolite of fluoxastrobin will persist in the environment for any extended period of time to reach surface water and/or leach into groundwater at any considerable amount. Therefore, residues of fluoxastrobin and its Z-isomer were considered in

the drinking water assessment.

Even though there are no monitoring data for fluoxastrobin because it's a new chemical, there is a potential for residues of fluoxastrobin and its Z-isomer in drinking water. Therefore, the Environmental Fate and Effects Division (EFED) provided Tier 1 and 2 EDWCs for use in drinking water assessments when fluoxastrobin is used according to proposed labeling for HEC 480 SC Fungicide. These estimates were generated using PRZM/EXAMS (PRZM 3.12 beta and EXAMS 2.98.04) for surface water, and SCIGROW (version 2.3) for groundwater. Both are deterministic models that use conservative assumptions of the chemical application and dissipation processes, and the climatic and hydrology conditions of the areas for the intended uses.

Surface Water
The Tier 2 surface water EDWC's presented in Table 6.2 are based on the Pennsylvania (PA) turf scenario. The PA turf scenario estimated the highest EDWCs amongst all scenarios for the proposed crops, mostly due to turf's high maximum annual application rate (4 ground applications of 0.55 lbs ai/A per application with a 21-day interval), and its high percent cropped area (PCA) factor compared to those of other crops included in the proposed labeling of HEC 480 SC Fungicide. Since surface drinking water estimation is based on an Index Reservoir watershed (a 172 hectare field drains into a 52,000 m^2 reservoir), PCA factor adjustment is needed to account for the percent of a watershed that is planted with specific crops. Currently, EFED uses a PCA value of 67% for potato, 56% for tomato, or 38% for peanuts. Since turf is a non-agricultural use, EFED uses a default value of 87%. The acute EDWC of 28 ppb represents the upper 1-in-10 year peak concentration and the chronic EDWC of 14 ppb represents the average of yearly means.

Groundwater
Unlike the Tier 2 pesticide concentration estimates for surface water, groundwater estimates by EFED using SCIGROW are not dependent on specific geographic locations or application methods, but instead, depend only on the pesticide use rate, the chemical persistency in soil, and its ability to leach. Therefore only the highest application rate was used as input for SCIGROW, which is the turf use rate. The Tier 1 groundwater EDWC from SCIGROW is < 1 ppb.

Table 6.2. Summary of Estimated Surface Water and Groundwater Concentrations

Exposure Duration	**Fluoxastrobin and its Z-isomer**	
	Surface Water Conc., ppb [a]	**Ground Water Conc., ppb [b]**
Acute (peak)	28	<1
Chronic (average of yearly means)	14	

[a] From the Tier 2 PRZM-EXAMS - Index Reservoir model. Input parameters are based on the turf use (4 ground applications of 0.55 lbs ai/A per application with a 21-day interval), which generates the highest EDWCs
[b] From the Tier 1 SCIGROW model, also based on turf use (4 ground applications of 0.55 lbs ai/A per application with a 21-day interval)

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Reference: *Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Fluoxastrobin on Peanuts, Leafy Vegetables, Fruiting Vegetables, Potatoes and Tuber Vegetables and Turf*. Barry O'Keefe. 12/9/04. DP Bar Code D289109, PC Code 028869.

There is potential for exposure to homeowners in residential settings from entering areas previously treated with fluoxastrobin, such as lawns where children might play, or golf courses that could lead to exposures for adults. As a result, risk assessments have been completed for residential postapplication scenarios. The registrant has indicated that turf applications are intended to be made by professional pest control operators (PCOs) only (communicated by Greg Mattern of Bayer CropScience via email to Sarah Winfield on 5/25/04). Therefore, residential handler exposure was not evaluated. The label should explicitly state that HEC 480 SC Fungicide is not intended for homeowner use (currently, the label does not indicate this restriction).

The best data and methodology currently available were used in the fluoxastrobin residential assessment. Since chemical-specific data were unavailable, the Agency used the current approaches for residential assessment, many of which include recent upgrades to the SOPs. For example, for the toddler hand-to-mouth calculations a 5% transferability factor was applied to calculate residue levels appropriate for this exposure pathway. Overall, the Agency believes that the calculated risks represent screening level estimates. Estimates are thought to be conservative, even when measures of central tendency (*e.g.*, most transfer coefficients) are used, because values that would be considered to be in the lower percentile aspect of any input parameter have not been used in the calculations. Maximum application rates have been used for all scenarios. Also, these risk estimates assume no dissipation of residues after day zero, and do not account for the periodic growth and cutting of the grass. Actual residues should be considerably lower, and intermediate-term exposures are therefore unlikely. Further, because a short-term dermal toxicity endpoint was not identified, the intermediate-term endpoint was used for all dermal risk estimates, even though the residential exposure duration is believed to be mostly short-term based on the use pattern.

6.3.1 Home Uses

Proposed use of fluoxastrobin on turf may result in individuals of varying ages potentially being exposed from activities in areas that have been treated. Potential routes of exposure include dermal (adults and children) and incidental oral ingestion (toddlers only). While it is assumed that most residential use will result in short-term (1 to 30 days) postapplication exposures, it is also believed that intermediate-term exposures (> 30 days to 180 days) are possible, albeit unlikely (see discussion above).

The highest use rate was chosen for the assessment (*i.e.* 0.55 lb ai/A). A summary of the estimated exposures and risks, along with the algorithms used for each turf exposure scenario are presented below in Tables 6.3.1a through 6.3.1d.

Table 6.3.1a. Dermal Exposure and Risk for Adults and Children from Treated Lawns (Intermediate-Term)

Subgroup exposed	Activity	Application Rate (lb ai/A)	Fraction of ai Available	Turf Transferrable Residue at Day "0" (µg/cm^2)[1]	Dermal Transfer Coefficient	Exposure Time (hrs/day)	Dermal Absorption Factor	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Intermediate-Term MOE[3]
Adult	Mowing turf	0.55	0.05	0.308	500	2	2.3%	70	0.0001	30000
Adult	Golf Course Reentry	0.55	0.05	0.308	500	4	2.3%	70	0.0002	15000
Adult	High Contact	0.55	0.05	0.308	7300	2	2.3%	70	0.00148	2000
Children	High Contact	0.55	0.05	0.308	2600	2	2.3%	15	0.00246	1200

[1] Turf Transferrable Residue (µg/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 µg/lb x 2.47E-8 A/cm^2
[2] Daily Dose = (Turf Transferrable Residue x Absorption Factor x 1E-3 mg/µg x Dermal Transfer Coefficient x Dermal Absorption Factor x Exposure Time)/Body weight
[3] Intermediate-Term Dermal MOE = Intermediate-Term Oral NOAEL (3 mg/kg/day) /Daily Dose

Table 6.3.1b. Oral Hand-to-mouth Exposure and Risk for Children from Treated Lawns (Short- and Intermediate-Term)

Exposure Duration	Application Rate (lb ai/A)	Fraction of ai Available	Turf Transferrable Residue at Day	Exposure Time (hrs/day)	Extraction by saliva	Hand Surface Area (cm^2/event)	Frequency (events/ hr)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	MOE[3]
Short-Term	0.55	0.05	0.308	2	0.5	20	20	15	0.00821	365
Intermediate-Term	0.55	0.05	0.308	2	0.5	20	9.5	15	0.0039	770

[1]Turf Transferrable Residue (µg/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 µg/lb x 2.47E-8 A/cm^2
[2] Daily Dose = (Turf Transferrable Residue (µg/cm^2) x Extraction by Saliva x Hand Surface Area (cm^2/event) x Frequency (events/hr) x 1E-3 mg/µg x ET (hrs/day)] / [Body Weight (kg)]
[3] MOE = Oral NOAEL (3 mg/kg/day) /Daily Dose

Table 6.3.1c. Oral Object-to-mouth (Turfgrass) Exposure and Risk for Children from Treated Lawns (Short- and Intermediate-Term)

Application Rate (lb ai/A)	Fraction of ai Available	Grass Residue at Day "0" (µg/cm^2)[1]	Surface Area Mouthed (cm^2/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short-/Intermediate-Term MOE[3]
0.55	0.2	1.23	25	15	0.00205	1500

[1]Grass Residue (µg/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 µg/lb x 2.47E-8 A/cm^2
[2] Daily Dose = [Grass residue (µg/cm^2) x Surface Area Mouthed (cm^2/day) x 1E-3 mg/µg] / [Body Weight (kg)]
[3] Short- / Intermediate-Term Oral MOE = Short- / Intermediate-Term Oral NOAEL (3 mg/kg/day) /Daily Dose

Table 6.3.1d. Exposure and Risk for Children from Ingestion of Soil from Treated Lawns (Short- and Intermediate-Term)

Application Rate (lb ai/A)	Fraction of ai Available	Soil Residue at Day "0" (µg/g)[1]	Ingestion Rate (mg/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Short- / Intermediate-Term MOE[3]
0.55	1	4.13	100	15	0.000028	110000

[1] Soil residue (µg/g) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 µg/lb x 2.47E-8 A/cm^2 x 0.67 cm^3/g soil]
[2] Daily Dose = [Soil residue (µg/g) x Ingestion rate (mg/day) x 1E-6 g/µg] / [Body Weight (kg)]
[3] MOE = Oral NOAEL (3 mg/kg/day) /Daily Dose

The MOEs for residential postapplication exposure to fluoxastrobin are all above 100, and therefore, do not exceed HED's level of concern.

The Agency combines risks resulting from exposures to individual chemicals when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population. Typically, the Agency only combines exposures from different activities when risks from the individual activities are not already a concern. Because the toxicity endpoint is the same for both dermal and incidental oral exposures, the total combined risk (*i.e.*, total MOE) for children is calculated by adding the daily doses from all relevant exposure routes and durations and activities and comparing this total to the common toxicity endpoint NOAEL. This is a screening level, conservative approach. The resulting risks, and are presented in Table 6.3.1e.

Table 6.3.1e. Children's Residential Combined Risk from Treated Turf

Scenario	Duration	Route	Daily Dose (mg/kg/day)	MOE	Total MOE[1]
High Contact Activities (HCA)	Intermediate-Term	Dermal	0.00246	1200	235
Hand-to-Mouth (HTM)	Short-Term	Oral	0.00821	365	
Object-to-Mouth (OTM)	Short-/Intermediate-Term	Oral	0.00205	1500	
Soil Ingestion (SI)	Short-/Intermediate-Term	Oral	0.000028	110000	

[1] Total MOE = $1 / (1/MOE_{HCA} + 1/MOE_{HTM} + 1/MOE_{OTM} + 1/MOE_{SI})$

The total MOE for children's combined risk from activities on treated turf is larger than 100, and therefore, does not exceed HED's level of concern.

6.3.2 Recreational Uses

Recreational exposures to turf are expected to be similar to, or in many cases less than, those evaluated in section 6.3.1 Home Uses; therefore, a separate recreational exposure assessment was not included. Additionally, golf courses exposures and risks were already assessed.

6.3.3 Other (Spray Drift, *etc.*)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial applications, but, to a lesser extent, could also be a potential source of exposure from ground application methods. As indicated in this assessment, fluoxastrobin is directly applied to residential turf and does not result in exposures of concern. Based on this assessment, HED believes that it is unlikely that there is a higher potential for risk of exposure to spray drift from agricultural uses of this chemical.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (*e.g.*, a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. For fluoxastrobin, potential exposures from food, drinking water and residential scenarios were considered, and aggregated. Although acute, short- and intermediate-term and chronic exposures may occur, acute exposures were not considered because an appropriate quantitative estimate of hazard (*i.e.*, an adverse effect attributable to a single dose) was not identified from the toxicological database to which an acute exposure estimate could be compared. Furthermore, fluoxastrobin is considered not likely to be carcinogenic to humans, and therefore, an aggregate cancer assessment was not conducted.

In order to determine if aggregate risks are of concern, HED calculates drinking water levels of comparison, or DWLOCs. The DWLOC is the maximum amount of a pesticide in drinking water that would be acceptable in light of combined exposure from the food and residential pathways. The calculated DWLOCs are then compared to the EDWCs provided by EFED. EDWCs can be based on water monitoring data or model-derived: because fluoxastrobin is a new ai, water monitoring data are not available; therefore, model estimates have been used to estimate fluoxastrobin residues in drinking water. If the model-derived EDWCs exceed the DWLOCs for surface water or groundwater, there may be a concern for dietary exposure to residues in drinking water, and refinement or mitigation may be required.

7.1 Short- and Intermediate-Term Aggregate Risk

There is potential short- and intermediate-term exposure to fluoxastrobin via the dietary (which is considered background exposure) and residential (which is considered primary) pathways. For adults, these pathways lead to exposure via the oral (background) and dermal (primary) routes. For children these pathways lead to exposure via the oral (background), and incidental oral and dermal (primary) routes.

As discussed above, DWLOCs were calculated to determine if aggregate short- and intermediate-term risks are of concern. The DWLOC calculation incorporates a quantitative hazard estimate. For adults, the DWLOC incorporates the intermediate-term dermal hazard estimate, which is based on body weight gain reduction, decreased food efficiency, liver toxicity (cholestasis) and kidney toxicity observed in the subchronic (90-day) toxicity study in the dog; and the exposure estimate for the intermediate-term dermal scenario is also considered in the DWLOC for adults. For children, the DWLOC incorporates the incidental oral and dermal quantitative hazard estimate for short- and intermediate-term durations, which are all based on the same adverse effects used in the adult DWLOC calculations; therefore, exposure estimates for short- and intermediate-term durations via the incidental oral and dermal routes are combined in the DWLOC calculation for children. The DWLOCs calculated for fluoxastrobin are screening level risk estimates, because conservative assumptions were employed, and short- and intermediate-term exposure estimates were combined for children, which is a conservative measure.

The DWLOC calculations for adult males, adult females and children also incorporate dietary and residential exposure (as well as standard assumptions, such as body weights, per HED policy). The dietary exposure estimates incorporated into the DWLOCs are the Tier 1 chronic dietary exposure estimates from DEEM-FCID™ (as these are slightly higher for the most highly exposed subgroup). The population subgroup with the highest dietary exposure estimate that would represent adult males, adult females and children, were used to calculate the DWLOCs (see section 6.1.2). The residential exposure estimates incorporated into the DWLOCs are also the most conservative (highest) for each respective subgroup. For adult males and adult females, the postapplication dermal exposure to turf, high contact scenario was used, and for children, the combined dermal and incidental oral postapplication exposure to turf scenario was used (see section 6.3).

The DWLOCs were then compared to the conservative EDWCs provided by EFED (see section 6.2). As shown in Table 7.1, the chronic DWLOCs are greater than the EDWCs; thus, short- and intermediate-term aggregate risks do not trigger HED concern.

Table 7.1. Short- and Intermediate-Term Aggregate Risk and DWLOC Calculations										
Population	**NOAEL mg/kg/day**	**Target MOE[1]**	**Max Exposure[2] mg/kg/day**	**Average Food Exposure mg/kg/day**	**Residential Exposure[3] mg/kg/day**	**Aggregate MOE (food and residential)[4]**	**Max Water Exposure[5] mg/kg/day**	**Ground-water EDWC[6] (ppb)**	**Surface Water EDWC[6] (ppb)**	**Short- and Int.-Term DWLOC[7] (µg/L)**
Adult Male[8]	3	100	0.03	0.00153	0.00148	1000	0.026990	<1	28	940
Adult Female[8]	3	100	0.03	0.00124	0.00148	1100	0.027280	<1	28	820
Child[8]	3	100	0.03	0.00372	0.0127	180	0.013580	<1	28	140

[1] This is based on the conventional uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation).

[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE

[3] Residential Exposure = Dermal Exposure (high contact, postapplication turf, for adults); = Dermal Exposure+ Incidental Oral Exposure (postapplication, child)

[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]

[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)

[6] The crop producing the highest level was used, *i.e.*, turf.

[7] $\text{DWLOC}(\mu g/L) = \frac{[\text{maximum water exposure (mg/kg/day)} \times \text{body weight (kg)}]}{[\text{water consumption (L)} \times 10^{-3}\ \text{mg}/\mu g]}$ *Assumptions:* Body Weights: 70 kg adult male; 60 kg adult female; 10 kg child
Water Consumption: Child, one liter/day; Adults, 2 liters/day

[8] Dietary exposures for these populations are based on the following population subgroups: Adult Male- U.S. Population; Adult Female - Females 13-49 years; and Child - Children 1-2 years.

7.2 Long-Term (Chronic) Aggregate Risk

There is potential chronic exposure to fluoxastrobin via food and drinking water, *i.e.*, the dietary route. As discussed above, DWLOCs were calculated to determine if aggregate chronic risks are of concern.

DWLOC calculations incorporate a quantitative hazard estimate, which for the chronic dietary exposure scenario is the cPAD; the cPAD for fluoxastrobin is based on liver effects (hepatocytomegaly and cytoplasmic changes associated with increased serum liver alkaline phosphatase indicative of cholestasis) observed in the chronic toxicity study in the dog.

The chronic DWLOC calculations used the Tier 1 exposure estimates from DEEM-FCID™ for the food portion of aggregate exposure (as these are slightly higher for the most highly exposed subgroup), as well as standard assumptions (per HED policy). The DWLOCs were then compared to the conservative EDWCs provided by EFED (see section 6.2). As shown in Table 7.2, the chronic DWLOCs are much greater than the EDWCs; thus, chronic aggregate risks do not trigger HED concern.

Table 7.2. Aggregate Risk Assessment for Chronic (Non-Cancer) Exposure to Fluoxastrobin

Population Subgroup[1]	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[2]	Ground Water EDWC (ppb)[3]	Surface Water EDWC (ppb)[3]	Chronic DWLOC (ppb)[4]
U.S. Population	0.015	0.00153	0.01347	<1	14	470
All Infants (<1 year old)	0.015	0.0009	0.014095	<1	14	140
Children 1-2 years	0.015	0.00372	0.01128	<1	14	110
Children 3-5 years	0.015	0.00305	0.01195	<1	14	120
Children 6-12	0.015	0.00209	0.01291	<1	14	130
Youth 13-19	0.015	0.00138	0.01362	<1	14	410
Adults 20-49	0.015	0.0013	0.0137	<1	14	480
Females 13+	0.015	0.00124	0.01376	<1	14	410
Adults 50+ years	0.015	0.00125	0.01375	<1	14	480

[1] The U.S. Population as a whole, as well as subsets of the U.S. Population whose risk from chronic dietary exposure might be substantially different from the U.S. Population due to differences in diet and/or the quantitative hazard estimate that the dietary exposure estimate would be compared to. Body weights for the U.S. Population, Adults 20-49 and Adults 50+ were assumed to be 70 kg, for All Infants (<1 year old), Children 1-2, 3-5 and 6-12, 10 kg; and for Youth 13-19 and Females 13+, 60 kg.

[2] Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]

[3] Based on the highest proposed use rate, turf (0.55 lb ai/A/application, 4 applications/year, 21-day intervals)

[4] Chronic DWLOC(µg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fluoxastrobin and any other substances and fluoxastrobin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fluoxastrobin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Reference: *Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Fluoxastrobin on Peanuts, Leafy Vegetables, Fruiting Vegetables, Potatoes and Tuber Vegetables and Turf*. Barry O'Keefe. 12/9/04. DP Bar Code D289109, PC Code 028869.

There is potential for occupational handler exposure from the application of fluoxastrobin on both food and non-food use sites resulting from handling fluoxastrobin products (*i.e.*, mixer/loaders and applicators); and there is potential for occupational postapplication exposure resulting from entering areas previously treated with fluoxastrobin. As a result, risk assessments have been completed for occupational handler and postapplication scenarios. Non-dietary exposure and risk assessments were prepared for professional mixer/loader/applicators and reentry workers during use of fluoxastrobin on peanuts, potato and tuber vegetables, fruiting vegetables, leafy vegetables, and turf. Assessments were also prepared for workers during seed treatment use on peanuts, seed potatoes, and turf seed, and for postapplication activities following use on turf, including on golf courses and on residential turf.

9.1 Short-/Intermediate-Term Handler Risk

The proposed uses of fluoxastrobin include several occupational use patterns (see Table 2.1b). Several occupational handler (mixers/loaders/applicators) scenarios were identified for which exposure to fluoxastrobin is expected (See Table 9.1a - 9.1d). No chemical-specific handler exposure data were submitted, and therefore the following data and assumptions were used to assess the proposed uses involving handler exposure and risk.

For Turf & Field Crops: Includes peanut, leafy vegetables, fruiting vegetables, potato and tuber vegetables, and turf: It is the standard practice of HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft SOP# 7, dated 2/18/99). Therefore, surrogate data from the PHED were used to assess the field crop and turf handler exposure scenarios (scenarios #1 through #6).

For Seed Treatment of Peanut & Turf Seeds: In order to assess the handler exposure from the seed treatment of peanut and turf seeds (scenarios #7 through #12), HED used the Agency's seed treatment SOPs (standard operating procedures); *i.e.*, SOP for Seed Treatment, Guidance No. 14, May 1, 2003 and SOP for Volume of Seed Treated or Planted, Guidance No. 15, November 1, 2003. Handler exposure scenarios included loader/applicators, sewers, baggers, multiple activities (*i.e.*, loading/applying, sewing, and bagging), and seed planters.

For Seed Treatment of Potato Seed Pieces: The Agency has no data addressing the potential exposures of individuals using fluoxastrobin to treat potato seed pieces prior to and during planting (scenarios #13 through #19). Therefore, exposures were estimated using surrogate data from a study published in the scientific literature measuring handler exposure to the pesticide captan during potato seed treatment and planting; *i.e.*, Stevens, E.R. and J.E. Davis (1981) Potential Exposure of Workers During Seed Potato Treatment with Captan. Bull. Environm. Contam. Toxicol. 26, 681-688. Potential dermal and respiratory exposures of workers to captan dust were monitored during the preparation and planting of potato seed pieces. In order to adjust for technical problems with the study, the authors adjusted the estimates using information from PHED.

General Assumptions for risk calculations:

- Average body weight of an adult handler is 70 kg, because the toxicity endpoint effects identified by HED are not gender-specific.
- All analyses were completed using surrogate exposure data that were deemed to be acceptable for the scenario in question.
- Exposure factors used to calculate daily exposures to handlers are based on applicable data if available. If not available, values from a similar scenario are used.
- The Agency uses the maximum application rates allowed by labels in its risk assessments in order to evaluate what is legally possible based on the label.
- The average occupational workday is assumed to be 8 hours.
- It is anticipated that occupational fluoxastrobin exposures will generally occur in short- and intermediate-term durations. There are no chronic exposures (>180 days per year) expected.

Occupational handlers may be exposed by the dermal route and by the inhalation route during mixing, loading and application of fluoxastrobin for both short- and intermediate-term durations. However, a short-term dermal endpoint was not identified. For this reason, and because the short- and intermediate-term inhalation endpoints are the same, only intermediate-term risks were assessed for handlers. Intermediate-term risk estimates should cover short-term risks, as well. Further, because common toxicity endpoints were identified for both dermal and inhalation routes, a combined risk from both routes of exposure is assessed. Tables 9.1a through 9.1d below present results of the occupational handler exposure/risk assessment.

TURF AND FIELD CROPS:

Table 9.1a. Occupational Handler Exposure and Risk Estimates for Fluoxastrobin

Exposure Scenario (Unit exposure from PHED unless otherwise indicated)	Personal Protective Equipment[1]	Crop/Use Site	Application Rate (lb ai/A)	Amount Treated per day (acres)	Exposure Route	Unit Exposure (mg/lb ai)	Data Confidence	Daily Dose[2] (mg/kg/day)	MOE[3]	Combined MOE[4]
(1) M/L Liquids: Open mixing (groundboom)	long sleeves long pants no gloves **(gloves)**	Turf	0.55	40	Dermal	2.9 (0.023)	High	0.021 (1.66E-4)	140 (18,000)	140 (5,500)
					Inhalation	0.0012	High	3.77E-4	8,000	
		Peanuts, Leafy Vegetables, Fruiting Vegetables	0.18	80	Dermal	2.9 (0.023)	High	0.014 (1.09E-4)	220 (28,000)	220 (8,400)
					Inhalation	0.0012	High	2.47E-4	12,000	
		Potato/Tuber Vegetables	0.12	80	Dermal	2.9 (0.023)	High	9.15E-3 (7.3E-5)	330 (41,000)	320 (13,000)
					Inhalation	0.0012	High	1.65E-4	18,000	
(2) M/L Liquids: Open mixing (aerial, chemigation)	long sleeves long pants no gloves **(gloves)**	Turf	0.55	350	Dermal	2.9 (0.023)	High	0.183 (1.46E-3)	16 (2,100)	16 (630)
					Inhalation	0.0012	High	3.51E-3	910	
		Peanuts, Leafy Vegetables, Fruiting Vegetables	0.18	350	Dermal	2.9 (0.023)	High	0.06 (4.76E-4)	50 (6,300)	49 (1,900)
					Inhalation	0.0012	High	1.08E-3	2,800	
		Potato/Tuber Vegetables	0.12	350	Dermal	2.9 (0.023)	High	0.04 (3.17E-4)	75 (9,500)	74 (2,900)
					Inhalation	0.0012	High	7.2E-4	4,200	
(3) Apply Liquids: groundboom (open cab)	long sleeves long pants no gloves	Turf	0.55	40	Dermal	0.014	High	1.01E-4	30,000	9,000
					Inhalation	0.00074	High	2.33E-4	13,000	
		Peanuts, Leafy Vegetables, Fruiting Vegetables	0.18	80	Dermal	0.014	High	6.62E-5	45,000	14,000
					Inhalation	0.00074	High	1.52E-4	20,000	
		Potato/Tuber Vegetables	0.12	80	Dermal	0.014	High	4.42E-5	68,000	21,000

Table 9.1a. Occupational Handler Exposure and Risk Estimates for Fluoxastrobin

Exposure Scenario (Unit exposure from PHED unless otherwise indicated)	Personal Protective Equipment[1]	Crop/Use Site	Application Rate (lb ai/A)	Amount Treated per day (acres)	Exposure Route	Unit Exposure (mg/lb ai)	Data Confidence	Daily Dose[2] (mg/kg/day)	MOE [3]	Combined MOE[4]
					Inhalation	0.00074	High	1.01E-4	30,000	
(4) Apply Liquids: aerial (enclosed cockpit)	long sleeves long pants no gloves	Turf	0.55	350	Dermal	0.005	Medium	3.16E-4	9,500	6,000
					Inhalation	0.000068	Medium	1.87E-4	16,000	
		Peanuts, Leafy Vegetables, Fruiting Vegetables	0.18	350	Dermal	0.005	Medium	1.04E-5	29,000	18,000
					Inhalation	0.000068	Medium	6.12E-5	49,000	
		Potato/Tuber Vegetables	0.12	350	Dermal	0.005	Medium	6.9E-5	43,000	27,000
					Inhalation	0.000068	Medium	4.08E-5	74,000	
(5) Flagging Liquids: aerially applied	long sleeves long pants no gloves	Turf	0.55	350	Dermal	0.011	High	6.95E-4	4,300	1,800
					Inhalation	0.00035	High	9.63E-4	3,100	
		Peanuts, Leafy Vegetables, Fruiting Vegetables	0.18	350	Dermal	0.011	High	2.28E-4	13,000	5,500
					Inhalation	0.00035	High	3.15E-4	9,500	
		Potato/Tuber Vegetables	0.12	350	Dermal	0.011	High	1.52E-4	20,000	8,300
					Inhalation	0.00035	High	2.1E-4	14,000	
(6) M/L/A Liquids: handgun (lawn) sprayer	long sleeves long pants **gloves**	Turf	0.55	5	Dermal	0.5*	High	4.51E-4	6,600	5,700
					Inhalation	0.0019*	High	7.46E-5	40,000	

[1] Gloves and no gloves scenarios are reported, since gloves are required on the proposed label.
[2] Daily Dose = [Application Rate * Amount Treated * Unit Exposure (mg/lb ai handled) * Absorption Factor (2.3% for dermal; 100% for inhalation)]/Body Weight (70 kg)
[3] MOE = NOAEL/Daily Dose. The oral NOAEL of 3 mg/kg/day was used for all calculations.
[4] Combined MOE = $1/[(1/MOE_{dermal}) + (1/MOE_{inhalation})]$
* Unit exposure values taken from ORETF study (OMA002) and are considered to be more reliable and applicable than PHED values for this scenario.

SEED TREATMENT:

Table 9.1b shows dermal and inhalation exposure values with different types of personal protective equipment (PPE) for activities related to seed treatment and planting treated seed (SOP for Seed Treatment, Guidance No. 14, May 1, 2003).

Table 9.1b. Summary of Exposure Values for Seed Treatment and Seed Planters				
Type	**Exposure Scenario**	**Dermal Unit Exposure (mg/lb ai)**	**Inhalation Unit Exposure (ug/lb ai)***	**PPE**
Commercial	**Loader/Applicator**	**0.023**	**0.34**	**single layer, glove**
	Loader/Applicator	**0.018**	**0.34**	**single layer, glove, coverall**
	Sewer	**0.0062**	**0.23**	**single layer, no glove**
	Bagger	**0.0091**	**0.16**	**single layer, no glove**
	Multiple Activities	**0.042**	**1.6**	**single layer, glove**
On-Farm	**On-Farm Treatment**	**12.6**	**1.2**	**single layer, glove**
Planters	**Seed Planters**	**0.25**	**3.4**	**single layer, glove****

* Inhalation unit exposure represents no respirator
** glove used for loading only

Table 9.1c. Peanut & Turf Seed Treatment Handler Risk Estimates

Scenario	Crop	Application Rate (lbs ai/lb seed)	seed treated daily (lbs)[1]	Absorption Factor (%)		Unit Exposure (mg/lb ai)		Daily Exposure (mg/kg/day)[2]		Short- & Intermediate-Term MOEs[3]		Combined MOE[4]
				Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	
(7) Loader/Applicator	Peanut	0.0001	120,000	2.3	100	0.023	0.00034	9.07E-5	5.83E-5	33,000	51,000	20,000
	Turf	0.0001	718,000	2.3	100	0.023	0.00034	5.43E-4	3.49E-4	5,600	8,600	3,400
(7) Loader/Applicator (with coveralls)	Peanut	0.0001	120,000	2.3	100	0.018	0.00034	7.10E-5	5.83E-5	42,000	51,000	23,000
	Turf	0.0001	718,000	2.3	100	0.018	0.00034	4.25E-4	3.49E-4	7,100	8,600	3,900
(8) Sewer	Peanut	0.0001	120,000	2.3	100	0.0062	0.00023	2.45E-5	3.94E-5	120,000	76,000	47,000
	Turf	0.0001	718,000	2.3	100	0.0062	0.00023	1.46E-4	2.36E-4	21,000	13,000	7,800
(9) Bagger	Peanut	0.0001	120,000	2.3	100	0.0091	0.00016	3.59E-5	2.74E-5	84,000	110,000	48,000
	Turf	0.0001	718,000	2.3	100	0.0091	0.00016	2.15E-4	1.64E-4	14,000	18,000	7,900
(10) Multiple Activities	Peanut	0.0001	120,000	2.3	100	0.042	0.0016	1.66E-4	2.74E-4	18,000	11,000	6,800
	Turf	0.0001	718,000	2.3	100	0.042	0.0016	9.91E-4	1.64E-3	3,000	1,800	1,100
(11) On-Farm Treatment	Peanut	0.0001	11,000	2.3	100	12.6	0.0012	4.55E-3	1.89E-5	660	160,000	660
	Turf	0.0001	56,000	2.3	100	12.6	0.0012	2.32E-2	9.60E-5	130	31,000	130
(12) Seed Planters	Peanut	0.0001	11,000	2.3	100	0.25	0.0034	9.04E-5	5.34E-5	33,000	56,000	21,000
	Turf	0.0001	56,000	2.3	100	0.25	0.0034	4.60E-4	2.72E-4	6,500	11,000	4,100

[1] Values obtained from HED Standard Operating Procedures (SOPs) for Volume of Seed Treated or Planted, Guidance No. 15, November 1, 2003; except for turf. Since no values exists for turf in the SOP, the following values were used: 1) for commercial seed treatment activities, the highest value for any crop was used (i.e., 718,000 lbs of seed per day); and 2) for On-Farm Treatment and for seed planters a high end value was generated (i.e., 56,000 lbs of seed per day = [700 lbs/acre x 80 acres/day]).

[2] Dose (mg/kg/day) = Rate (lb ai/lb seed) x Unit Exposure (mg/lb ai) x Seeds treated (lb seed/day) x Absorption Factor (2.3% for dermal; 100% for inhalation) / Body Weight (70 kg)

[3] MOE = NOAEL (3 mg/kg/day) / Dose (mg/kg/day)

[4] Combined MOE = $1 / (1/MOE_{Dermal} + 1/MOE_{Inhalation})$

Table 9.1d. Potato Seed Piece Treatment Handler Risk Estimates[1]									
Operation	Acres Planted/Day	Application Rate (lb ai/lb potatoes)	Dermal Unit Exposure (mg/hr)	Inhalation Unit Exposure (mg/hr)	Dermal Daily Exposure[2] (mg/kg/day)	Inhalation Daily Exposure[3] (mg/kg/day)	Dermal MOE[4]	Inhalation MOE[5]	Combined MOE[6]
(13) Filling Hopper Located Outside (Rocky Seed)	50	0.0001	22	1.7	1.29E-2	4.32E-2	230	**69**	**53**
(14) Filling Hopper Located Outside (Clean Seed)	50	0.0001	12	0.61	7.01E-3	1.55E-2	430	190	130
(15) Filling Hopper Located Inside (Clean Seed)	50	0.0001	2.0	0.15	1.17E-3	3.81E-3	2,600	790	600
(16) Cutting, Cutter Inside and Duster Outside	50	0.0001	0.14	0.042	8.17E-5	1.07E-3	37,000	2,800	2,600
(17) Cutting, Complete Operation Inside	50	0.0001	0.80	0.037	4.67E-4	9.40E-4	6,400	3,200	2,100
(18) Tractor Driving Pulling Planter	50	0.0001	0.71	0.037	4.15E-4	9.40E-4	7,200	3,200	2,200
(19) Observer Riding on Rear of Planter	50	0.0001	0.63	0.027	3.68E-4	6.85E-4	8,200	4,400	2,800

[1] Assumptions: 2.3% dermal absorption rate; 100% inhalation absorption rate; 70 kg adult handler; Exposure Period of 3 to 25 days of planting; NOAEL = 3 mg/kg/day.
[2] Dermal Exp = Dermal Unit Exp (mg/hr) x 8 (hr/day) x Dermal Absorp Factor (0.023) x [Fluoxastrobin 50 Acres/day / Captan 30 Acres/day] x [Fluoxastrobin Applic Rate (0.0001 lb ai/lb potatoes) / Captan Applic Rate (0.00075 lb ai/lb potatoes)] / 70 kg
[3] Inhalation Exp = Inhal Unit Exp (mg/hr) x 8 (hr/day) x Inhal Absorp Factor (1.0) x [Fluoxastrobin 50 Acres/day / Captan 30 Acres/day] x [Fluoxastrobin Applic Rate (0.0001 lb ai/lb potatoes) / Captan Applic Rate (0.00075 lb ai/lb potatoes)] / 70 kg
[4] Dermal MOE = NOAEL (3 mg/kg/day) / Dermal Exposure (mg/kg/day)
[5] Inhalation MOE = NOAEL (3 mg/kg/day) / Inhalation Exposure (mg/kg/day)
[6] Combined MOE = 1 / [1/Dermal MOE + 1/Inhalation MOE]

Turf & Field Crops: The calculated MOEs for turf and field crop-related occupational handler exposure scenarios are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern.

Seed Treatment of Peanut & Turf Seeds: The calculated MOEs for commercial and on-farm peanut and turf seed treatment occupational handler exposure scenarios are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern.

Seed Treatment of Potato Seed Pieces: The calculated MOEs for most of the potato seed piece treatment occupational handler exposure scenarios are greater than 100 with workers wearing baseline clothing and gloves, and therefore, do not exceed HED's level of concern. One scenario (*i.e.*, #13 - filling hopper located outside [rocky seed]) resulted in a combined MOE of 53 (dermal MOE of 230 and inhalation MOE of 69), which exceeds HED's level of concern. However, this combined MOE risk estimate is probably not a real risk concern, for several reasons: First, the inhalation component clearly appears to be the route of concern, this inhalation risk estimate is a conservative screening level estimate that uses surrogate data from a captan dust formulation, while fluoxastrobin is a soluble concentrate, liquid formulation. Also, fluoxastrobin is not volatile (vapor pressure is 5.63×10^{-10} Pa at 20°C and 8.72×10^{-10} Pa at 25°C). Additionally, the fluoxastrobin liquid formulation should result in considerably less inhalation exposure than the captan dust formulation, unless it is aerosolized (if the fluoxastrobin liquid formulation is aerosolized, then inhalation exposure could be of concern). Lastly, the dermal risk estimates are also conservative screening level estimates, because they are intermediate-term estimates, while the actual exposures are short- and intermediate-term in duration (a short-term dermal endpoint was not identified).

9.2 Short-/Intermediate-Term Postapplication Risk

Fluoxastrobin has been proposed for both food (*i.e.*, agricultural) and non-food (*i.e.*, residential and commercial) use sites. Agricultural postapplication exposures may occur from a variety of activities following treatment of peanut, leafy vegetable, fruiting vegetable and potato and tuber vegetable crops. Use sites with potential residential exposures include golf course turf, turf farms, recreational turf, and residential lawns. Generally, residential applications do not involve occupational postapplication exposure because the professional applicators are not required to re-enter the use site. However, golf course maintenance activities and turf farm re-entry activities have been identified as occupational postapplication exposure scenarios for fluoxastrobin's proposed non-food uses. Therefore, short- and intermediate-term dermal exposure to workers entering fluoxastrobin-treated areas to perform a variety of agricultural/occupational tasks, has been estimated and risk has been assessed. Inhalation exposure is expected to be negligible for postapplication scenarios, and therefore is not considered in the occupational postapplication risk assessments.

The registrant did not submit any study data depicting the amount of dislodgeable foliar residue (DFR) or turf transferable residue (TTR) to expect on use sites following application of fluoxastrobin end use product. Therefore, HED default assumptions and SOPs were used to determine the DFR and TTR values used in this assessment. The transfer coefficients used in this

assessment are from an interim transfer coefficient guidance document developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP#3.1). It is the intention of HED's Science Advisory Council for Exposure that the transfer coefficient (TC) SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

The intermediate-term MOEs were estimated for "Day 0" exposure (*i.e.,* the day of application), and are presented in Table 9.2.

Table 9.2. Exposure and Risk Assessment for Occupational Postapplication Activities. All estimates are for zero days after the final application.

Crop Group	Application Rate (lb ai/A)	Dermal Transfer Coefficient (cm^2/hr)	Postapplication Day (t)	Dislodgeable Foliar Residue [1] (ug/cm^2)	Daily Dose [2] (mg/kg/day)	Intermediate-Term Dermal MOE [3]
Golf Course Maintenance	0.55	3400: mow, seed, mechanical weed, aerate, fertilize and prune	0	0.308	0.00276	1100
Turf Farms	0.55	6800: mow, scout, mechanical weed and irrigate	0	0.308	0.00552	540
Peanuts	0.18	100: hand weeding	0	0.404	0.000105	28000
		1500: irrigation, scouting			0.00159	1900
Potato/Tuber Vegetables	0.12	300: hand weeding	0	0.269	0.000212	14000
		1500: irrigation, scouting			0.00105	2800
		2500: hand harvesting			0.00177	1700
Leafy Vegetables	0.18	500: hand weeding	0	0.404	0.000531	5600
		1500: irrigation, scouting			0.00159	1900
		2500: hand harvest, thinning			0.00265	1100
Fruiting Vegetables	0.18	500: hand weeding	0	0.404	0.000531	5600
		700: irrigation, scouting			0.000744	4000
		1000: tying, training, stalking, thinning, hand pruning, hand harvesting			0.00106	2800

[1] Dislodgeable Foliar Residue = Application Rate (lb ai/A) x 4.54E+8 µg/lb x 24.7E-9 A/cm^2 x Percent Residue Available Day Zero (5% for turf; 20% all other crops)
[2] Daily Dose = [Dislodgeable Foliar Residue x (0.001 mg/µg) x Dermal Transfer Coefficient x Dermal Absorption Factor (2.3%) x Exposure Time (8 hr)] / [Body weight (70 kg)]
[3] MOE = NOAEL/Daily Dose. Intermediate-Term Oral NOAEL = 3 mg/kg/day.

The MOEs for all occupational/agricultural postapplication activities exceed 100 on the day of treatment (*i.e.*, day 0) for all reentry tasks for all proposed use sites, and therefore, do not exceed HED's level of concern.

Technical fluoxastrobin has a Toxicity Category III for acute dermal and primary eye irritation, and Toxicity Category IV for acute inhalation and primary skin irritation. Therefore, the REI of 12 hours appearing on the proposed fluoxastrobin end use label is acceptable.

10.0 Data Needs and Label Requirements

10.1 Toxicology

870.7800 - Immunotoxicity - Mouse (Subacute Feeding Study)

The only data deficiency that exists is the requirement for additional information on the mouse subacute immunotoxicity study (for potential upgrade). However, this study is not required for risk assessment.

10.2 Residue Chemistry

HED has examined the residue chemistry database for the new ai fluoxastrobin. Pending submission of a revised Section F (which replaces the proposed tolerances with the recommended tolerances listed below) and the resolution of the deficiencies noted below, there are no residue chemistry issues that would preclude granting a conditional registration for this fungicide. The details follow:

Bayer CropScience has proposed the establishment of permanent tolerances for residues of fluoxastrobin [[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazin-3-yl)methanone-*O*-methyloxime] in/on primary and rototational crop RACs, and for the establishment of permanent tolerances for residues of fluoxastrobin and its phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol], calculated as parent equivalents, in cattle commodities.

The petitioner must revise the proposed tolerance expression to reflect the fact that fluoxastrobin E-isomer, and not the mixture of E- and Z-isomers, is the proposed active ingredient. The tolerance expression for plant commodities should be:

> combined residues of fluoxastrobin [(1*E*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime] and its Z-isomer [(1*Z*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime

The tolerance expression for livestock commodities should be:

> combined residues of fluoxastrobin [(1*E*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime], its Z-isomer [(1*Z*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-

methyloxime, and its phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol], calculated as parent equivalents

Pending receipt of the required storage stability and weather data, the available crop field trial data will support tolerances for residues of fluoxastrobin and its Z-isomer in/on peanut, peanut hay, peanut refined oil, tomato paste, the fruiting vegetable group, the leaf petioles subgroup, and the tuberous and corm subgroup. The available data indicate that the proposed tolerance of 5.0 ppm for residues in/on the leaf petioles subgroup is too high; a revised tolerance level of 4.0 ppm should be proposed. The available processing data indicate that the proposed tolerances for residues in/on peanut refined oil and tomato paste (0.10 and 2.0 ppm, respectively) are too high, and that revised tolerance levels of 0.03 and 1.5 ppm, respectively, should be proposed.

Pending receipt of the required storage stability, soil characteristics, and weather data, the available field rotational crop data will support tolerances for residues of fluoxastrobin and its Z-isomer in/on alfalfa forage, alfalfa hay, cotton gin byproducts, cereal grain forage, cereal grain hay, cereal grain straw, cereal grain stover, grass forage, grass hay, legume seed, legume forage, and legume hay. The available data indicate that a tolerance for legume seed is not needed, since no quantifiable residues of fluoxastrobin and its Z-isomer were found in any representative commodities of the legume vegetable group. The available data indicate that the proposed tolerance of 1.0 ppm for residues in/on alfalfa hay is too high, and that a revised tolerance level of 0.10 ppm should be proposed.

The available livestock feeding study data indicate that the proposed tolerances for milk and milk fat are too low and the proposed tolerance for cattle meat byproducts is too high. The proposed tolerances for cattle fat and meat are adequate. Tolerances for the fat, meat, and meat byproducts of goat, horse, and sheep must be proposed. The appropriate levels for these tolerances are listed in the table below. The cattle feeding study data indicate that tolerances for hog commodities are not needed.

The proposed tolerances should be revised to reflect the correct commodity definitions as specified in the table below:

Tolerance Summary for Fluoxastrobin.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Primary crop tolerances for residues of fluoxastrobin and its Z-isomer:			
Peanut	0.01	0.010	
Peanut, hay	20	20.0	
Peanut, refined oil	0.10	0.030	
Tomato, paste	2.0	1.50	
Vegetable, fruiting, group	1.0	1.0	*Vegetable, fruiting, group 8*
Vegetable, leafy, petioles, except *Brassica*, subgroup	5.0	4.0	*Leaf petioles subgroup 4B*
Vegetable, tuberous and corm, subgroup	0.01	0.010	*Vegetable, tuberous and corm, subgroup 1C*

Tolerance Summary for Fluoxastrobin.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Rotational crop tolerances, for residues of fluoxastrobin and its Z-isomer:			
Alfalfa, forage	0.05	0.050	
Alfalfa, hay	1.0	0.10	
Cotton, gin byproducts	0.02	0.020	
Grain, cereal, forage	0.10	0.10	*Grain, cereal, forage, fodder and straw, group 16*
Grain, cereal, hay	0.10		
Grain, cereal, straw	0.10		
Grain, cereal, stover	0.10		
Grass, forage	0.10	0.10	
Grass, hay	0.50	0.50	
Legume, seed	0.01	Remove	No tolerance needed
Legume, forage	0.05	0.050	*Vegetable, foliage of legume, group 7*
Legume, hay	0.05		
Livestock commodity tolerances, for residues of fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite:			
Cattle, fat	0.10	0.10	
Cattle, meat	0.05	0.050	
Cattle, meat byproducts	0.20	0.10	
Milk	0.01	0.020	
Milk, fat	0.10	0.50	
Livestock commodity tolerances to be proposed, for residues of fluoxastrobin, its Z-isomer, and its phenoxy-hydroxypyrimidine metabolite:			
Goat, fat	None proposed	0.10	
Goat, meat	None proposed	0.050	
Goat, meat byproducts	None proposed	0.10	
Horse, fat	None proposed	0.10	
Horse, meat	None proposed	0.050	
Horse, meat byproducts	None proposed	0.10	
Sheep, fat	None proposed	0.10	
Sheep, meat	None proposed	0.050	
Sheep, meat byproducts	None proposed	0.10	

For the following guideline studies, data deficiencies exist, and are outlined below:

860.1200 Directions for Use

- The petitioner must modify the proposed label to include the correct name for the active ingredient. Currently, the proposed label does not specify that the E-isomer is the active

ingredient. The product label must be modified to state that application may not be made to fruiting vegetables grown in a greenhouse.

860.1300 Nature of the Residue - Livestock

- To allow HED to determine that the metabolite profile in fat, liver, and kidney did not change over the course of the goat metabolism study reported in MRID 45865507, the petitioner should: (i) provide comparison peak area and peak identification data for the initial and final chromatograms for fat and liver (chromatogram codes BO1237.09/09A and BO 1287.01/01A for fat, and BO1283.01 and BO1293.23/23A for liver); and (ii) provide the HPLC data for the first kidney extract analysis (chromatogram code BO1237.21/21A) and compare these data to the results of the other kidney HPLC analyses.

860.1340 Residue Analytical Method - Plant Commodities

- No confirmatory method was included with either proposed enforcement method, Method Nos. 00604 and 00649. Although the methods use MS/MS detection, because only one transition is monitored for each analyte, a confirmatory method is needed. Alternatively, the petitioner may conduct an interference study to investigate whether other pesticides registered on the same commodities interfere with determination of residues of fluoxastrobin and its Z-isomer or modify the method to monitor an additional ion.

- The petitioner should confirm that Method No. 00649 is not intended for enforcement of tolerances for any rotated crop commodities other than those in crop group 6 and, therefore, not needed for tolerance enforcement to support the proposed uses.

- The proposed enforcement method(s) must be rewritten to include instructions for the analysis of all crops (and their associated processed commodities) for which the petitioner is requesting tolerances. Method No. 00604 must be revised to include specific directions for the use of an internal standard for quantitation, because independent validation of Method No. 00604 was conducted using internal standard quantitation.

- The proposed enforcement Method No. 00604 has been forwarded to ACB for PMV. Pending completion of the PMV and submission of additional information, the proposed enforcement Method No. 00604 is adequate for the enforcement of tolerances in conjunction with a conditional registration. Modification of the method as outlined above and per the PMV should be made a condition of the registration of fluoxastrobin.

860.1340 Residue Analytical Method - Livestock Commodities

- Method No. 00691, Modification 001 must be modified to include a confirmatory method. Alternatively, the petitioner may submit an interference study for all pesticides for which tolerances for milk and/or cattle tissues have been established (see further discussion below). The method must also be modified to specify whether calculated results for the phenoxy-hydroxypyrimidine metabolite are reported in terms of The phenoxy-hydroxypyrimidine metabolite or in terms of parent equivalents. Because the method specifies that calibration standards for the method contain equimolar amounts of the three

analytes, the results calculated from the calibration curve for The phenoxy-hydroxypyrimidine metabolite would be expressed as parent equivalents. However, this issue is currently only addressed in the section describing preparation of the standards and, therefore, is unclear.

- Before HED can conclude that the submitted ILV study was actually conducted by an "independent" laboratory, the petitioner must submit a discussion of the amount of work conducted by the ILV laboratory on the method prior to the initiation of the recovery trials that are reported in the ILV submission (MRID 45865527). In addition, the following information pertaining to the ILV submission must be submitted: (1) the number of trials that were required for each tested matrix to yield the recovery results reported in the submission; (2) the number of samples that comprise "one set" (to define the number of samples that may be analyzed in one day; see page 26 of the submission); (3) a description of any problems encountered and a written description of any changes or modifications that were made during the ILV; (4) a discussion of any steps considered critical, *i.e.*, steps where little variation is allowable or directions must be followed precisely; and (5) a discussion of any contact between the independent laboratory and the method developers or others familiar with the method, including the reasons for the contact, any changes in the method that resulted, and the time of this communication with respect to the progress of the confirmatory trial (*i.e.*, after the first set, during the second set, *etc.*).

860.1380 Storage Stability

- To support the results of the submitted storage stability data, the petitioner must submit confirmatory raw data, including a description of the preparation of the samples prior to storage (*e.g.*, were samples chopped or homogenized prior to fortification), a more detailed description of the storage conditions (types of containers, *etc.*), the dates of fortification, a more detailed description of the methods used for sample analysis, and representative chromatograms. The petitioner should provide an explanation if the sample storage conditions differed from those of samples from the crop field trials and rotational crop studies that the study is intended to support.

860.1500 Crop Field Trials

- The submitted field trial residue data are inadequate to satisfy data requirements but may be upgraded with the submission of additional information. For each of the crop field trial submissions (MRIDs 45865530-45865533), the petitioner must provide a summary of the weather conditions for the growing season for each trial, stating whether conditions were normal or whether any unusual conditions were observed.

860.1520 Processed Food and Feed

- The submitted processing data for peanuts are inadequate to satisfy data requirements as the processing factor determined for peanut oil exceeded the theoretical concentration factor. The submission of a new peanut processing study should be made a condition of the registration of fluoxastrobin.

860.1550 Proposed Tolerances

- A revised Section F is required to adjust some tolerance levels, revise the tolerance expression, and revised the commodity nomenclature. Details on revising the Section F are included in the Proposed Tolerances section of this memorandum.

860.1650 Submittal of Analytical Reference Standards

- Based on the proposed enforcement methods, the following analytical reference standards must be submitted to the EPA National Pesticide Standards Repository:
  - fluoxastrobin
  - fluoxastrobin Z-isomer
  - phenoxy-hydroxypyrimidine metabolite [6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol]
  - fluoxastrobin-d_4
  - fluoxastrobin-d_4, mixture with deuterated Z-isomer
  - Phenoxy-hydroxypyrimidine -d_4

860.1900 Field Accumulation in Rotational Crops

- For each rotational crop field trial from which samples were analyzed (for both the limited and extensive field rotational crop studies reported in MRIDs 45865606-45865611), the petitioner must provide soil characteristics data as well as a summary of the weather conditions for the growing season, stating whether conditions were normal or whether any unusual conditions were observed.

- The petitioner must also provide an explanation for grass forage and hay samples from the Stilwell, KS extensive rotational crop field trial which appear to have been harvested over one year (410-481 days) following planting of the grass crop.

10.3 Occupational and Residential Exposure

Label amendments are required which:

- explicitly state homeowner application of HEC 480 SC Fungicide on turf is prohibited (PCO application on residential turf only).

- explicitly state that the maximum seasonal application rate for turf includes seed treatment.

References:

Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Fluoxastrobin on Peanuts, Leafy Vegetables, Fruiting Vegetables, Potatoes and Tuber Vegetables and Turf. Barry O'Keefe. 12/9/04. DP Bar Code D289109, PC Code 028869.

Fluoxastrobin: Chronic Dietary Exposure Assessments for the Section 3 Use on Peanuts, Tuberous and Corm Vegetables Subgroup, Leaf Petiole Vegetables Subgroup, Fruiting Vegetables Group, and Seed Treatment of Peanut and Potato. William Wassell. 11/XX/04. D290107, PC Code 028869.

Revised Drinking Water Assessment for the Section 3 Registration of the New Chemical Fluoxastrobin (HEC5725) for Uses on Peanut , Potato and Tuber Vegetables, Leaf Petioles subgroup, Fruiting Vegetables, and Turf; and Seed Treatments for Potato, Peanut and Turf. Thuy Nguyen. 11/23/2004. D289104 S3NC, PC Code 028869.

PP#3F6556. *Fluoxastrobin. Petition for the Establishment of Permanent Tolerances for Use on Peanuts, Tuberous and Corm Vegetables Subgroup, Leaf Petiole Vegetables Subgroup, Fruiting Vegetables Group, and Seed Treatment of Peanut and Potato*. William Wassell. 12/XX/04. D289106 and D289107, PC Code 028869.

Ad hoc fluoxastrobin MARC meeting, 9/14/2004.

HED/RAB3 fluoxastrobin hazard meetings, October and November 2004.

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food use for fluoxastrobin are in the following table. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irri4tation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	CR[1]	NR[1]
870.3465	90-Day Inhalation	CR[1]	NR[1]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	-	-
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	-	-
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	NR[1]	yes
870.6200b	90-day Neurotox. Screening Battery (rat)	CR[1]	yes
870.6300	Develop. Neurotox.	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes

[1]CR = Conditionally required; NR = Not required.

2.0 NON-CRITICAL TOXICOLOGY STUDIES

2.1 Non-Critical Studies Using Active Ingredient

90-Day Oral Toxicity (feeding)-Rat

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 45865627), Fluoxastrobin (98.3% a.i., Batch # NLL 6112-12a) was administered to 10 Wistar rats/sex/dose in the diet at concentrations of 0, 125, 1000, or 8000 ppm (equivalent to 0, 8.7, 70.4, or 580.0 mg/kg/day) for males and 0, 250, 2000, or 16000 ppm (equivalent to 0, 21.5, 162.9, or 1416.1 mg/kg/day, respectively) for females. An additional five rats/sex/dose were administered the same dose levels for five weeks for immunotoxicity assays, and 10 rats/sex/dose were administered 0 or 8000 ppm (males) and 0 or 16000 ppm (females) for 13 weeks followed by a 4-week recovery period. At necropsy, liver samples were assayed for cytochrome P-450 and Phase I and Phase II enzyme activities.

There were no significant treatment related adverse effects on mortality, clinical signs, or ophthalmologic parameters, nor was there evidence of immunotoxicity in either sex. Body weights were decreased throughout the study in males at 8000 ppm [80%-90% of control], as were body-weight gains, with the largest deficit occurring initially [weeks 0-1 (56% of control); weeks 1-7 (67% of control); weeks 0-13 (76% of control)]. Reduced food consumption by the males that received 8000 ppm appeared to correlate with the reduced body weight/gain. Females displayed comparable body weight and body-weight gains among the groups, although initially [weeks 0-1] the 16000 ppm females gained less weight [77% of control] than controls. Females at 16000 ppm displayed slight reductions in RBC, hemoglobin and hematocrit values mainly at week 4, and males at 1000 ppm and 8000 ppm displayed decreased reticulocytes at week 4 only. A slight increase in calcium concentration in the plasma of both sexes was observed at their respective mid- and high-dose levels. Dose-related decreased were observed in AST and ALT in both sexes at the 1000 ppm and 8000 ppm dose levels in males and at the 2000 ppm and 16000 ppm dose levels in females at both time points. The 16000 ppm females also displayed a significant reduction in alkaline phosphatase at both time points. Although the toxicological significance of these reduced enzyme levels is not known, this is a reproducible effect of treatment [observed in the chronic study and in 4 subchronic studies in rats], and the magnitude of some of the reductions at the high-dose level in both sexes reached 40%-50%. HEC 5725 induced significant decreases in Phase I enzymes [ECOD, EROD, ALD] at all dose levels in females and in Phase II enzymes [EH, GS-T, and/or GLU-T], mainly at the high-dose level in both sexes. Increased amounts of calcium oxalate crystals were found in the urine sediment of males at $\geq$125 ppm in week 13. This was consistent with the necropsy and histopathological findings of the thickened urinary bladder wall, stones in the urinary bladder, the calculi formation (renal pelvis, urethra) with moderate to marked diffused hyperplasia of the transitional epithelium (renal pelvis, urinary bladder urethra) and inflammation of the urinary bladder and kidney in males at 8000 ppm. The stone formation with resultant inflammation may have resulted from the disturbance of calcium homeostasis due to treatment with HEC 5725. Increased liver weight was observed in females at the 16000 ppm dose level.

Under the conditions of this study, the LOAEL for HEC 5725 in male Wistar rats is 8000 ppm (580.0 mg/kg/day) based on decreased body weight and body-weight gain, reduced food

intake, vacuolation in the zona fasciculate of the adrenal cortex, calculi formation in the urethra and kidney, and histological lesions in kidney, urinary bladder, and urethra; the LOAEL for females is 16000 ppm (1416.1 mg/kg/day) based on increased liver weight. The NOAELs are 1000 ppm (70.4 mg/kg/day) for males and 2000 ppm (162.9 mg/kg/day) for females.

This 90-day oral toxicity study in Wistar rats is **Acceptable/Guideline,** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408).

90-Day Oral Toxicity Feeding- Mouse

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (1998, MRID 45865626) HEC 5725 (fluoxastrobin, 100.2% a.i., batch/lot # NLL 6112-17) was administered to 10 Crl:CD-1(ICR)BR mice/sex/dose in diet at dose levels of 0, 450, 1800, or 7000 ppm (reported as equivalent to 0, 81, 313, or 1304 mg/kg bw/day in males, and 0, 135, 539, or 2257 mg/kg bw/day in females). Feed intake for females for females was notably higher than for males resulting in the compound intakes of females (low- to high-dose) reported as 167%, 172%, and 173% of the corresponding male groups. However, there was no effect on food efficiency.

Increased liver weights in both sexes were noted in all dosed groups in a dose related manner. The increases were more pronounced in males (low to high: 14%, 17%, and 47% in absolute weight) and were all statistically significant. Absolute and relative hepatic weight increases in the mid- and high-dose females (absolute: 19% and 35%, respectively) were statistically significant. Aspartate aminotransferase (ASAT) was *reduced* in a dose-related manner in both sexes and the values were statistically reduced at 1800- and 7000 ppm. *Reductions* in alanine aminotransferase (ALAT) were even more pronounced, and dose-related in both sexes (males, low to high-dose: 27%, 57%, and 72% reduced, respectively; females, low to high-dose: 44%, 67%, and 78%, respectively). The reductions in ALAT were statistically significant in all treated groups. Cholesterol levels were mildly elevated in all treated groups, and appeared to be dose-related in females. Albumin values were mildly increased in the 1800- and 7000 ppm female groups. Blood elements possibly suggesting anemia were noted in the high dose group but were within historical control ranges. Histopathologically, hepatocellular hypertrophy with cytoplasmic changes in 6 of 10 high-dose males were noted. Mild hydropic degeneration of single or small clusters of liver cells occurred in only one high-dose female, suggesting that the finding was of unlikely toxicological significance. The kidney represented a possible target organ as suggested by the statistically significant increases in absolute and relative renal weight in the high-dose males (14% and 13% respectively). Minimal to moderate tubular hypertrophy was noted in mid- and high-dose females at nearly double the incidence as in the control (5 and 6 of 10 mid- and high-dose females, respectively, vs 3 affected control females). These findings were of uncertain toxicological relevance. This study demonstrates that only possible changes of questionable *toxicological* significance result from mice dosed with 450, 1800 or 7000 ppm of fluoxastrobin. Such possible treatment related effects will be further investigated in the definitive cancer study. No NOAEL and LOAEL are being set for this study but the study provides sufficient data to select doses for the definitive carcinogenicity study.

This study was classified as **Acceptable/Non-Guideline** and does not precisely satisfy the guideline requirement for a subchronic oral toxicity study in mice [OPPTS 870.3100 (§82-1a)

OECD 408]. The study provides sufficient data to meet its intended purpose of providing data to help establish the dose levels to be used for the definitive cancer study.

28-Day Dermal Toxicity - Rat

EXECUTIVE SUMMARY: In a 4-week dermal toxicity study (MRID 45865630), HEC 5725 (94.3% a.i., Batch #06261/0008) was applied to the shaved skin of Wistar SPF HsdCpb:WU rats/sex/dose at dose levels of 0 (water), 100, 300, or 1000 mg/kg bw/day, 6 hours/day, 5 days/week during the first three weeks of the study and on all seven days during the fourth week of the study.

There were no treatment-related clinical observations, dermal reactions, neurological effects, or effects on body weight food consumption, ophthalmology, hematology, organ weight, or gross or histopathology. **Based on the results of this study, the systemic and dermal LOAELs for HEC 5725 in male and female rats are not identified, and the systemic and dermal NOAELs are the limit dose of 1000 mg/kg/day.**

This 28-day dermal toxicity study in the rat is **Acceptable/Guideline.** It satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

Bacterial system, *e.g.*, *Salmonella*/mammalian activation gene mutation assay

EXECUTIVE SUMMARY: In independent reverse gene mutation assays (initially by plate incorporation; repeated by the preincubation variation), cultures of five histidine-auxotrophic (*i.e.*, deficient, *his*$^-$) strains of *Salmonella typhmurium* (TA1535, TA1537, TA98, and TA102) were exposed to HEC 5725 (Batch No. NLL 1612-4, 98.9% a.i., dissolved in dimethyl sulfoxide, DMSO) at concentrations of: 16, 50, 158, 500, 1581 and 5000 *u*g/plate using plate incorporation, or: 10, 32, 100, 316, 1000 and 3162 *u*g/plate following preincubation, in the presence and absence of exogenous metabolic activation provided by the 9000 g supernatants of liver homogenates (S9) from male Sprague-Dawley rats treated with Aroclor 1254. In addition to cultures exposed to the solvent, DMSO, alone (acting as "negative control"), others were treated with strain-specific reference mutagens, to serve as positive controls. After incubation at 37°C for 48 hours, revertant prototrophic (*i.e.*, wild-type, *his*$^+$) bacterial colonies in test cultures were compared to solvent controls.

Cytotoxicity was observed in test article-treated cultures at the highest concentration tested (HCT) under plate incorporation (5000 *u*g/plate) but not at the HCT under preincubation (3162 *u*g/plate). Precipitation, beginning at 1581 *u*g/plate in plate incorporation and 1000 *u*g/plate in the preincubation assay, proceeded to a degree which prevented appropriate analysis for reverse mutation at the HCT in both assays.

In neither assay, however, were increased frequencies of revertants found in any test article-treated strain at any concentration in the presence or absence of activation. On the other hand, all cultures exposed to strain-specific mutagens responded with marked increases in revertants.

Therefore, HEC 5725 technical is considered non-mutagenic in *S. typhimurium* cultures treated up to cytotoxic/precipitating levels.

This study is classified as **acceptable/guideline** and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

Mammalian cells in culture; gene mutation assay in V79 cells

EXECUTIVE SUMMARY: In independent, repeat mammalian cell gene mutation assays (MRID 45865709), cultures of Chinese hamster lung (V79) cells, carrying the X-chromosome-linked hypoxanthine guanine phosphoribosyl transferase (*hprt*$^+$) gene, were exposed to HEC 5725 technical (Batch No.NLL 6112-4, 98.9%/99.4% a.i., dissolved in dimethyl sulfoxide, DMSO) at concentrations ranging from 1 to 200 ug/mL, in the presence and absence of metabolic activation provided by the 9000 g hepatic fraction from Aroclor 1254-treated rats. In addition to untreated cultures and cultures exposed to solvent, DMSO (negative/vehicle controls), others were treated with the reference mutagens, ethylmethanesulfonate (EMS), and dimethylbenzanthracene (DMBA), to serve as positive controls for the non-activated and activated test series, respectively.

In a preliminary cytotoxicity test at eight concentrations ranging from 6.25 ug/mL to 800 ug/mL, both non-activated and activated cultures showed adverse effects (decreases in relative population growth) at all concentrations, as well as precipitation $\leq$ 200 *u*g/mL. At no concentration in any mutation assay up to the highest tested level (200 *u*g/mL) ± S9-mix, however, did the test substance increase the mutant frequency (to *hprt*$^-$) over negative or vehicle controls, in contrast to marked induced increases induced by positive controls.

Therefore, HEC 5725 technical is considered non-mutagenic in the *in vitro* forward mutation V79-HPRT test.

This study is classified as **acceptable/guideline** and satisfies the FIFRA Test Guideline for mammalian cell (forward gene mutation) data.

***In vitro* mammalian chromosome aberrations in Chinese hamster lung (V79) cells**

EXECUTIVE SUMMARY: In independent repeat assays (MRID 45865710), cultures of Chinese hamster V79 cells were exposed for 4 hours to HEC 5725 technical (Batch No. NLL 6112-4, 98.9% a.i., dissolved in dimethyl sulfoxide, DMSO) initially: at concentrations of 0, 20, 40, 80, 160 and 320 *u*g/mL, and harvested 18 hours after the beginning of exposure; in repeat assays: at 0, 80, 160 and 320 *u*g/mL, and harvested 30 hours after the beginning of treatment; both assays, in the presence and absence of metabolic activation provided by hepatic post-mitochondrial microsomes (S9) from Aroclor 1254-treated Wistar rats. In addition to cultures exposed to the solvent, DMSO (acting as a "negative" control), others were treated with the reference clastogenic mutagens, mitomycin-C (MMC, 0.1 *u*g/mL) and cyclophosphamide (CP, 2.0 *u*g/mL), to serve as positive controls for the non-activated and activated test series. Two hours prior to harvesting, all cultures were treated with the mitotic-arresting (in metaphase) alkaloid, Colcemid, and the incidence of structural and numerical aberrations determined.

In preliminary cytotoxicity testing --- as measured by mitotic index (MI) and cell survival --- significant ($p < 0.01$) reductions in MI were found in non-activated test cultures at $\geq$ 20 ug/mL and at $\geq$ 80 ug/mL under activation, and relative cell survival at $\geq$ 40 *u*g/mL ± S9. Precipitation

was also observed beginning in non-activated cultures at 40 *u*g/mL and in activated cultures at 20 *u*g/mL.

At no testable concentration in either HEC 5725-treated assay, however, were statistically significant increases over negative controls in metaphase chromosome aberrations, either structural or numerical, found.

By contrast, both positive controls manifested markedly increased cytogenetic effects.

Therefore, HEC 5725 technical is considered to be negative for clastogenicity in this *in vitro* mammalian cell test.

This study is classified as **acceptable/guideline** and satisfies the requirements for FIFRA Test Guideline (*in vitro* chromosome aberration) data.

***In vivo* mammalian cytogenetics - micronucleus assay in the mouse**

EXECUTIVE SUMMARY: In an *in vivo* cytogenetic (micronucleus) assay (MRID 45865711), mice (2 groups of 5 males each/dose) were injected intraperitoneally (i.p.) twice (separated by 24 hours) with HEC 5725 technical (Batch No. 06261/0008, 94.5% a.i., in 2% aqueous "Cremophor") at doses of 75, 150 and 300 mg/kg/day. Femoral bone marrow cells were extracted 24 hours after the second dose and examined for the incidence of micronucleatic polychromatic erythrocytes (mPCEs). An additional 5 males were administered the test article at 300 mg/kg to serve as replacement for animals dying at the highest dose. In addition to males injected with the vehicle, Cremophor (acting as the "negative" control), two groups of 5 males each were injected once with the clastogenic mutagen, cyclophosphamide (CP, 20 mg/kg), and bone marrow extracted 24 hours later. The ratio of polychromatic erythrocytes (PCEs) to the derivative normochromatic erythrocytes (NCEs) was determined at each dose level, as a measure of erythropoietic cytotoxicity.

Dose-related adverse clinical effects (apathy, roughened fur, sternal recumbency, spasms, shivering and difficulty in breathing) were observed in mice treated at $\geq$ 75 mg/kg/day. Three of 8 males treated at 150 mg/kg/day died during the test period. The ratio of PCEs to NCEs decreased with increased dose and reached significance ($p < 0.01$) at the high dose, indicating dose-related test article-cytotoxicity to the bone marrow.

At no dose of HEC 5725 technical in any group, however, were statistically significant increases in mPCEs compared to concurrent vehicle (negative) control values found, in contrast to the marked increases of CP (positive control) treatment. [Although only males were used in the definitive assay, results from a preliminary test showed no substantial differences in toxicity between the sexes.]

Therefore, HEC 5725 technical is considered to be non-clastogenic (as indicated by no increases in micronuclei) in bone marrow from male mice treated by i.p. injection up to clinical and erythropoietic toxicities.

This study is classified as **acceptable/guideline** and satisfies the FIFRA Test guideline 84-2

requirement for *in vivo* cytogenetic (micronucleus) data.

Metabolism - Rat

EXECUTIVE SUMMARY: A study (MRID 45865714) was conducted in male rats to assess the metabolism and disposition of [chlorophenyl-UL-^{14}C]HEC 5725 (Fluoxastrobin; >99% radiochemical purity, batch no. 12712/1, 12712/5 for radioisotopes, 98.9% chemical purity, batch no. M0358 or non-labeled) following a single oral dose of 1 mg/kg. A whole-body autoradiography study (MRID 45865715) was also conducted in male and female rats given a single 3 mg/kg oral dose. Additionally, the metabolism and disposition of the metabolite, [phenyl-UL-^{14}C]2-chlorophenol (>98% radiochemical purity, lot no. 12071/1), was examined in male rats give a single 5 mg/kg oral dose (MRID 45865720).

Recovery of administered radioactivity was an acceptable 91-102% among the reviewed studies. Results of the Tier 1 study (MRID 45865714) clearly indicated that [chlorophenyl-UL-^{14}C]HEC 5725 (Fluoxastrobin) was rapidly absorbed and metabolized by male rats following a single 1 mg/kg oral dose. Excretion and tissue/organ burden data showed that absorption was nearly 100%. Peak plasma concentrations were achieved within 30 minutes and plasma clearance was rapid. Approximately 77% of administered radioactivity was excreted in the feces and about 14% was excreted in the urine. Excretion via expired air was ≤0.2%. Overall excretion of administered radioactivity was >90% and complete within 24 hours. Bile duct cannulation experiments revealed that nearly 100% of the fecal radioactivity was contributed by the bile in the form of hydroxylation, methylation, and conjugation products. Metabolite characterization efforts indicated that HEC5725 was extensively metabolized primarily via hydroxylation and subsequent methylation, followed by glucuronide or sulfate conjugation. Approximately 19 fractions were identified in the 24-hour bile samples from rats dosed with the [chlorophenyl-UL-^{14}C]HEC5725. These metabolites collectively represented approximately 44% of the administered 1 mg/kg dose with HPLC characterized metabolites and unidentified polar compounds accounting for a an additional 33% of the administered dose. The most prevalent of the biliary metabolites was methoxy-OH-GA-dioxazine-OH and methoxy-OH-GA each representing about 6% of the administered dose. In the matrices analyzed, parent compound never accounted for more than 3% of the dose. The proposed metabolism pathway for [chlorophenyl-UL-^{14}C]HEC5725 appears to be consistent with the findings of the study reports.

In the initial experiments of MRID 45865714, tissue/carcass burdens were only slightly in excess of 1% of the administered radioactivity at 48 hours post dose. Most of this radioactivity was associated with the liver (~0.42%) and gastrointestinal tract (0.44%). Autoradiography experiments (MRID 45865715) in which rats were terminated at 1, 4, 8, 24, 48, 72, 120, and 168 hours post dose, revealed that radioactivity was widely distributed but that most was associated with the gastrointestinal tract, blood, organs/tissues involved with elimination, and fat. There was no indication of sequestration of the test article or its metabolites.

The study report (MRID 45865720) on the metabolism and disposition of 2-chlorophenol metabolite in male rats showed that this metabolite of HEC5725 was also rapidly and thoroughly absorbed following oral administration, and was extensively metabolized. More than 99% of the radioactivity from a single oral dose of [^{14}C]-2-chlorophenol was excreted in the urine. The majority of urinary radioactivity was associated with a glucuronide conjugate (~64% of the

administered dose) and sulfate conjugate (~28% of the administered dose) of 2-chlorophenol. The metabolites and parent compound (2-chlorophenol) represented essentially all (>98%) of the administered dose of the 2-chlorophenol metabolite of HEC5725 (Fluoxastrobin).

These metabolism studies in the rat (MRID 45865714, 45865715, and 45865720) are collectively classified **Acceptable/Guideline** and satisfy the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. They should be considered with the other rat metabolism studies using different ring labels, namely, [methoxyiminotolyl-ring-UL-^{14}C] HEC5725 (MRIDs 45865716 and 45865717) and [pyrimidine-2-^{14}C]HEC 5725 (MRIDs 45865718 and 45865719).

Cont. Metabolism - Rat

EXECUTIVE SUMMARY: A metabolism and kinetics study (MRID 45865716) was conducted in which young male and female Wistar rats (4/sex/group) were given a single (1 mg/kg or 100 mg/kg) dose of [methoxyiminotolyl-ring-UL-^{14}C]HEC5725 (Fluoxastrobin; lot nos. 11675/1, 12250/1, and 12250/17; >99% radiochemical purity). For multiple-dose experiments, rats received 14 consecutive daily gavage doses (1 mg/kg) of non-labeled HEC5725-E-isomer (lot no. M00358, 98.8% purity) followed by a single dose (1 mg/kg) of radiolabeled test article. Biliary excretion was assessed using an additional group of 12 male rats with bile cannulae. Metabolism and disposition, including plasma kinetics, were determined up to 72 hours post dose. An autoradiography study (MRID 45865717) assessed disposition of [methoxyiminotolyl-ring-UL-^{14}C]HEC5725 (Fluoxastrobin; lot nos. 12250/1, and 12250/37; >99% radiochemical purity) in male and female rats over 48 hours following a single 3 mg/kg gavage dose.

Mass balance for administered radioactivity in all experiments was an acceptable 91-107%. Excretion profiles and plasma concentration data showed that HEC5725 was rapidly and thoroughly absorbed following single or multiple low (1 mg/kg) doses (t_{max} of 0.4-1.4 hrs) but absorption appeared to be saturated at the 100 mg/kg dose (t_{max} of 5.4-8.0 hrs). Limited absorption was reflected by the AUC values (54.10 - 61.30 µg/mL·hr for the high dose groups vs. 1.18 - 1.52 µg/mL·hr for the low and multiple-dose groups), and by C_{max} values that were 14 - 33 fold greater than the low-dose groups.

Plasma elimination was biphasic with an initial phase at 0.7-3.5 hrs for the low single or multiple dose groups and 2.3-4.1 hrs for the high-dose groups and a secondary phase at ~10 hours and 7 hours for the low and high-dose groups, respectively. Plasma concentration-time plots were suggestive of enterohepatic circulation but this was minimal and still allowed for relatively rapid and complete excretion of administered radioactivity. Distribution and kinetic data did not indicate potential for sequestration at the dose regimens tested and revealed no gender-related variability.

The major route of excretion was via the bile and subsequently the feces. Urinary excretion was a secondary but significant route. Elimination via expired air was inconsequential (0.02%). Urinary excretion was essentially complete (>90%) at 24 hours postdose and accounted for 16.9-20.2% of the administered low dose and 11.0-14.9% of the high dose. The majority of fecal excretion of radioactivity occurred within 24 hours. In rats without bile cannulae, fecal excretion accounted for 70.4-84.7% of the administered low dose over 48 hours. In high-dose groups, fecal excretion

was slightly higher (86.4-91.1%) with much of the fecal radioactivity (43-54% of administered dose) attributed to parent compound due to saturated absorption. In rats with bile cannulae, biliary excretion represented 87.4% of the dose and fecal excretion was correspondingly lower (10.6%). Repeated dosing did not affect excretion profiles and there was no biologically relevant gender-related variability.

Tissue/organ/carcass burdens were minimal (<1% of administered radioactivity), findings which were confirmed by the autoradiography experiments. Most radioactivity was associated with the gastrointestinal tract, blood, and organs/tissues directly associated with metabolism and excretion. Tissues levels rapidly diminished after 8 hours to non-detect levels at 48 hours.

HEC5725 was extensively metabolized as shown by the extensive metabolite profiles from urine, feces and bile and the relative absence of parent compound (except in the feces of rats given the 100 mg/kg dose). There were no significant qualitative or quantitative differences in metabolite profiles among the test groups or between males and females. The urinary metabolites were primarily the result of cleavage between the second and third rings of the parent compound. Biliary metabolites were primarily products resulting from cleavage of rings 2, 3 and 4, and subsequent hydroxylation, methoxylation, and conjugation with glucuronic acid. HEC5725-E-des-chlorophenyl and HEC5725-des-chlorophenyl-dioxazine-OH were the major metabolites in all excretion matrices.

Some of the rat metabolites seem to be in common with metabolites in studies from lactating goat (*e.g.*, HEC5725-di-OH and its dioxazine-OH, HEC5725-E-des-chlorophenyl and its derived ketone, dioxazine-OH, and glycol, in addition to several dioxazine phenyl two ring metabolites) and laying hen (*e.g.*, several glucuronide conjugates of HEC5725- including mono- and di-OH-GA, and oxime-GA in addition to mono- and bi-ring fragments including dioxazine-oxime, 2-cyanophenol, and salicylic acid).

These metabolism studies (MRID 45865716, 45865717) of methoxyiminotolyl-ring-UL-labeled HEC 5725 (Fluoxastrobin) are collectively classified **Acceptable/Guideline** and satisfy the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. They should be considered with the other rat metabolism studies using different ring labels, namely, [chlorophenyl-UL-^{14}C]HEC 5725 (MRIDs 45865714 and 45865715) and [pyrimidine-2-^{14}C]HEC 5725 (MRIDs 45865718 and 45865719).

Cont. Metabolism - Rat

EXECUTIVE SUMMARY: A study (MRID 45865718) was conducted in male rats to assess the metabolism and disposition of [pyrimidine-2-^{14}C]HEC 5725 (Fluoxastrobin; >98% radiochemical purity, batch no. KML2621-A) and non-radiolabeled HEC 5725 (98.8% chemical purity, batch no. M00358) over 48 hours following a single oral dose of 1 mg/kg. A whole-body autoradiography study (MRID 45865719) over a 168-hour period was also conducted in male and female rats given a single 3 mg/kg oral dose of [pyrimidine-2-^{14}C]HEC 5725 (radiochemical purity >99%, lot no.12216/1).

Recovery of administered radioactivity in the initial study (MRID 45865718) was 84.9-86.7% of the administered dose and is considered acceptable for the 48-hour duration. In the whole-body

autoradiography experiment, recovery of administered radioactivity was 104-112%. Both studies affirmed the rapid absorption and complete excretion of pyrimidine-labeled HEC 5725. Peak plasma concentration was attained at 6-8 hours following dosing in the initial metabolism/ disposition study. Excretion via the feces was the major route of elimination (72-73% of the dose over 48 hours in MRID 45865718) and 94-99% of the dose over the 168-hour duration whole-body autoradiography study (MRID 45865719). Renal excretion was a secondary route (12-16%), and elimination of radioactivity via expired air was inconsequential (~0.1%) but confirmed stability of the label. Tissue/carcass burdens accounted for about 1% of the administered radioactivity at 48 hours post dose. Most of this radioactivity was associated with the liver, skin (each ~0.2%) and gastrointestinal tract (~0.4%). Autoradiography experiments confirmed that radioactivity was greatest in organs and tissues associated with absorption/ excretory function (*e.g.*, gastrointestinal tract, liver, kidneys). Time-course analysis indicated that test material and/or metabolites reached greatest concentrations within 1 hour of dosing and decreased rapidly thereafter. For all tissues/organs, radioactivity residue was approaching or below LOD or LOQ at 168 hours post dose. Results of the whole-body autoradiography experiments showed no significant gender-related differences in the tissue distribution and disposition of [pyrimidine-2 - ^{14}C]HEC 5725.

Metabolite characterization studies of [pyrimidine-2-^{14}C]HEC 5725 indicated that the test article is extensively metabolized. The urinary and fecal metabolites accounted for 57-61% of the administered dose. Eight components, representing about 7% of the 1 mg/kg dose, were identified in the 48-hour urine samples. These metabolites were primarily hydroxylation/ conjugation products. No parent compound was detected in the urine. Twelve metabolites and parent compound were detected in the feces. Fecal metabolites were also primarily hydroxylation products, the most prevalent being HEC 5725-di-OH, isomer 2 (11.6% of the dose), HEC5725-di-OH-dioxazine-OH, isomer 2 (9.3% of the dose), and HEC5725-E-des- chlorophenyl (7.2% of the dose). All fecal radioactivity was accounted for by identified metabolites and parent compound being approximately 54% and 1%, respectively, of the administered dose. Other metabolism/disposition studies on [methoxyiminotolyl-ring-UL-^{14}C] HEC 5725 (reviewed separately in MRID 45865716) have shown that biliary contributions account for most fecal radioactivity and that the metabolism of the test article is not a function of bacterial flora. The results of these studies are consistent with the proposed metabolism pathway.

These metabolism studies of [pyrimidine-2-^{14}C]HEC 5725 in the rat (MRID 45765718, 45865719) are collectively classified **Acceptable/Guideline** and satisfy the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. They should be considered with the other rat metabolism studies using different ring labels, namely, [chlorophenyl-UL-^{14}C]HEC 5725 (MRIDs 45865714 and 45865715) and [methoxyiminotolyl-ring-UL-^{14}C] HEC5725 (MRIDs 45865716 and 45865717).

***In Vivo* Dermal Penetration Study - Monkey**

EXECUTIVE SUMMARY: A preliminary study (MRID 45911501) was conducted in which a single 20 µCi (200 µg) dose of [^{14}C]HEC 5725 (lot no. 12250/39, purity >99%) was administered intravenously or dermally (EC 100 formulation) to one male rhesus monkey. The intravenous dose served as a reference for 100% bioavailability. For the main study (MRID 45911502) a single 15 µCi (150 µg) dose of [^{14}C]HEC 5725 (lot no. 12250/39, purity >99%) was administered

dermally (EC 100 formulation) to five male rhesus monkeys. The dermal application was for eight hours. Excreta were monitored for up to 192 hours (intravenous dose) or 120 hours (dermal application).

There were no significant adverse effects that could be attributed to the test article. One monkey vomited and another (both in the dermal exposure group; main study) exhibited soft stools at 4 hours post-application. Actual doses were 195 µg (i.v.), 172 µg (preliminary dermal), and 148µg (main dermal). These doses correspond to 60.9 µg/kg, 7.17 µg/cm^2, and 6.12 µg/cm^2; only 2.5, 14, and 1% from nominal, respectively. Radioactivity mass balances for the respective test groups were acceptable at 94.0, 102.0, and 93.4%. Following intravenous administration, 52.99% of the administered radioactivity was excreted via the urine, 19.91 via feces, and an additional 21.1% was recovered from cage debris/rinses over the 192-hour experimental period. Approximately 93% of excretion in the urine occurred by 48 hours. Fecal excretion of radiolabel following intravenous administration, although significant (19.91%), was approximately 37.6% of that for urine. Following the 8-hour dermal application, the majority of radioactivity was associated with the dermal swabs and the extracts of those swabs (~84.3-88.4% of applied radioactivity). Only 2.7-12.9% of the radioactivity was associated with the cover material affirming the investigators' contention that most of the applied dose was available for absorption and not bound to the appliance materials.

The results of the preliminary study clearly showed that following intravenous administration allowing for 100% bioavailability, HEC 5725 is rapidly and nearly totally excreted in the urine and feces within 48 hours. Following an 8-hour dermal application in a male monkey, absorption was negligible (1.16% preliminary, 2.16% main). As the intravenous dose was not given to the animals of the main dermal group, a normalized absorption value for the main study could not be calculated.

This study was a combined preliminary and definitive investigation into the disposition of [^{14}C]HEC 5725 in male monkeys following intravenous and dermal administration. The study protocol designated only a single dose and a limited exposure period. This study in the monkey is **Acceptable/NonGuideline.** There is no the guideline for a dermal penetration study in the monkey.

Immunotoxicity - Mouse

EXECUTIVE SUMMARY: In a subacute immunotoxicity study (MRID 45865726), HEC 5725 (94.2% a.i.; Batch No. 06261/0008) was fed in the diet to CD1 male and female mice at nominal dietary concentrations of 0, 450, 1800, or 7000 ppm (equivalent to 0, 106.8, 367.3, and 1534.4 mg/kg/day for males and 0, 157.3, 659.6, and 2383.3 mg/kg/day for females) for 5 weeks. At study completion, the mice were sacrificed and a plaque forming cell assay was done.

No clinical signs of toxicity or mortality were found and no treatment-related effects were found on body weight, food intake, or B-cell activated, T-cell mediated IgM response to SRBC. However, the study is considered unacceptable because of uncertainty in dietary test material intake, failure to report spleen weight of each mouse at necropsy, and failure of the laboratory to demonstrate its capability in performing this type of assay.

This study is classified as **Unacceptable/guideline** and does not satisfy the guideline requirements for an immunotoxicity study (OPPTS 870.7800).

2.2 Non-Critical Mode of Action or Metabolite Studies

Nine Week Oral Toxicity (feeding) - Rat

EXECUTIVE SUMMARY: In a 9-week oral toxicity study (MRID 45865721) HEC 5725 [Fluoxastrobin , 97.1% a.i., Batch # NLL6112-(20-22)] was administered to 10 male rats/dose in the diet at dose levels of 0, 62.5, 125, 1000, or 8000 ppm (equivalent to 0, 3.6, 7.3, 59.7, or 520.3 mg/kg bw/day) and to 10 female rats/dose at dose levels of 0, 125, 250, 2000, or 16,000 ppm (equivalent to 0, 9.0, 18.3, 146.3, or 1544.2 mg/kg bw/day). Satellite groups were administered 1% NH_4Cl in the drinking water (to assess the effects of urinary acidification) ad libitum and consisted of 10 male rats/dose with test substance administered in the diet at dose levels of 0 or 8000 ppm (equivalent to 0 or 476.5 mg/kg bw/day) and 10 female rats/dose with HEC 5725 administered at dose levels of 0 or 16,000 ppm (equivalent to 0 or1590.6 mg/kg bw/day).

There were no treatment-related effects on mortality, clinical signs, organ weight, or gross pathology. There was a marginal decrease in body weight and body weight gain in high-dose female rats. Blood parathyroid hormone activity showed no HEC 5725-related changes. Serum Vitamin D concentration showed no toxicologically significant differences among groups. The main target organs appear to be the adrenal cortex, kidney and possibly bone. This study tested whether the increased calcium excretion and calcium oxalate crystal formation in high dose animals was a result of the HEC 5725-induced pH changes, by acidifying the urine via administration of 1% NH_4Cl in the drinking water. Cotreatment with HEC 5725 maintained the urinary pH at about main group control levels but also induced increases in serum calcium (males), calcium excretion (males), and calcium oxalate crystal formation (male and female) in the absence of a more alkaline environment. HEC 5725 caused excretion of a highly alkaline urine and disturbances in calcium homeostasis reflected in slightly increased serum calcium together with increased urinary excretion of calcium as well as urinary calcium oxalate crystal formation; these effects were seen in males at $\geq$ 1000 and females at 16,000 ppm. Fine vacuolation of the zona fasciculata of the adrenal cortex suggestive of increased metabolic activity was seen in high-dose males, in both main and satellite groups.

The subchronic oral LOAEL for HEC 5725 for male rats is 1000 ppm (59.7 mg/kg bw/day) and for female rats is 16,000 ppm (1544.2 mg/kg bw/day), based on markedly increased urinary pH in males at $\geq$ 1000 ppm and on increases in urinary calcium excretion resulting in calcium oxalate crystal formation in males at $\geq$ 1000 ppm and females at 16,000 ppm. The NOAEL for male rats is 125 ppm (7.3 mg/kg/day) and for female rats is 2000 ppm (146.3 mg/kg bw/day).

This two-month oral toxicity study in the rat is **Acceptable/Non-guideline.**

Four-Week Subacute Oral (feeding) - Rat

EXECUTIVE SUMMARY: In a 4-week oral toxicity study (MRID 45865725) HEC 5725 N

[99.3% a.i., (90% E-isomer, 10% Z-isomer) batch no. NLL6112-24] in Altromin® 1321 diet (with 1% peanut oil) was administered to five Wistar HsdCpb:WU (SPF) rats/sex/dose at dose levels of 0, 100, 500, 2500, or 10,000 ppm (0, 9.7, 49.4, 237.1, or 1016.8 mg/kg/day for males and 0, 8.6, 43.4, 221.6, or 891.8 mg/kg/day for females, respectively). In addition, five additional rats/sex/dose were used to conduct immunotoxicity assays. Following HED's request, the identity of HEC 5725 N (E:Z = 90:10%) was provided in a separate Bayer's file [HEC 5725: Dossier according to directive 91/414 EEC, Document N, Tier 3, Annex II/Annex III (480 SC), Summary Documentation, 9 pages, dated April 2003].

No effects were observed on mortality, clinical signs, or in immunotoxicity assays. Food and water consumption of treated animals were comparable to the controls; however, overall body weight was slightly decreased in females in the 10,000 ppm group, ranging from 8% less than the control group on day 7 to 13% less on day 28. There were slight dose-related decreases in female body weight gain at doses ≥500 ppm (83, 79, and 72% of the control for the 500, 2500, or 10,000 ppm dose groups, respectively). The decreases appeared to correlate with the lower food efficiency throughout the study in females. Males administered 10,000 ppm showed decreases in hemoglobin (6%, $p<0.01$) and MCHC (2%, $p<0.05$) compared with the controls. Females administered 10,000 ppm had a decrease in hemoglobin (9%, $p<0.01$). In addition, the females showed slight decreases in hematocrit 6, 6 and 8% than the controls for the 500, 2500 and 10,000 ppm groups, respectively and did not appear to be dose or treatment-related. Decreases in enzyme activities of blood and liver and increases in P-450 activity were within the normal range of variation. Urine calcium concentrations were elevated to 384 and 288% of the control values in the males and females that were treated with 10,000 ppm HEC 5725N. This is consistent with the disturbance of calcium homeostasis reported in a subchronic study (MRID 45865627). There were no absolute organ weight changes observed; however, relative liver weight of the highest dose groups of males and females increased 17 and 15% (both $p<0.01$) over the controls, respectively. Immunotoxicity assays showed no dose-related or statistically significant changes due to treatment with HEC 5725N.

Under the conditions of this study, the LOAEL for HEC 5725N administered in the diet to Wistar HsdCpb:WU (SPF) rats, for 4 weeks is 10,000 ppm for males (1016.8 mg/kg/day) based on a biologically significant decrease in hemoglobin and an increase in urine calcium concentration and 10,000 ppm for females (891.8 mg/kg/day) based on biologically significant decreases in hemoglobin and body weight and an increase in urine calcium concentration. The NOAEL is 2500 ppm for males (237.1 mg/kg/day) and for females (221.6 mg/kg/day).

This four week oral toxicity study in rats is classified as **Acceptable/Nonguideline** and provides information useful in setting doses for longer term studies.

Four-Week Subacute Oral (feeding) - Rat

EXECUTIVE SUMMARY: In a subacute (28-day) study (MRID 45865727), HEC 5725 [95.1% a.i. (98.8 % E-isomer, 1.2 % Z-isomer), Batch # 06261/0008] and HEC 5725 A [97.7% a.i. (62.5% E-isomer, 35.2% Z-isomer), Batch # NLL 6112-31] were each administered to 5 Wistar rats/sex/dose in the diet at concentrations of 0, 100, 500, 2500, or 10,000 ppm (except that HEC 5725A had no 0 ppm group). In males, these doses were equivalent to 0, 8.3, 41.5, 209.7, or

1005.6 mg/kg bw/d HEC 5725 and in females to 0, 10.0, 52.7, 261.2, or 1451.7 mg/kg bw/d. Doses were equivalent to 8.5, 42.1, 226.6, or 1001.5 mg/kg bw/d HEC 5725A in males, and to 8.8, 47.7, 247.6, or 1419.5 mg/kg bw/d in females. Actual mean test intake of HEC 5725A may have been up to 20% less than the nominal values due to limited stability in the diet resulting in test compound levels as low as 60% in dietary mixtures at the end of the weekly feeding periods.

There were no treatment-related effects on mortality, clinical signs, hematology, or gross pathology. There was a marginal decrease in body weight of high-dose male rats treated with both HEC 5725 and HEC 5725 A and in body weight gain of all high-dose groups, male and female, treated with both test substances. There were no toxicologically significant effects on urinalysis parameters and no toxicologically significant effects were seen on absolute or relative organ weight. Adrenal cortical cytomegaly with fine vacuolization was seen in all high dose groups (male and female) treated with both test substances and in one female each at 2500 ppm in the HEC 5725 and HEC 5725 A groups. The effects of HEC 5725 and HEC 5725 A were very similar despite the stability problem with the latter.

The LOAEL for HEC 5725 and HEC 5725 A in male rats is 10,000 ppm (1005.6 mg/kg/day and 1001.5 mg/kg bw/day, respectively) and for female rats is 2500 ppm (261.2 mg/kg bw/day and 247.6 mg/kg bw/day for HEC 5725 and HEC 5725 A, respectively), based on decreased body weight in males and adrenal cytomegaly with fine cytoplasmic vacuolation in both sexes. The NOAEL for male rats is 2500 ppm (209.7 mg/kg/day and 226.6 mg/kg bw/day for HEC 5725 and HEC 5725 A, respectively) and for female rats is 500 ppm (52.7 mg/kg bw/day and 47.7 mg/kg bw/day for HEC 5725 and HEC 5725 A, respectively).

This four-week oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a subacute oral toxicity study (OPPTS 870.350 (§82-1a); OECD 407).

Bacterial system, *e.g., Salmonella typhimurium*/mammalian activation gene mutation assay using HEC 5725 N (MRID 45865705)

EXDECUTIVE SUMMARY: In independent repeat (initial plate incorporation, repeated by the preincubation variation), five histidine-auxotrophic (*i.e.,* deficient, *his*$^-$) strains of *Salmonella typhimurium* (TA1535, TA100, TA1537, TA98, and TA102) were exposed to HEC 5725 N (Batch No. HUW 4202-3-3, 99.7% a.i., dissolved in dimethyl sulfoxide, DMSO) at concentrations of 16, 50, 158, 500, 1581 and 5000 *u*g/plate (by plate incorporation, as well as following preincubation), in the presence and absence of exogenous metabolic activation provided by Aroclor 1254-induced supernatants (S9) of hepatic homogenates from male rats. In addition to cultures exposed to the solvent, DMSO (acting as a "negative control"), others were treated with strain-specific reference mutagens, to serve as positive controls. After 48 hours incubation at 37°C, the frequencies of revertant, prototrophic (*i.e.,* wild type, *his*$^+$) colonies in test cultures were compared to negative controls.

No cytotoxicity was observed up to the highest concentration tested (HCT), but increasing precipitation, starting in nonactivated cultures treated at 1581 *u*g/plate, made analysis only partially interpretable at the HCT,5000 *u*g/plate.

At no concentration in any test substance-treated culture in either assay, however, was an increase

in revertant colonies over concurrent solvent controls observed, nor when compared to the laboratory's historical negative control data. By contrast, all positive controls responded with marked increases in revertants.

Therefore HEC 5725 N is considered non-mutagenic in this *S. typhimurium*/microsome test.

This study is classified as **acceptable/guideline**, and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

Bacterial system, *e.g.*, *Salmonella*/mammalian activation gene mutation assay using HEC 5725-Phenoxy-Hydroxypyrimidine (MRID 45865706)

EXECUTIVE SUMMARY: In independent repeat (plate incorporation, repeated by the pre-incubation modification) reverse gene mutation assays (MRID 45865706), five histidine-auxotrophic (*i.e.*, deficient, *his*$^-$) strains of *Salmonella typhimurium* LT2 (TA1535, TA100, TA1537, TA98, and TA102) were exposed to the test article (Batch No. KTS 9653-4-1, 98.2% a.i., dissolved in dimethylsulfoxide, DMSO) at concentrations of 16, 50, 158, 500, 1581 and 5000 ug/plate in the plate incorporation assay, or 100, 200, 400, 800, 1600, and 3200 ug/plate following pre-incubation, both assays in the presence and absence of exogenous metabolic activation provided by Aroclor 1254-induced hepatic microsomes from male Sprague-Dawley rats. Revertant prototrophic (*i.e.*, wild-type, *his*$^+$) bacterial colonies were counted after 48 hours incubation at 37°C. In addition to cultures exposed to the solvent, DMSO, others were treated with strain-specific reference mutagens. Only single replicates were used for test concentrations and the solvent or positive controls.

Cytotoxicity was evident at concentrations ≥ 500 ug/plate in test article-treated TA1537 (plate incorporation), but only at a higher concentration (≥ 1581 ug/plate) in two other tester strains treated in the plate incorporation assay, and at the highest concentrations tested (5000 ug/plate and 3200 ug/plate) in the plate incorporation and pre-incubation procedures, respectively.

At no test concentration in any strain treated in the presence or absence of metabolic activation, however, was an increase in revertant colonies over that in concurrent solvent controls found, in contrast to the positive controls which all manifested marked increases.

Therefore HEC 5725-phenoxy-hydroxy-pyrimidine is considered non-mutagenic in this *S. typhimurium* test.

This study is classified as **unacceptable/guideline** and does not satisfy the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data. Only single replicates were used for the test material concentrations and the solvent or positive controls. However, an acceptable and negative study that satisfies the requirements for Guideline 84-2 was also conducted with HEC 5725 (MID 45865707).

Bacterial system, *e.g.*, *Salmonella typhimurium*/mammalian activation gene mutation assay using HEC 5725-Phenoxy-Hydroxypyrimidine (MRID 45865707)

EXECUTIVE SUMMARY: In independent, repeat (initially by plate incorporation, repeated by

the preincubation variation) assays (MRID 45865707), five histidine-auxotrophic (*i.e.*, deficient:*his* $^{-}$) strains of *Salmonella typhimurium* (TA1535, TA100, TA1537, TA98, and TA102) were exposed to HEC 5725-phenoxy-hydroxy-pyrimidine (Batch No. KTS9653-4-1, 98.6% a.i, dissolved in dimethyl sulfoxide, DMSO) at concentrations of: 16, 50, 158, 500, 1581 and 5000 ug/plate by plate incorporation, or: 5, 16, 50, 158, 500, and 1581 ug/plate following preincubation, in the presence and absence of metabolic activation provided by Aroclor 1254-induced supernatants (S9) derived from treated male Sprague-Dawley rats. In addition to cultures exposed to the solvent, DMSO (serving as "negative" controls), others were treated with strain-specific mutagens, to serve as positive controls. After incubation at 37°C for 48 hours, revertant prototrophic (*i.e.*, wild-type, *his* $^{+}$) bacterial colonies in test article-treated cultures were compared to solvent controls.

Cytotoxicity was observed at concentrations ≥ 500 ug/plate in treated TA 1537 following preincubation, but only at higher concentrations (≥1581 ug/plate) in the plate incorporation assay (all strains). At no test concentration in either assay ± S9, however, was evidence of mutagenic activity (increased revertant counts) found in test article-treated cultures when compared to solvent controls. In contrast, all positive controls manifested marked increases in revertants.

Therefore, HEC 5725-phenoxy-hydroxypyrimidine is considered non-mutagenic in this *S. typhimurium* test.

This study is classified as **acceptable/guideline** and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data. These negative findings were confirmed in an earlier study (MRID 45865706).

Bacterial system, *e.g.*, *Salmonella typhimurium*/mammalian activation gene mutation assays using HEC 5725-dihydroxypyrimidine (MRID 45865708)

EXECUTIVE SUMMARY: In independent, repeat (initial plate incorporation, repeated by pre-incubation) assays (MRID 45865708), five histidine-auxtrophic (*i.e.*, deficient, *his* $^{-}$) strains of *Salmonella typhimurium* (TA1535, TA100, TA1537, TA98, and TA102) were both exposed to HEC 5725-dihydroxypyrimidine (Batch No. JSU7016-1, 83.0% a.i., dissolved in dimethyl sulfoxide, DMSO) at six concentrations ranging from 16 to 5000 *u*g/plate, in the presence and absence of metabolic activation provided by Aroclor 1254-induced supernatants of homogenates from Aroclor 1254-treated male Sprague-Dawley rats. In addition to cultures exposed to the solvent, DMSO, alone (acting as a "negative control"), others were treated with strain-specific reference mutagens. After incubation at 37°C for 48 hours, revertant prototrophic (*i.e.*, wild-type, *his* $^{+}$) bacterial colonies in test-article treated cultures were compared to negative controls. Only one replicate was used for the test material concentrations and the solvent or positive controls.

Cytotoxicity was observed in the plate incorporation assay at ≥ 500 ug/plate in test article-treated TA100 and TA102 cultures, but only at higher concentrations (≥ 1600 *u*g/plate) in the other test strains; there was no cytotoxicity at any concentration in the pre-incubation assay. At no concentration in either assay in the presence or absence of activation, however, were revertant counts increased over concurrent negative controls. In contrast, all positive controls showed marked increases in revertant counts.

Therefore, HEC 5725-dihydroxyprymidine is considered non-mutagenic in this *S. typhimurium* test.

This study is classified as **unacceptable/guideline**, and does not satisfy the requirement for FIFRA Test guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data. Only single replicates were prepared for the test material concentrations and the negative or positive controls.

3.0 METABOLISM CONSIDERATIONS

Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.

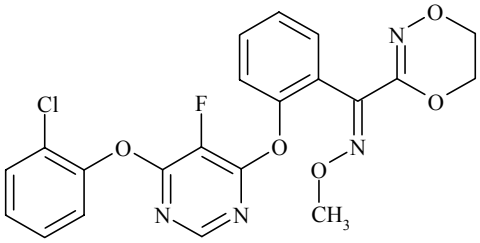
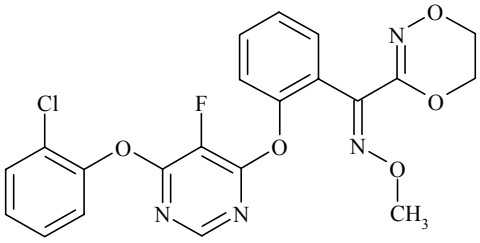
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Fluoxastrobin, E isomer [Parent] (1*E*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime	Tomato	94.8		
	Wheat Forage	23.6		
	Wheat Hay	74.3		
	Wheat Straw	59.0		
	Wheat Grain	70.1		
	Peanut	61.4 (hay)	NF (nutmeat)	
	Milk		1.48	
	Muscle (goat)		6.59	
	Fat (goat)	44.4		
	Liver (goat)		6.82	
	Kidney (goat)		3.76	
	Egg		9.8	
	Liver (poultry)		0.9	
	Muscle (poultry)	18.7		
	Fat (poultry)	46.8		
	Rat	Yes		
	Water	Yes		
	Rotational Crops	Yes		
Fluoxastrobin Z-isomer (1*Z*)-[2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime	Tomato		3.4	
	Wheat Forage		4.3	
	Wheat Hay	17.7		
	Wheat Straw	21.3		
	Wheat Grain	15.9		
	Peanut	23.7 (hay)	NF (nutmeat)	
	Milk		NF	
	Muscle (goat)		NF	
	Fat (goat)		1.64	
	Liver (goat)		0.46	
	Kidney (goat)		NF	
	Egg	0.7		
	Liver (poultry)	--		
	Muscle (poultry)	0.4		
	Fat (poultry)	0.9		

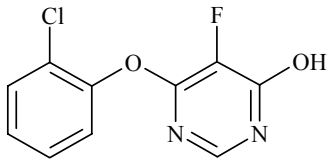
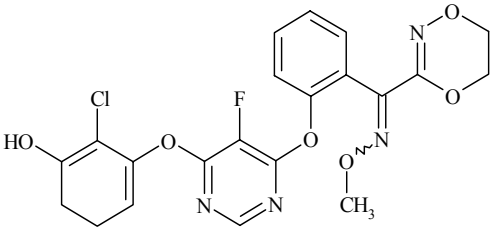
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
	Rat		NF	
	Water	Yes		
	Rotational Crops		Yes	
Phenoxy-hydroxypyrimidine metabolite [HEC7154] 6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinol	Tomato		NF	
	Wheat Commodities		Yes (straw)	
	Peanut		0.4 (hay), NF (nutmeat)	
	Milk	10.6		
	Muscle (goat)	52.9		
	Fat (goat)	29.0		
	Liver (goat)		8.29	
	Kidney (goat)	25.1		
	Egg	25.0		
	Liver (poultry)	20.8		
	Muscle (poultry)	34.5		
	Fat (poultry)	21.2		
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-3-hydroxyphenyl [2-[[6-(2-chloro-3-hydroxyphenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazine-3-yl)-methanone *O*-methoxime	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		Yes (all tissues)	
	Rat		Yes	
	Water		Yes	
	Rotational Crops		Yes	

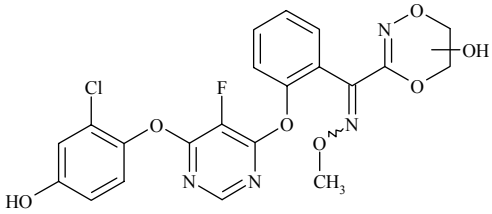
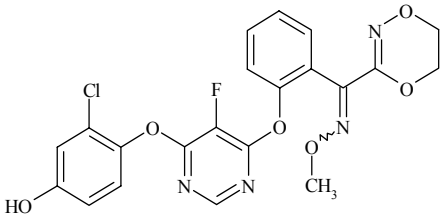
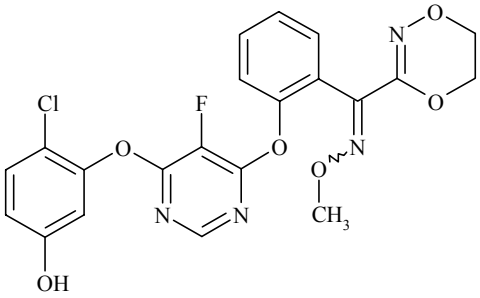
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-4-OH-dioxazine-OH	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Milk		NF	
	Goat Commodities		Yes (liver & kidney)	
	Poultry Commodities		NF	
	Rat	Yes		
	Water		NF	
	Rotational Crops		NF	
HEC5725-4-hydroxyphenyl [2-[[6-(2-chloro-4-hydroxyphenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazine-3-yl)-methanone *O*-methoximine	Tomato		NF	
	Wheat Commodities		Yes (hay, straw, & grain)	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		Yes	
	Rotational Crops		Yes	
HEC5725-5-hydroxyphenyl {2-[6-(2-chloro-5-hydroxy-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-(5,6-dihydro-[1,4,2]dioxazin-3-yl)-methanone *O*-methyl-oxime	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		Yes	

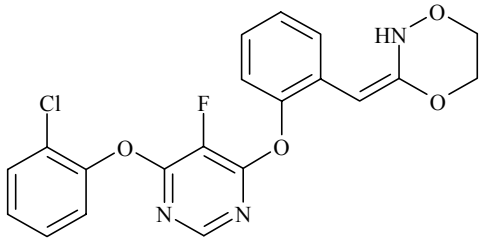
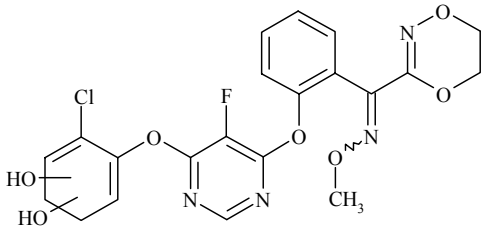
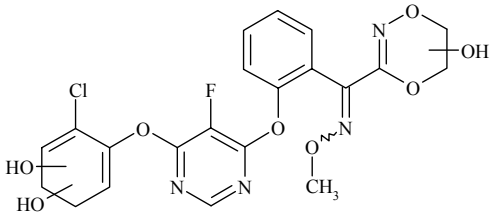
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-des-oxime-ether 3-{2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-benzylidene}-[1,4,2]dioxazinane	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		Yes (all tissues)	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-di-OH-diene	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (all tissues)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-di-OH-diene-dioxazine-OH	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (all except liver)	
	Poultry Commodities		NF	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	

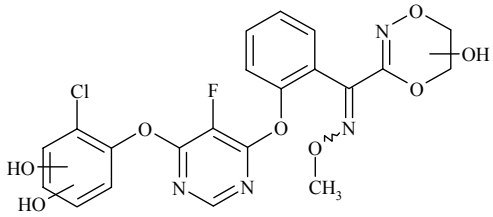
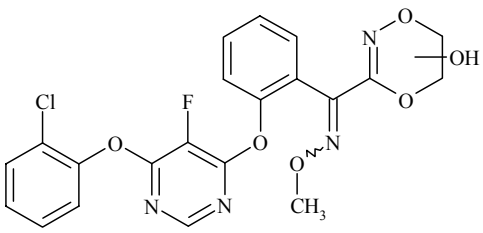
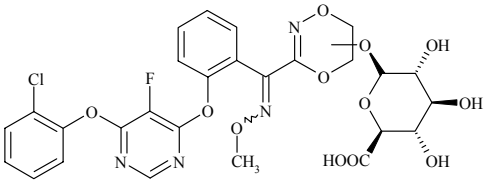
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-di-OH-dioxazine-OH	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (milk, liver, & kidney)	
	Poultry Commodities		NF	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-dioxazine-OH	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		Yes (all tissues)	
	Rat		Yes	
	Water		NF	
	Rotational Crops		Yes	
HEC5725-dioxazine-OH-GA	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (liver only)	
	Poultry Commodities		Yes (liver only)	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	

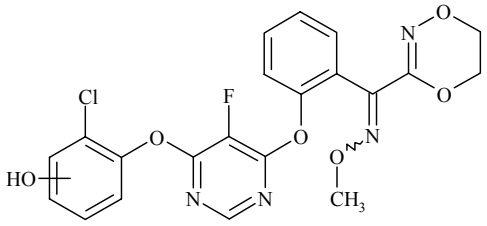
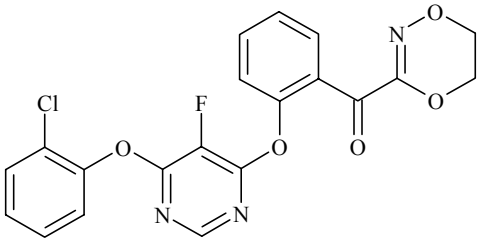
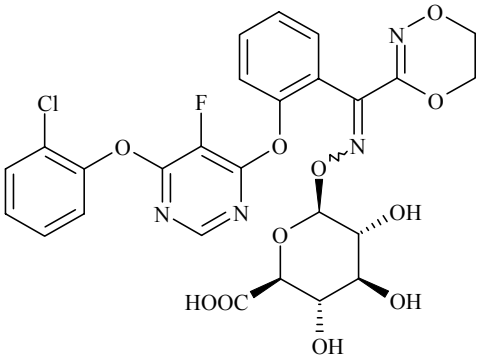
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-hydroxyphenyl	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Milk		1.7	
	Muscle (goat)		1.9	
	Fat (goat)	12.9		
	Liver (goat)	11.4		
	Kidney (goat)		2.39	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		Yes	
	Rotational Crops		NF	
HEC5725-ketone {2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-(5,6-dihydro-[1,4,2]dioxazin-3-yl)-methanone	Tomato		Yes	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		Yes (milk)	
	Poultry Commodities		Yes (fat)	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-oxime-GA 6-[{2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-(5,6-dihydro-[1,4,2]dioxazin-3-yl)-methyleneaminooxy]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (liver & kidney)	
	Poultry Commodities		Yes (all tissues)	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	

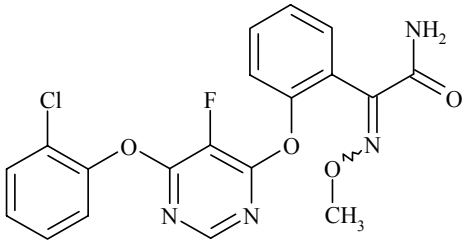
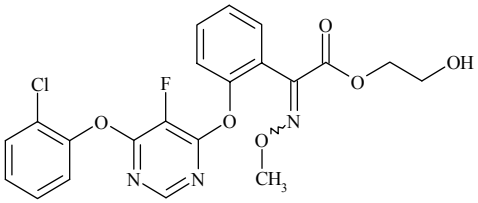
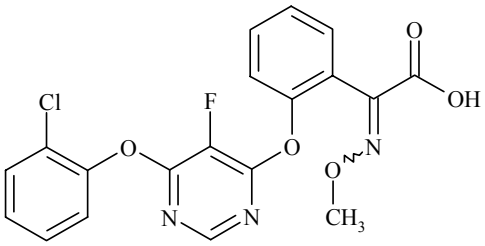
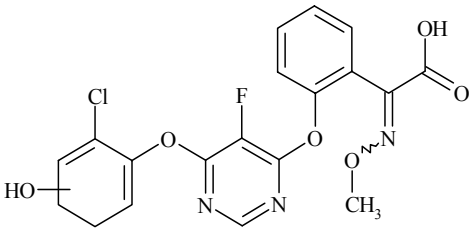
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-amide 2-{2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-2-methoxyimino-acetamide	Tomato		Yes	
	Wheat Commodities		Yes (all matrices)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		Yes (all tissues)	
	Rat		Yes	
	Water		Yes	
	Rotational Crops		Yes	
HEC5725-CA-glycol ester 2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-methoxyimino-acetic acid 2-hydroxy-ethyl ester	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-carboxylic acid {2-[6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-yloxy]-phenyl}-methoxyimino-acetic acid	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		Yes (liver & muscle)	
	Rat		NF	
	Water		Yes	
	Rotational Crops		NF	
HEC5725-OH-CA	Tomato		NF	
	Wheat Commodities		Yes (straw & hay)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		NF	

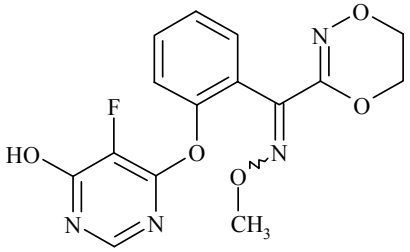
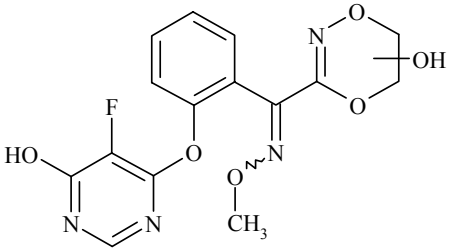
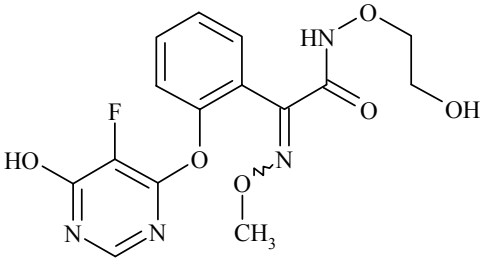
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
	Rat		Yes	
	Water		NF	
	Rotational Crops	20.5		
HEC5725-des-chlorophenyl (5,6-dihydro-[1,4,2]dioxazin-3-yl)-[2-(5-fluoro-6-hydroxy-pyrimidin-4-yloxy)-phenyl]-methanone *O*-methyl-oxime	Tomato		NF	
	Wheat Commodities		Yes (forage, hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		Yes (all except fat)	
	Poultry Commodities		NF	
	Rat	Yes		
	Water		Yes	
	Rotational Crops	25.3		
HEC5725-des-chlorophenyl-dioxazine-OH	Tomato		NF	
	Wheat Commodities		Yes (all matrices)	
	Peanut		NF	
	Goat Commodities		Yes (all except fat)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops	13.5		
HEC5725-des-chlorophenyl-glycol 2-{2-[(5-fluoro-6-hydroxypyrimidin-4-yl)oxy]phenyl}-N-(2-hydroxyethoxy)-2-(methoxyimino)acetamide	Tomato		NF	
	Wheat Commodities	20.5 (straw)		
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		Yes	

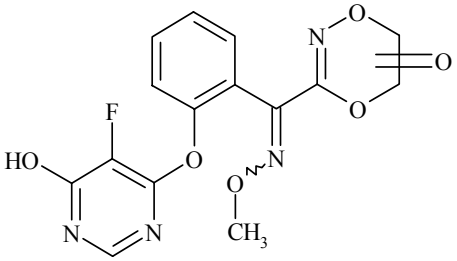
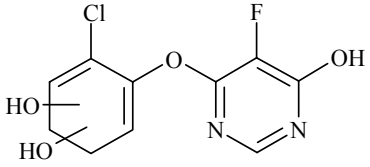
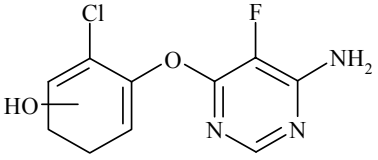
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-des-chlorophenyl-keto-dioxazine	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		NF	
	Water		NF	
	Rotational Crops	12.5		
HEC5725-di-OH-diene-pyrimidine-OH	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities	21.8		
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-OH-phenoxy-amino-PMD	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		Yes	

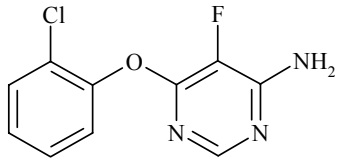
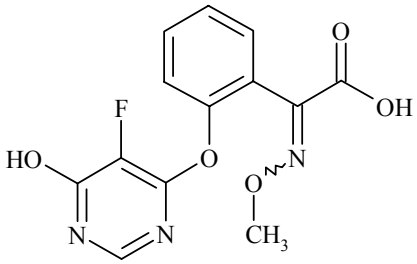
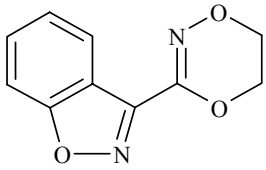
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-phenoxy-aminopyrimidine 6-(2-chloro-phenoxy)-5-fluoro-pyrimidin-4-ylamine	Tomato		Yes	
	Wheat Commodities		Yes (hay)	
	Peanut		Yes (hay & straw)	
	Goat Commodities		NF	
	Poultry Commodities		Yes (liver)	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-des-chlorophenyl-carboxylic acid; HEC5725-des-chlorophenyl-CA [2-(5-fluoro-6-hydroxy-pyrimidin-4-yloxy)-phenyl]-methoxyimino-acetic acid	Tomato		NF	
	Wheat Commodities		Yes (straw	
	Peanut		NF	
	Goat Commodities		NF	
	Poultry Commodities		NF	
	Rat		NF	
	Water		NF	
	Rotational Crops		Yes	
HEC5725-benz-isoxazole 3-(5,6-dihydro-[1,4,2]dioxazin-3-yl)-benzo[d]isoxazole	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (all matrices except kidney)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	

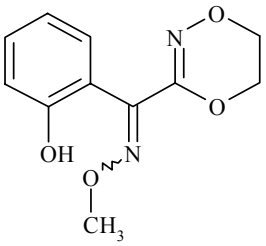
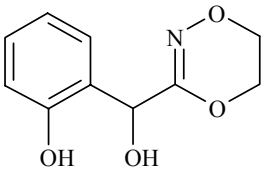
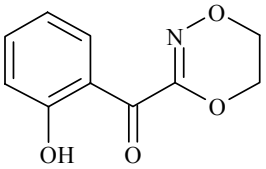
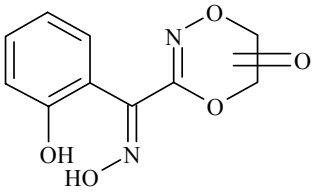
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-des-pyrimidine (5,6-dihydro-[1,4,2]dioxazin-3-yl)-(2-hydroxy-phenyl)-methanone *O*-methyl-oxime	Tomato		NF	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		Yes (hay)	
	Goat Commodities		Yes (all except fat)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops	12.5		
HEC5725-dioxazinyl-alcohol 2-[(5,6-dihydro-[1,4,2]dioxazin-3-yl)-hydroxy-methyl]-phenol	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		Yes (hay)	
	Goat Commodities	15.7 (liver)		
	Poultry Commodities		Yes (liver)	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-dioxazinyl-phenylketone (5,6-dihydro-[1,4,2]dioxazin-3-yl)-(2-hydroxy-phenyl)-methanone	Tomato		Yes	
	Wheat Commodities		Yes (hay & straw)	
	Peanut		NF	
	Goat Commodities		Yes (all matrices)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-E-oxo-dioxazine-oxime	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (all matrices)	

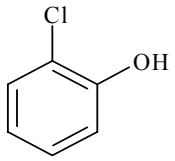
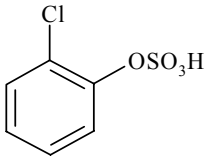
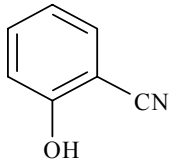
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
	Poultry Commodities		NF	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	
HEC5725-2-chlorophenol 2-chlorophenol	Tomato		NF	
	Wheat Commodities		Yes (hay, straw & grain)	
	Peanut		NF	
	Goat Commodities		Yes (liver)	
	Poultry Commodities		Yes (all)	
	Rat	Yes		
	Water		NF	
	Rotational Crops		NF	
HEC5725-2-chlorophenol-SA sulfuric acid mono-(2-chlorophenyl) ester	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (all except fat)	
	Poultry Commodities		Yes (egg & muscle)	
	Rat	Yes		
	Water		NF	
	Rotational Crops		NF	
HEC5725-2-cyanophenol 2-cyanophenol	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities		Yes (All matrices)	
	Poultry Commodities		Yes (All matrices)	
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	

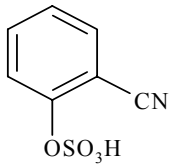
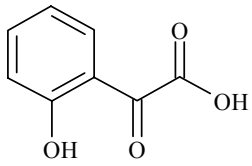
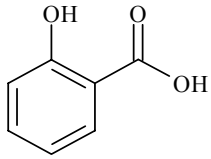
Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.				
Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
HEC5725-2-cyanophenol-SA sulfuric acid mono-(2-cyanophenyl) ester	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		NF	
	Goat Commodities	22.7 (milk)		
	Poultry Commodities		Yes (muscle)	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-2-OH-phenylglyoxylic acid; HEC5725-phenylglyoxylic acid; HEC5725-ketocarboxylic acid 2-(hydroxyphenyl)oxo-acetic acid	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		Yes (hay)	
	Goat Commodities		Yes (muscle)	
	Poultry Commodities		Yes (liver & muscle)	
	Rat		NF	
	Water		NF	
	Rotational Crops		NF	
HEC5725-salicylic acid salicylic acid [2-hydroxybenzoic acid]	Tomato		NF	
	Wheat Commodities		NF	
	Peanut		Yes (hay)	
	Goat Commodities		NF	
	Poultry Commodities	12.5		
	Rat		Yes	
	Water		NF	
	Rotational Crops		NF	

Table 3.0-appendix. Tabular Summary of Metabolites & Degradates of Fluoxastrobin.

Chemical Name	Matrix	Percent TRR		Structure[1]
		Major Residue (>10%TRR)	Minor Residue (<10%TRR)	
Tomato: 3-day PHI.	MRID 45865511; [chlorophenyl-UL-^{14}C]fluoxastrobin; 3 x 0.128 lb ai/A/application (0.5x rate); maturity; 3-day PHI. MRID45865512; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 3 x 0.128 lb ai/A/application (0.5x rate); maturity; 3-day PHI.			
Wheat:	MRID 45865513; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 0.05 lb ai/A (seed treatment), 2 x 0.27-0.28 lb ai/A/application (rate: no proposed use for wheat); maturity; 9- to 47-day PHIs. MRID 45865514; [chlorophenyl-UL-^{14}C]fluoxastrobin; 0.06 lb ai/A (seed treatment), 2 x 0.28 lb ai/A/application (rate: no proposed use for wheat); maturity; 10- to 63-day PHIs. MRID 45865515; [pyrimidine-2-^{14}C]fluoxastrobin; 0.05 lb ai/A (seed treatment), 2 x 0.25-0.28 lb ai/A/application (rate: no proposed use for wheat); maturity; 10- to 48-day PHIs. MRID 45865516; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 0.048 lb ai/A (seed treatment) (rate: no proposed use on wheat); maturity; 63- to 152-day PHIs.			
Peanut:	MRID 45856617; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 4 x 0.21-0.245 lb ai/A/application (1x rate); maturity; 14-day PHI. MRID 45856618; [pyrimidine-2-^{14}C]fluoxastrobin; 4 x 0.23-0.244 lb ai/A/application (1x rate); maturity; 14-day PHI.			
Livestock (goat):	MRID 45856607; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 180 ppm in the diet x 3 days (15x rate). MRID 45856608; [chlorophenyl-UL-^{14}C]fluoxastrobin; 256 ppm in the diet x 3 days (15x rate).			
Livestock (hen)	MRID 45856609; [chlorophenyl-UL-^{14}C]fluoxastrobin; 187 ppm in the diet x 3 days (75,000x rate). MRID 45856610; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 198 ppm in the diet x 3 days (79,000x rate).			
Rat:	MRID 45865714 [chlorophenyl-UL-^{14}C]fluoxastrobin; oral dose: 1 x 1 mg/kg. MRID 45865715; [chlorophenyl-UL-^{14}C]fluoxastrobin; oral dose: 1 x 3 mg/kg. MRID 45865720; [phenyl-UL-^{14}C]2-chlorophenol; oral dose: 1 x 5 mg/kg. MRID 45865716.[methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin; 1 x 1 mg/kg or 1 x 100 mg/kg. MRID 45865716.[methoxyiminotolyl-ring-UL-^{14}C]fluoxastrobin; 1 x 1 mg/kg. MRID 45865718; [pyrimidine-2-^{14}C]fluoxastrobin; 1 x 1 mg/kg. MRID 45865719; [pyrimidine-2-^{14}C]fluoxastrobin; 1 x 3 mg/kg.			
Rotational Crops:	MRID 45865603; [pyrimidine-2-^{14}C]fluoxastrobin; 1 x 0.75 lb ai/A/application (1x rate); 30-, 157-, and 301-day PBIs. MRID 45865604; [methoxyiminotolyl-UL-^{14}C]fluoxastrobin; 1 x 0.75 lb ai/A/application (1x rate); 30-, 162-, and 314-days. MRID 45865605; [chlorophenyl-UL-^{14}C]fluoxastrobin; 1 x 0.75 lb ai/A/application (1x rate); 30-, 175-, and 328-days.			

Minor metabolites (<10% TRR) that were found in only one study or matrices were not included in this table.
NF = not found.

[1] When indicated in the metabolite name, E isomers were assigned by the petitioner based on spectroscopic results. Because the LC/MS analyses used for identification of metabolites could not distinguish between the E and Z isomers of fluoxastrobin metabolites containing the C=N-OCH_3 group, all other compounds are drawn without stereospecificity. When chemical names were not provided by the petitioner, the chemical naming feature of ISIS/Draw was used to generate the name.