



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 29-APR-2019

SUBJECT: **Ethiprole.** Human Health Risk Assessment for a Proposed Tolerance without US Registration in/on Imported Coffee, Green Bean.

PC Code: 005550

Decision No.: 530769

Petition No.: 7E8586

Risk Assessment Type: NA

TXR No.: NA

MRID Nos.: NA

DP Barcode: D446179

Registration No.: NA

Regulatory Action: Tolerance without U.S. Registration

Case No.: NA

CAS No.: 181587-01-9

40 CFR: §180.652

FROM: Julie L. Van Alstine, MPH, Branch Chief  for
Yung G. Yang, Ph.D., Toxicologist 
Risk Assessment Branch 6 (RAB6)
Health Effects Division (HED; 7509P)

THROUGH: Richard Fehir, Acting Branch Chief
RAB 6, HED (7509P) 

TO: Carmen Rodia, Risk Manager Reviewer
Richard Gebken, Product Manager 10
Marion Johnson, Chief
Invertebrate & Vertebrate Branch 2
Registration Division (RD; 7504P)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED 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 all registered and proposed uses of ethiprole, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfinyl)-1*H*-pyrazole-3-carbonitrile. A summary of the findings and an assessment of human risk resulting from the registered and proposed uses for ethiprole are provided in this document. The hazard characterization was provided by Yung Yang and the residue chemistry, dietary exposure, and risk assessments were provided by Julie Van Alstine.

The most recent human health risk assessment was conducted in conjunction with a request for tolerances without US registrations for residues of ethiprole in rice and tea (Memo, D366355, S. Piper, 01-DEC-2010).

Table of Contents

1.0	Executive Summary	5
2.0	HED Recommendations	6
2.1	Data Deficiencies.....	6
2.2	Tolerance Considerations	7
2.2.1	Enforcement Analytical Method	7
2.2.2	Recommended Tolerances.....	7
2.2.3	Revisions to Petitioned-For Tolerances.....	7
2.2.4	International Harmonization.....	7
2.3	Label Recommendations	8
3.0	Introduction.....	8
3.1	Chemical Identity	8
3.2	Physical/Chemical Characteristics	9
3.3	Pesticide Use Pattern	9
3.4	Anticipated Exposure Pathways.....	10
3.5	Consideration of Environmental Justice.....	10
4.0	Hazard Characterization and Dose-Response Assessment.....	10
4.1	Toxicology Studies Available for Analysis.....	10
4.2	Absorption, Distribution, Metabolism, & Elimination (ADME)	11
4.2.1	Dermal Absorption	11
4.3	Toxicological Effects.....	12
4.4	Safety Factor for Infants and Children (FQPA Safety Factor).....	13
4.4.1	Completeness of the Toxicology Database	13
4.4.2	Evidence of Neurotoxicity.....	13
4.4.3	Evidence of Sensitivity/Susceptibility in the Developing or Young Animal.....	13
4.4.4	Residual Uncertainty in the Exposure Database.....	14
4.5	Toxicity Endpoint and Point of Departure (POD) Selections	14
4.5.1	Dose-Response Assessment	14
4.5.2	Recommendation for Combining Routes of Exposures for Risk Assessment	14
4.5.3	Cancer Classification and Risk Assessment Recommendation.....	15
4.5.4	Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment.....	15
5.0	Dietary Exposure and Risk Assessment	15
5.1	Residues of Concern Summary and Rationale	15
5.2	Food Residue Profile	16
5.3	Water Residue Profile.....	16
5.4	Dietary Risk Assessment.....	16
5.4.1	Description of Residue Data Used in Dietary Assessment.....	16
5.4.2	Percent Crop Treated Used in Dietary Assessment.....	16
5.4.3	Acute Dietary Risk Assessment	17
5.4.4	Chronic Dietary Risk Assessment	17
5.4.5	Cancer Dietary Risk Assessment.....	17
5.4.6	Summary Table.....	17
6.0	Residential (Non-Occupational) Exposure/Risk Characterization	17
7.0	Aggregate Exposure/Risk Characterization.....	17
8.0	Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates	18

9.0	Non-Occupational Spray Drift Exposure and Risk Estimates	18
10.0	Cumulative Exposure/Risk Characterization.....	18
11.0	Occupational Exposure/Risk Characterization	19
12.0	References.....	19
Appendix A. Toxicology Profile and Executive Summaries.....		20
A.1	Toxicology Data Requirements	20
A.2	Toxicity Profiles	21
Appendix B. International Residue Limit Status Sheet.		25

1.0 Executive Summary

Ethiprole, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfinyl)-1*H*-pyrazole-3-carbonitrile, is a non-systemic phenyl-pyrazole insecticide that is effective against a wide range of insects. Under PP# 7E8586, Bayer CropScience has petitioned for a tolerance without US registration for residues of ethiprole in coffee. Currently, there are established tolerances without US registrations for residues of ethiprole in dried tea (30 ppm) and rice grain (1.7 ppm). There are no registrations for use of ethiprole in the US.

The toxicology database for ethiprole is complete for establishing tolerances without US registration purposes. The Hazard and Science Policy Council (HASPOC) recommended that a comparative thyroid assay (CTA) is not required at this time for tolerances without US registrations. Ethiprole is a non-systemic phenyl-pyrazole insecticide. In insects it acts by interfering with the passage of chloride ions through the insect GABA (γ -aminobutyric acid) regulated chloride channel, thereby disrupting central nervous system activity and causing death.

In the mammalian toxicology database, the critical effects of ethiprole are hepatotoxicity and thyroid toxicity. The rat was the most sensitive species overall after administration of ethiprole. Evidence of hepatotoxicity is seen in the rat, dog, and mouse and was manifested as increased liver weight and hepatocellular hypertrophy and changes in clinical chemistry such as increased alanine transaminase and alkaline phosphates activities; increased cholesterol and triglycerides levels; and increased total protein concentration. Thyroid toxicity was observed in the rat and was manifested as increased thyroid weight, thyroid follicular hypertrophy along with higher TSH plasma levels, and reduced T4 (thyroxine) plasma levels. Mechanism studies of thyroid toxicity suggested that ethiprole acts by disrupting thyroid hormone homeostasis and indirectly influences the thyroid by inducing the hepatic microsomal enzyme T4-glucuronyl transferase.

Ethiprole is neither a reproductive nor a developmental toxicant. Although no teratogenic effects were observed in the existing database, there is uncertainty regarding the potential impact of ethiprole on thyroid hormone homeostasis in the developing organism. Based on the hazard and exposure data, the ethiprole risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X since the recommended and established tolerances are tolerances without US registrations. Should a petition be submitted for uses within the US, the CTA study requirement will be re-evaluated and the FQPA SF may be retained.

In the acute neurotoxicity study, clinical signs showed consistent effects that might be anticipated for a chemical interacting with neurotransmitter chloride channels, including low arousal levels, increased eye closure, increased incidence of body tremors, and decreased rearing counts in females at the mid dose. However, no neurotoxicity effects were noted in the subchronic neurotoxicity study up to and including the highest dose of 400 ppm (33.0 mg/kg/day). There were no effects on neuropathology in any of the studies.

Ethiprole is classified as “Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential” based on increased incidences of hepatocellular adenomas in females at the highest dose tested in the carcinogenicity study in mice. There is no indication of

mutagenicity or clastogenicity. Ethiprole has low acute toxicity *via* the acute oral and dermal routes of exposure.

An acute reference dose for the general population was established from the acute neurotoxicity study based on decreased locomotor activity and functional observational battery (FOB) findings in both sexes on the day of treatment. A separate endpoint for the females age 13-49 population subgroup was not identified; there was no prenatal toxicity observed in the developmental or reproductive animal studies that could be attributed to a single exposure. The chronic reference dose was selected from the combined chronic/carcinogenicity study in rats based on observed effects in the thyroid and/or liver (histopathologic changes, increased organ weights, and/or altered thyroid hormone or bilirubin levels). No incidental oral, dermal, or inhalation endpoints were identified since ethiprole is not registered for application in the US, and all existing and proposed tolerances are tolerances without US registration.

The nature of the residue in plants and livestock is adequately understood. Adequate magnitude of the residue, processing, and storage stability data are available. The residue of concern for tolerance enforcement is the parent, ethiprole, and the residues of concern for risk assessment purposes are the parent, ethiprole, and its sulfone metabolite, RPA 097973. An adequate enforcement method is available to enforce the recommended tolerance for residues in coffee, green bean.

Unrefined acute and chronic dietary exposure and risk assessments were conducted using tolerance-level residues and assuming 100% crop treated. Drinking water was not included in the assessment since there are no registered uses of ethiprole in the US. The acute and chronic dietary exposure and risk estimates are below HED's level of concern [$<100\%$ of the acute or chronic population adjusted dose (aPAD/cPAD)].

There are no residential uses for ethiprole; therefore, residential handler and post-application exposure and risk were not assessed. Additionally, since there are no registered residential uses, the acute and chronic aggregate assessments include food only exposures and are not of concern.

Non-occupational bystander post-application inhalation, non-occupational spray drift, and occupational exposures are not anticipated because ethiprole is not registered for use in the US. Therefore, exposure and risk assessments were not conducted for these scenarios.

2.0 HED Recommendations

Provided a revised Section F is submitted, there are no toxicology or residue chemistry considerations that would preclude granting the requested registration and establishing the recommended tolerances for residues of ethiprole in/on coffee commodities. The specific tolerance recommendations are discussed in Table 2.2.2.

2.1 Data Deficiencies

None at this time. HED notes that should a petition be submitted for uses within the US, the CTA study requirement will be re-evaluated and the FQPA SF may be retained.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The HPLC/MS-MS enforcement method, Method 01128, is acceptable for determination of residues of both ethiprole and its sulfone metabolite RPA 097973 for data collection in plant commodities. The GC-ECD method (Report No. B003572) is suitable for determining residues of parent ethiprole and RPA 097973 in milk, eggs, and tissues.

The FDA multiresidue method testing study for ethiprole is adequate and indicates that PAM multiresidue methods are not suitable for enforcing tolerances for residues of ethiprole.

2.2.2 Recommended Tolerances

The ethiprole residue definition in 40 CFR §180.652 should be updated to comply with the S. Knizner 5/27/09 memo. The tolerance expression should read as follows:

(a) *General*. Tolerances are established for residues of ethiprole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only ethiprole, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfinyl)-1H-pyrazole-3-carbonitrile.

The HED-recommended tolerances for residues of ethiprole are summarized in Table 2.2.2.

Table 2.2.2. Tolerance Summary for Ethiprole.			
Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (correct commodity definition)
Coffee beans, green	0.1	0.1	Coffee, green bean ¹
Coffee beans, roasted	0.1	--	Tolerances are not needed since residues of ethiprole did not concentrate in these processed commodities.
Coffee, Instant	0.1	--	

¹ Tolerance without US registration.

2.2.3 Revisions to Petitioned-For Tolerances

HED is not recommending separate tolerances for residues in/on coffee, instant and coffee, roasted bean because the submitted processing studies indicated that residues of ethiprole did not concentrate in these processed commodities.

2.2.4 International Harmonization

Codex and Canada have not established maximum residue limits (MRLs) for residues of ethiprole in coffee commodities; therefore, there are no harmonization issues at this time. Brazil currently has an MRL established for residues in coffee, green bean. The US and Brazilian residue definitions are not harmonized; however, the US tolerance-level recommendation is

harmonized with the Brazilian MRL, as requested by the Petitioner. The International Residue Limit Status Sheet can be found in Appendix B.

2.3 Label Recommendations

None.

3.0 Introduction

Ethiprole is a non-systemic phenyl-pyrazole insecticide (MOA Group 2), which disrupts central nervous system activity and causes death by interfering with the passage of chloride ions through the insect GABA (γ -aminobutyric acid) regulated chloride channel. It is effective against a wide range of insects, including plant and stink bugs, weevils, plant hoppers, grasshoppers, dioptera leaf miners, and thrips.

3.1 Chemical Identity

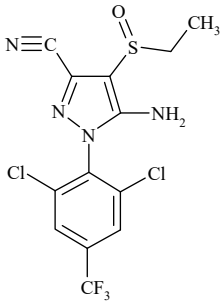
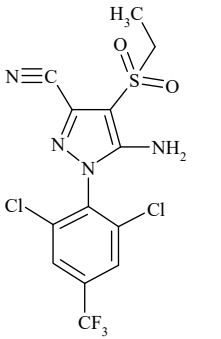
Table 3.1. Nomenclature of Ethiprole and Ethiprole Sulfone.	
Chemical structure	
Common name	Ethiprole
Company experimental name	RPA107382; AE 0316423
IUPAC name	(±)-5-amino-1-(2,6-dichloro- α,α,α -(trifluoro-p-tolyl)-4-ethylsulfinylpyrazole-3-carbonitrile
CAS name	(±)-5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(ethyl)-sulfinyl]-1H-pyrazole-3-carbonitrile
CAS registry number	181587-01-9
Molecular weight	397.21
End-use products (EPs)	Curbix 200 SC
Chemical structure	
Common name	Ethiprole sulfone

Table 3.1. Nomenclature of Ethiprole and Ethiprole Sulfone.	
Company experimental name	RPA 097973; AE 0316424
IUPAC name	(±)-5-amino-1-(2,6-dichloro- α,α,α -(trifluoro-p-tolyl)-4-ethylsulfonylpyrazole-3-carbonitrile
CAS name	(±)-5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(ethyl)-sulfonyl]-1H-pyrazole-3-carbonitrile
CAS registry number	120068-68-0
Molecular weight	413.21

3.2 Physical/Chemical Characteristics

Table 3.2. Physicochemical Properties of Technical Grade of Ethiprole.		
Parameter	Value	Reference
Melting point/range	No melting point observed before decomposition at 165.5°C	Ethiprole Monograph, Annex B.2 (MRID 47622834)
pH	not available	
Relative density	1.54-1.56	
Water solubility (g/L at 20°C)	9.2	
Solvent solubility (g/L)	acetone	90.7
	acetonitrile	24.5
	dichloromethane	19.9
	ethyl acetate	24.0
	n-heptane	0.004
	toluene	1.0
	methanol	47.2
	n-octanol	2.4
Vapor pressure (at 25°C)	9.1 x 10 ⁻⁸ Pa	
Dissociation constant, pKa	-3.9	
Octanol/water partition coefficient, Log(KOW) at 20°C	2.9	
UV/visible absorption spectrum in methanol (molar absorption coefficients for the absorbance maximum)	3,641 L/mol·cm at 292.5 nm 2,880 L/mol·cm at 295.0 nm 1,977 L/mol·cm at 300.0 nm 1,247 L/mol·cm at 305.0 nm 761 L/mol·cm at 310.0 nm	

3.3 Pesticide Use Pattern

The following use information was provided by the Petitioner, Bayer CropScience. The Petitioner indicated that the use information corresponds to the Brazilian critical GAP (Good Agricultural Practices). HED notes that since the petition is for a tolerance without a US registration, additional label information is not needed at this time.

Table 3.3. Summary of Use Pattern Information for Ethiprole on Coffee Submitted for a Tolerance without US Registration.				
Crop	Formulation	Maximum Number of Applications	Maximum Application Rate	PHI (Days)
Coffee	Curbix 200 SC	2	1.0 lb ai/A (202 g ai/A)	60

3.4 Anticipated Exposure Pathways

In the US, humans may be exposed to ethiprole through the consumption of imported food commodities containing ethiprole residues. There are no residential uses of ethiprole, so exposure in residential or non-occupational settings is not likely. Additionally, since all proposed and established tolerances are tolerances without US registrations, non-occupational bystander post-application inhalation, non-occupational spray drift, occupational, and drinking water exposures are not anticipated. This risk assessment considers all of the aforementioned exposure pathways based on the proposed and registered tolerances for residues of ethiprole.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database for ethiprole is complete for establishing tolerances without US registrations. Previously, the HASPOC determined that a CTA is required based on a weight-of-evidence (TXR 0056927, U. Habiba, 04/01/2014). Subsequently, the Registrant (Bayer) submitted a request for a CTA waiver based on its statement that future submission will be for tolerances without US registrations only, and that the Registrant will not be pursuing domestic uses of ethiprole. The HASPOC recommended that a CTA is not required at this time for tolerances without US registrations (TXR 0057433, U. Habiba, 05/24/2016). The toxicology

studies for ethiprole are summarized in Appendix A. The database includes the following studies:

- Subchronic: 28-day oral (rat, and mouse); 90-day oral toxicity (rat, mouse, and dog)
- Chronic: combined oral chronic toxicity/carcinogenicity (rat); carcinogenicity (mouse); one-year oral toxicity (dog)
- Neurotoxicity: acute and subchronic neurotoxicity (rat)
- Developmental: developmental toxicity (rat and rabbit)
- Reproduction: one and two-generation reproduction study (rat)
- Other: acute toxicity battery, mutagenicity battery; immunotoxicity (rat); metabolism (rat)

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Ethiprole was rapidly absorbed ($\geq 89\%$ of a low dose of 5 mg/kg/bw within 24 hours) with no differences between sexes. Maximum blood concentrations were measured at 8 hours after administration in both sexes. A single oral dose of 5 mg/kg/bw resulted in the highest residue levels in the liver (14.5 or 13.3 $\mu\text{g/g}$ of male or female rats, respectively) and renal fat (ca. 11.5 $\mu\text{g/g}$ in both sexes). Although residues were measured in the liver and renal fat, ethiprole did not remain in these tissues since almost all residues were metabolized by 168 hours after oral dosing. Minimal residues were also identified in the kidney (0.06 or 0.09 $\mu\text{g/g}$ in males or females), thyroid (0.04 or 0.06 $\mu\text{g/g}$ in males or females), and adrenal gland (0.03 or 0.04 $\mu\text{g/g}$ in males or females) with lower levels in other organs. At 168 hours after oral administration, less than 1% of the dose (5 mg/kg/bw) was observed in organs and tissues indicating very little potential of accumulation.

Based on an evaluation of the doses at which ethiprole toxicity occurs over time, it is apparent that the toxicity does not increase with increasing duration of exposure. This suggests that ethiprole is rapidly metabolized and excreted. This is supported by a study in which approximately 85% of an oral administered dose (5 mg/kg/bw) of [^{14}C]-Ethiprole was excreted by both sexes within 48 hours after administration. After administration of 168 hours, urinary excretion amounted to 24% (males) or 36% (females) of the dose and fecal excretion accounted for 67% (males) or 55% (females) of the dose. Thus, total excretion amounted to 92% and 94% of the oral dose in male and female rats. The major route of excretion was via the bile as observed in a bile duct cannulation experiment. [^{14}C]-Ethiprole was extensively metabolized in the rat. The major metabolic pathways were comprised of: 1) Hydrolysis of the nitrile group to form the amide RPA 112916; 2) Reduction of the sulfoxide group to form the sulfide RPA 107566 followed by subsequent alkyl oxidation to form the carboxylic acid RPA 112716; and 3) Oxidation of the sulfoxide group to form the sulfone RPA 097973 as the major metabolite followed by alkyl hydroxylation, alkyl oxidation, oxidative desalkylation and conjugation to form sulfates and glucuronides.

4.2.1 Dermal Absorption

No acceptable dermal absorption study is available for ethiprole. However, a dermal absorption factor is not needed since a quantitative dermal assessment was not performed.

4.3 Toxicological Effects

The mode of action of ethiprole in insects is through interference with the passage of chloride ions through the insect GABA (γ -aminobutyric acid) regulated chloride channel, thereby disrupting central nervous system activity and causing death.

In the mammalian toxicology database, the critical effects of ethiprole are hepatotoxicity and thyroid toxicity after subchronic and chronic exposure in the rat, dog, and mouse. The rat was the most sensitive species overall after administration of ethiprole. Evidence of hepatotoxicity was manifested as increased liver weight and hepatocellular hypertrophy and changes in clinical chemistry such as increased alanine transaminase and alkaline phosphates activities; increased cholesterol and triglycerides levels and increased total protein concentration. Thyroid toxicity was observed in the rat and was manifested as increased thyroid weight, thyroid follicular hypertrophy along with higher TSH plasma levels and reduced T4 (thyroxine) plasma levels. Mechanism studies of thyroid toxicity suggested that ethiprole acts by disrupting thyroid hormone homeostasis and indirectly influences the thyroid by inducing the hepatic microsomal enzyme T4- glucuronyl transferase. Ethiprole does not inhibit the synthesis of T4 or T3, therefore, it does not directly affect thyroid function.

Ethiprole is neither a reproductive nor a developmental toxicant. The minor findings observed in juvenile animals occurred in the presence of maternal toxicity. However, in the two-generation toxicity study, thyroid hormone levels were not evaluated and the thyroids from pups were not evaluated histopathologically. Consequently, no data regarding the potential effects of ethiprole on thyroid homeostasis in infants and children are available. While late maturation of UDPGT enzymes may result in increased activity in adults compared to the fetus or neonatal rat, no data are available and there is little understanding of the pharmacodynamic differences of ethiprole exposure in adult vs. the young. This lack of characterization creates uncertainty with regards to potential life stage sensitivities due to exposure to ethiprole and raises the Agency's level of concern.

In the acute neurotoxicity study, clinical signs showed consistent effects that might be anticipated for a chemical interacting with neurotransmitter chloride channels, including low arousal levels, increased eye closure, increased incidence of body tremors, and decreased rearing counts in females at the mid-dose. However, no neurotoxicity effects were noted in the subchronic neurotoxicity study up to and including the highest dose of 400 ppm (33.0 mg/kg/day). There were no effects on neuropathology in any of the studies.

Ethiprole is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential" based on increased incidences of hepatocellular adenomas in females at the highest dose tested in the carcinogenicity study in mice. There is no indication of mutagenicity or clastogenicity. Ethiprole has a low acute toxicity *via* the acute oral, inhalation, and dermal routes of exposure. It is not an irritant to eyes or skin and is not a skin sensitizer.

4.4 Safety Factor for Infants and Children¹ (FQPA Safety Factor)

Based on the hazard and exposure data, the ethiprole risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X. As described previously, hormonal changes (decrease T4 plasma levels, increase TSH plasma levels and alteration in thyroid weights) were observed in several studies following oral administration of ethiprole to adult animals, no thyroid data is available in the young, thus there is concern for potential life stage susceptibility. However, since the registrant is only pursuing tolerances without US registrations, the HASPOC recommended that a CTA is not needed at this time.

4.4.1 Completeness of the Toxicology Database

The toxicology database is complete including developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, acute and subchronic neurotoxicity studies rats. Should a petition be submitted for uses within the US, the CTA study requirement will be re-evaluated and the FQPA SF may be retained.

4.4.2 Evidence of Neurotoxicity

In insects, ethiprole acts by interfering with the passage of chloride ions through the insect GABA (γ -aminobutyric acid) regulated chloride channel and thereby disrupting central nervous system activity and causing death. In mammals, however, no neurotoxic effects were observed during the subchronic neurotoxicity study in which adverse effects of increased thyroid and liver weights were observed in males and females, respectively. The acute neurotoxicity study showed decrease locomotor activity (both sexes, Day 1) and the FOB findings in both sexes on the day of treatment (4 hours after dosing). The FOB findings included increase tremors (females), decreased grooming (both sexes), decreased arousal alert (females), increased number of animals for which no assessment of gait was possible (females), increase eye closure (females), increased standing/sitting hunched (females), decreased activity and rearing counts (females), increased hindlimb and forelimb grip strength (males), and decreased forelimb grip strength (day 8) (females), decreased splay (females, day 1), increase splay (males, Day 8). As discussed previously, the similarity in the NOAELs from the acute neurotoxicity and subchronic neurotoxicity studies are consistent with the metabolism data suggesting that the compound is not accumulated in the system. A developmental neurotoxicity (DNT) study is not required.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Although no teratogenic effects were observed in the exiting database, there is uncertainty regarding the potential impact of ethiprole on thyroid hormone homeostasis in the developing organism. Observations demonstrated that thyroid hormones were affected in several studies throughout the ethiprole database. Thyroid hormones may play a critical role in the development of the nervous system.

¹OPP's standard approaches are also consistent with EPA's children's environmental health policy. <https://www.epa.gov/children/epas-policy-evaluating-risk-children>.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary exposure and risk assessment was conducted using tolerance-level residues and HED does not believe that the assessment underestimates exposures.

4.5 Toxicity Endpoint and Point of Departure (POD) Selections

There have been no changes to the prior endpoints/point of departure (PODs) selected for risk assessment and cancer classification. It should be noted that the endpoints and PODs presented in the Table 4.5.1 was based on the previous risk assessment (D366355, S. Piper, 01-DEC-2010). The endpoint selection and point of departure may be re-evaluated during the registration review process.

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint for All Populations, Including Infants and Children and Females 13-49 Years of Age: An acute neurotoxicity in rats (MRID 47622822) is selected with a NOAEL of 35 mg/kg/day and a LOAEL of 250 mg/kg/day based on increase tremors (females), decrease grooming (both sexes), decreased arousal alert (females), increased number of animals for which no assessment of gait was possible (females), increase eye closure (females), increased standing/sitting hunched (females), decreased activity and rearing counts (females), increased hindlimb and forelimb grip strength (males), and decreased forelimb grip; strength (day 8) (females), decreased splay (females, day 1), increase splay (males, Day 8). An uncertainty factor of 100X (10X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied. The acute reference dose (aRfD) and acute population adjusted dose (aPAD) is 0.35 mg/kg/day.

Chronic Dietary Endpoint for the General Population: A combined chronic/carcinogenicity feeding study in rats (MRID 47622813) is selected with a NOAEL of 0.85 mg/kg/day and a LOAEL of 3.21/4.40 mg/kg/day (M/F) based on observed effects in the thyroid and/or liver (histopathologic changes, increased organ weights, and/ or altered thyroid hormone or bilirubin levels). An uncertainty factor of 30X (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied. The interspecies uncertainty factor (used to account for animal to human differences in toxicokinetics and toxicodynamics) was reduced to 3X with respect to observed thyroid effects in the rat because of several important quantitative dynamic differences between rats and humans with respect to thyroid function (Interim Guidance on Thyroid Disrupting Pesticides, dated 11/01/2005). The chronic reference dose (cRfD) and the chronic population adjusted dose (cPAD) is 0.03 mg/kg/day.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

The aggregate assessment considers food only exposures since there are no proposed or registered uses of ethiprole in the US that would result in drinking water or residential exposures; therefore, recommendations for combining exposures are not required at this time.

4.5.3 Cancer Classification and Risk Assessment Recommendation

The HED Cancer Assessment Review Committee (CARC) classified ethiprole (TXR 0055516, J. Kidwell, 10/28/2010) as “Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential.” This was based on the increased incidences of hepatocellular adenomas in females at the highest dose tested in the carcinogenicity study in mice. There is no indication of mutagenicity or clastogenicity.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.1. Toxicological Doses and Endpoints for Ethiprole for Use in Dietary Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty Factors/ FQPA SF	RfD/PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children and Females 13-49 years of age)	NOAEL= 35 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF =1x Combined UFs = 100x	aRfD/aPAD = 0.35 mg/kg/day	Acute neurotoxicity in rats (MRID 47622822) LOAEL= 250 mg/kg/day based on decreased locomotor activity and functional observational battery (FOB) findings in both sexes on the day of treatment.
Chronic Dietary (All populations)	NOAEL= 0.85 mg/kg/day	UF _A = 3x UF _H = 10x FQPA SF =1x Combined UFs = 30x	cRfD/cPAD =0.03 mg/kg/day	Combined Chronic/carcinogenicity study in rats (MRID 47622813) LOAEL = 3.21/4.40 mg/kg/day (M/F), based on observed effects in the thyroid and/or liver (histopathologic changes, increased organ weights, and/ or altered thyroid hormone or bilirubin levels).
Cancer	Classification: “Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential”			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The residues of concern for dietary risk assessment and the tolerance expression are summarized in Table 5.1. The parent compound is an adequate indicator of misuse, and is the only residue included in the tolerance expression. The residues of concern for risk assessment purposes are ethiprole and metabolite RPA 097973. Further information on the metabolism and degradation may be found in the previous risk assessment (Memo, D366355, S. Piper, 01-DEC-2010).

Table 5.1 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 Crop	Ethiprole + RPA 097973	Ethiprole
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Ethiprole + RPA 097973	Ethiprole + RPA 097973
	Poultry	Ethiprole + RPA 097973	Ethiprole + RPA 097973
Drinking Water		Not Applicable	Not Applicable

Ethiprole = RPA 107382 = 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfinyl)-1H-pyrazole-3-carbonitrile
 Ethiprole-sulfone = **RPA 097973** = 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(ethylsulfonyl)-1H-pyrazole-3-carbonitrile

5.2 Food Residue Profile

Adequate data have been submitted to support a tolerance without a US registration for residues of ethiprole in coffee, green bean and to conduct a risk assessment. The submitted field trial data reflect the Brazilian critical GAP, are supported by adequate storage stability data, and were analyzed using an adequate method. Residues of ethiprole did not decrease significantly over the decline intervals. Additionally, residues of ethiprole did not concentrate in processed coffee commodities (coffee, instant and coffee, roasted bean).

5.3 Water Residue Profile

There are no registered or proposed US uses of ethiprole. As a result, estimated drinking water concentrations (EDWCs) were not included in the dietary exposure and risk assessment because residues of ethiprole and its degradates are not anticipated to be present in US drinking water.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Ethiprole and its sulfone metabolite RPA097973 are the residues of concern for risk assessment purposes. Since the total (ethiprole + RPA 097973) highest average field trial (HAFT) values are less than the HED-recommended and established tolerances, use of a tolerance-level residue is protective of both the parent and metabolite for risk assessment purposes for this assessment. Therefore, unrefined acute and chronic dietary exposure and risk assessments were conducted using tolerance-level residues.

Drinking water was not included in the assessment since all proposed and established tolerances are tolerances without US registrations.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic assessments assumed 100% crop treated for all commodities.

5.4.3 Acute Dietary Risk Assessment

The acute dietary exposure and risk estimates are below HED's level of concern (<100% of the aPAD) at the 95th exposure percentile for the general US population and all other population subgroups. The general US population utilized <1% of the aPAD, and the most highly-exposed population subgroup, all infants (<1 year old), utilized 2.1% of the aPAD.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary exposure and risk estimates are below HED's level of concern (<100% of the cPAD) for the general US population and all other population subgroups. The general US population utilized 2.0% of the cPAD, and the most highly-exposed population subgroup, all infants (<1 year old), utilized 5.7% of the cPAD.

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary assessment was not conducted because ethiprole is classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential."

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food Only) Exposure and Risk Estimates for Ethiprole. ^{1,2}						
Population Subgroup	Acute Dietary (95 th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General US population	0.002673	<1	0.000601	2.0	N/A	N/A
All Infants (<1 year old)	0.007495	2.1	0.001704	5.7		
Children 1-2 years old	0.005439	1.6	0.001091	3.6		
Children 3-5 years old	0.004802	1.4	0.000914	3.0		
Children 6-12 years old	0.002884	<1	0.00056	1.9		
Youth 13-19 years old	0.001979	<1	0.000398	1.3		
Adults 20-49 years old	0.002730	<1	0.000644	2.1		
Adults 50-99 years old	0.002001	<1	0.000482	1.6		
Females 13-49 years old	0.002260	<1	0.000507	1.7		

¹ aPAD= 0.35 mg/kg/day; cPAD= 0.03 mg/kg/day

² The most highly-exposed population subgroup exposure and risk estimates are bolded.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no residential uses registered or proposed for ethiprole. Therefore, residential handler and post-application exposures and risks were not assessed.

7.0 Aggregate Exposure/Risk Characterization

In accordance with FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures

(residential or other non-occupational exposures). Since there are no registered or proposed uses of ethiprole that result in residential exposure, the acute and chronic aggregate exposure and risk assessments are equal to the acute and chronic dietary exposure and risk estimates (food only), respectively. The acute and chronic dietary (food only) exposure and risk estimates were not of concern (Section 5.4.6). Drinking water was not included in the assessment because there are no registered US uses of ethiprole that would result in drinking water exposures.

Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of ethiprole that result in residential exposures. Additionally, since ethiprole is classified as “Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenicity Potential,” a cancer aggregate assessment was not required.

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Non-occupational bystander post-application inhalation exposures are not anticipated since ethiprole is not registered for use in the US.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Non-occupational spray drift exposures are not anticipated since ethiprole is not registered for use in the US.

10.0 Cumulative Exposure/Risk Characterization

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 ethiprole and any other substances and ethiprole does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that ethiprole has a common mechanism of toxicity with other substances. In 2016, EPA’s Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework>]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)² and conducting cumulative risk assessments (CRA)³. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for ethiprole suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-

² *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

³ *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

Occupational exposures are not anticipated since ethiprole is not registered for use in the US.

12.0 References

Table 12. References.			
Author	Barcode	Date	Title
J. Van Alstine	D446357	29-APR-2019	Ethiprole: Acute and Chronic Dietary (Food Only) Exposure and Risk Assessment for a Tolerance Without U.S. Registration in/on Coffee, Green Bean.
J. Van Alstine	D444714	29-APR-2019	Ethiprole. Request for Tolerance without U.S. Registration in/on Imported Coffee, green bean. Summary of Analytical Chemistry and Residue Data.
S. Piper, <i>et al.</i>	D366355	01-DEC-2010	Ethiprole: Human Health Risk Assessment for Proposed Uses on Imported Rice and Tea.
U. Habiba	TXR 0056927	01-APR-2014	Ethiprole: Summary of Hazard and Science Policy Council (HASPOC) Meeting on March 13, 2014: Recommendations on Data Requirement for Thyroid Assays in Pregnant Animals, Fetuses, Postnatal Animals, and Adult Animals.
U. Habiba	TXR 0057433	24-MAY-2016	Ethiprole: Summary of the Special Hazard and Science Policy Council (HASPOC) Meeting on March 2, 2016: Recommendations on Data Requirement for the Comparative Thyroid Assay in Pregnant Animals, Fetuses, Postnatal Animals, and Adult Animals.
J. Kidwell	TXR 0055516	28-OCT-2010	Ethiprole: Report of the Cancer Assessment Review Committee

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for ethiprole are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study	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 Acute Eye Irritation.....	yes	yes
870.2500 Acute Dermal Irritation	yes	yes
870.2600 Skin Sensitization	yes	yes
870.3100 90-Day Oral Toxicity in Rodents	yes	yes
870.3150 90-Day Oral Toxicity in Nonrodents.....	yes	yes
870.3200 21/28-Day Dermal Toxicity	yes	no
870.3250 90-Day Dermal Toxicity	no	NA
870.3465 90-Day Inhalation Toxicity	no	no
870.3700a Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction and Fertility Effects	yes	yes
870.4100a Chronic Toxicity (rodent).....	yes	yes
870.4100b Chronic Toxicity (nonrodent).....	yes	yes
870.4200a Carcinogenicity (rat).....	yes	yes
870.4200b Carcinogenicity (mouse)	yes	yes
870.5100 Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test ..	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations...	yes	yes
870.5550 Mutagenicity – Other Genotoxic Effects	yes	yes
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	no	-
870.7485 Metabolism and Pharmacokinetics.....	yes	yes
870.7600 Dermal Penetration.....	no	-
870.7800 Immunotoxicity	yes	yes

A.2 Toxicity Profiles

Note: Table information was extracted from previous risk assessment document (D366355, S. Piper, 1-DEC-2010).

Table A.2.1. Acute Toxicity Profile - Ethiprole				
Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute oral - Rat	47622801	LD ₅₀ > 7080 mg/kg	IV
870.1200	Acute dermal – Rat		LD ₅₀ > 2000 mg/kg	--
870.1300	Acute inhalation - Rat		LC ₅₀ > 5.2 mg/L	--
870.2400	Acute eye irritation - Rabbits		Non-irritant	--
870.2500	Acute dermal irritation - Rabbits		Non-irritant	--
870.2600	Dermal sensitization - Guinea Pig		Not a skin sensitizer (Buehler method)	--

Note: Table is extracted from previous risk assessment document (D366355, S. Piper, 01-DEC-2010).

Table 2.2. Subchronic, Chronic and Other Toxicity Profile -Ethiprole		
Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.3100 28-Day- feeding Mice	MRID 47622828 (1999) 50, 250, 1000, 2500 ppm 0, 9.3, 47.4, 186.2, 458 mg/kg/d (M) 0, 11.8, 57.9, 234.4, 513 mg/kg/d (F) Acceptable/Guideline	NOAEL = 9.3/11.8 mg/kg/day (M/F), LOAEL = 47.4/57.9 mg/kg/day based on Lower total bilirubin (↓64-69%), increased liver weights (↑10-16%) and histopathologic changes in the liver.
870.3100 28-Day feeding Rats	MRID 47622804 (2001) 0, 20, 100, 500, 2500 ppm 0, 1.8, 9.2, 46.1, 219.3 mg/kg/d (M) 0, 2.0, 9.6, 46.3, 220.2 mg/kg/d (F) Acceptable/Guideline	NOAEL = 9.2/9.6 mg/kg/day (M/F) LOAEL = 46.1/46.3 mg/kg/day based on higher prothrombin time, ALAT activity, cholesterol, triglyceride and total protein concentration, imbalance of thyroid hormones, increased liver weights (35%/96%; M/F), thyroid weight (41%/40%; M/F) and adrenals weights (16%/15%; M/F).
870.3100 90-Day oral Rats	MRID 47622806 (2002) 0, 5, 100, 500 or 2500 ppm 0, 0.3, 1.2, 30.5, 154.8 mg/kg/day (M) 0, 0.4, 1.5, 37.6 and 187.9 mg/kg/day (F) Acceptable/Guideline	NOAEL = 1.2/1.5 mg/kg/day (M/F) LOAEL = 30.5/37.6 mg/kg/day based on mortality, higher prothrombin prothrombin time, Cholesterol, Triglyceride, Total protein, Calcium concentrations and lower chloride concentration, imbalance of thyroid hormones, increased liver weight (57%/96%; M/F) and thyroid weight (48%/44%; M/F) and histopathologic changes in the liver and thyroid
870.3150 90-Day oral (diet) Beagle dogs	MRID 47622807 (2001) 0, 30, 90 200, ppm 0, 1.0, 3.2, 7.6 mg/kg/day (M) 0, 1.1, 3.6, 8.5 mg/kg/day (F) Acceptable/Guideline	NOAEL = 1.0/3.6 mg/kg/day (M/F), LOAEL = 3.2/8.5 mg/kg/day based on Males: decrease prostate weight (↓59%), testis weight (↓31%) and epididymis weight (↓34%) and increase thymus weight (29%). Females: Mortality, increased alkaline phosphatase activity and thymic atrophy

Table 2.2. Subchronic, Chronic and Other Toxicity Profile -Ethiprole

870.4100 One-year oral (diet) Beagle dogs	MRID 47622811 (2001) 0, 9, 30, 90 ppm 0, 0.27, 0.70, 2.73 mg/kg/day (M) 0, 0.22, 0.76, 2.51 mg/kg/day (F) Acceptable/Guideline	NOAEL = 0.7/0.76 mg/kg/day (M/F) LOAEL = 2.73/2.51 mg/kg/day (M/F) based on reduced overall body weight gain.
870.4200 Carcinogenicity C57BL/6 mice	MRID 47622812 (2001) 0, 10, 50, 150, 300 ppm 0, 1.7, 8.6, 25.6, 50.8 mg/kg/day (M) 0, 1.7, 12.5, 36.3, 73.5 mg/kg/day (F) Acceptable/Guideline	NOAEL = 50.8/36.3 mg/kg/day (M/F); LOAEL = 50.8/73.5 mg/kg/day (M/F) based on reduced survival rate. Slight increased in the incidence of hepatocellular adenomas (↑12%) in females
870.4300 Combined Chronic/ Carcinogenicity feeding (104 weeks) Wistar rats	MRID 47622813 (2001) 0, 5, 20, 75, 250 ppm 0, 0.22, 0.85, 3.2, 10.8 mg/kg/day (M) 0, 0.29, 1.17, 4.4, 14.7 mg/kg/day (F) Acceptable/Guideline	NOAEL = 0.85/1.17 mg/kg/day (M/F) LOAEL = 3.2/4.4 mg/kg/day (M/F) based on higher liver weight (↑13%, F) and thyroid weight (↑27%/22%; M/F) associated with hepatocellular hypertrophy and thyroid follicular hypertrophy. Higher TSH plasma levels and reduced T4 plasma levels No evidence of tumors at any dose in either sex.
870.3700a Developmental toxicity SD rats	MRID 447622808 (2000) 0, 3, 10, 30 mg/kg/day (GD 6-20) Acceptable/Guideline	Maternal toxicity: NOAEL = 3 mg/kg/day; LOAEL = 10 mg/kg/day based on increased mean liver weight (↑15%) and body weight loss (↓43%). Developmental toxicity: NOAEL = 3 mg/kg/day LOAEL = 10 mg/kg/day based on incidences of ossification delay for a few bones
870.3700b Developmental toxicity Rabbits	MRID 47622809 (2000) 0, 0.25, 0.5, 2.0, 4.0 mg/kg/day (GD 6-28) Acceptable/Guideline	Maternal toxicity: NOAEL = 0.5 mg/kg/day; LOAEL = 2.0 mg/kg/day based on increased number of abortions, reduced body weight gains and food consumption. Developmental toxicity: NOAEL = 0.5 mg/kg/day LOAEL = 2.0 mg/kg/day based on skeletal variations (incomplete ossification of pubis, metacarpal and/or middle phalanges).
870.3800 Reproductive toxicity Rats	MRID 47622810 (2001) 0, 10, 75, 500 ppm 0, 0.66-0.80, 4.77-6.03, 32.33-39.63 mg/kg/day (M) 0, 0.78-0.91, 5.82-6.76, 37.36-45.20 mg/kg/day (F) Acceptable/Guideline	Parental toxicity: NOAEL = 4.8/5.8 mg/kg/day, M/F LOAEL = 32.3/37.4 mg/kg/day, M/F based on decreased body weights and occasionally decreased weight gain, organ weight changes (liver, thyroid, adrenals, pituitary) and liver, thyroid and kidney histopathology (findings noted in one or both generations and sexes). Reproductive toxicity: NOAEL = 32.3/37.4 mg/kg/day, M/F (HDT) LOAEL was not established. Offspring toxicity: NOAEL = 4.8/5.8 mg/kg/day, M/F LOAEL = 32.3/37.3 mg/kg/day, M/F based on decreases in F1 and F2 pup body weights

Table 2.2. Subchronic, Chronic and Other Toxicity Profile -Ethiprole

		during lactation (beginning on Day 4 for F1 and on Day 14 for F2 offspring) and into the postweaning/prebreeding period, with associated delays in acquisition of puberty.
870.6200 Acute neurotoxicity Rats	MRID 47622821 (2001) 0, 100, 500, 2000 mg/kg Acceptable/Guideline	NOAEL = Not established LOAEL = 100 mg/kg based on decreased landing foot splay (both sexes) and a lower level of activity compared with controls (females only).
870.6200 Acute neurotoxicity Rats	MRID 47622822 (2001) 0, 10, 25, 35, 250 mg/kg/day Acceptable/Guideline	NOAEL = 35 mg/kg/day (M/F) LOAEL = 250 mg/kg/day based on decreased locomotor activity, increased incidence of being awkward to handle, and increased fore- and hindlimb grip strength, decreased rearing counts, increased incidence of body tremors, indications of a lower level of arousal, and a higher incidence of closure of the eyes.
870.6200 Subchronic neurotoxicity Rats	MRID 47622823 (2001) 0, 20, 100, 400 ppm 0, 1.4, 7.2, 28.7 mg/kg/day (M) 0, 1.7, 8.4, 33.0 mg/kg/day (F) Acceptable/Guideline	Neurotoxicity NOAEL = 28.7/33.0 mg/kg/day (M/F), HDT. LOAEL = Not established.
870.7800 Immunotoxicity Rats (female only)	MRID 48016801 (2010) 0, 20, 100, or 500 ppm 0, 1.6, 8.4, or 41.2 mg/kg/day Acceptable/Guideline	Immunotoxicity NOAEL = 41.2 mg/kg/day, HDT LOAEL = Not established.
870.5100 Bacterial reverse mutation (<i>Salmonella/E. coli</i>)	MRID 47622814 (1998) Acceptable/Guideline	Negative up to the limit dose (5000 µg/plate +/- S9)
870.5300 Mammalian cell gene mutation (mouse lymphoma cells, MLA)	MRID 47622817 (1999) Acceptable/Guideline	Negative up to cytotoxic dose (500 µg/ml/ +/-S9).
870.5375 <i>In vitro</i> cytogenetics assay/chromosome aberration (human blood lymphocyte)	MRID 47622818 (1998) Acceptable/Guideline	Negative up to the solubility limit (800 µg/ml +/-S9). No evidence of chromosome aberrations induced over background.
870.5395 Mouse bone marrow micronucleus assay	MRID 47622819 (1999) Acceptable/Guideline	Negative up to limit dose of 2000 mg/kg/day.
870.5550 Unscheduled DNA synthesis (primary rat hepatocytes)	MRID 47622820 (2001) Acceptable/Guideline	Negative up to limit concentration of 2000 µg/ml.
870.7485 Metabolism – Rats	MRID 47622824 (1999) Acceptable/Guideline	Ethiprole is rapidly absorbed, metabolized and excreted. The major route of excretion was via the bile as observed in a bile duct cannulation experiment. [¹⁴ C]-Ethiprole was extensively metabolized in the rat. The major

Table 2.2. Subchronic, Chronic and Other Toxicity Profile -Ethiprole

		metabolic pathways were comprised of: 1) Hydrolysis of the nitrile group to form the amide RPA 112916; 2) Reduction of the sulfoxide group to form the sulfide RPA 107566 followed by subsequent alkyl oxidation to form the carboxylic acid RPA 112716; 3) Oxidation of the sulfoxide group to form the sulfone RPA 097973 as the major metabolite followed by alkyl hydroxylation, alkyl oxidation, oxidative desalkylation and conjugation to form sulfates and glucuronides.
--	--	--

Appendix B. International Residue Limit Status Sheet.

Table A.3 Summary of US and International Tolerances and Maximum Residue Limits.					
Residue Definition:					
US	Canada	Mexico ³	Codex	Brazil	
40 CFR 180.652: Plants: Ethiprole [5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(ethyl)-sulfinyl]-1 <i>H</i> -pyrazole-3-carbonitrile]				See Footnotes ¹	
Commodity ²	Tolerance (ppm) /Maximum Residue Limit (mg/kg)				
	US	Canada	Mexico ³	Codex	Brazil
Coffee beans, green	0.10	0.1 ⁴	--	--	0.1
Coffee beans, roasted	--	--	--	--	--
Coffee, instant	--	--	--	--	--
Completed by: J. Van Alstine using Global MRL 09-JAN-2018					

¹os LMRs referem-se à soma de etiprole e seus metabólitos 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethylsulfonylpyrazole-3-carbonitrile (RPA 097973) e 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethylsulfonylpyrazole-3-carboxamide (RPA 112916).

² Includes only commodities of interest for this action.

³ Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

⁴ Default MRL