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PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: January 20, 2010

SUBJECT: **Chlorantraniliprole; Human Health Risk Assessment for Proposed Use on Tobacco.**

PC Code: 090100
Decision No.: 404619
Petition No.: 9F7513
Risk Assessment Type: Single Chemical, Aggregate
TXR No.: NA
MRID No.: NA

DP Number: 369224
Registration No.: 352-729
Regulatory Action: Section 3 Registration
Case No.: NA

CAS No.: 500008-45-72
40 CFR§180.628

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Introduction

This memorandum is a follow-up to Agency memorandum DP#361397 (D. Rate, 01/12/2010) which addresses an action submitted to the Agency by E.I. du Pont de Nemours and Company (DuPont) and the Interregional Research Project 4 (IR-4) who are collaboratively working to increase the number of crops on which chlorantraniliprole may be registered. The subject memorandum will address the proposed use of chlorantraniliprole (DuPont™ Coragen® SC Insect Control (EPA Reg. No. 352-729), a 1.67 lb ai/gal suspension concentrate (SC) formulation) on tobacco and the exposure and risk associated with this use.

Although the use of a pesticide on tobacco is considered non-food and does not require a tolerance or exemption, the Agency does require field trial data (magnitude of the residue study) and a pyrolysis study to assess exposure to humans from pesticide residues in tobacco smoke. In conjunction with numerous agricultural food uses and a petition for tolerances, the Agency has considered the exposure to humans from chlorantraniliprole residues in tobacco smoke as well as major exposure pathways (food and drinking water and residential) in this exposure/risk assessment.

ARIA has no objections to the proposed use pattern for tobacco to be added to the product label for Coragen® (EPA Reg. No. 352-729). The requested new use for tobacco is not supported by residue data; however, the petitioners have requested a data translation from leafy vegetables (Crop Group 4). ARIA/HED determined that this data translation is adequate. There are no data deficiencies that need to be addressed prior to registering chlorantraniliprole for this use. No tolerances are needed for tobacco commodities, and the associated exposure and risk from the use of chlorantraniliprole treated tobacco is below the Agency's level of concern.

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1.0 Executive Summary

Chlorantraniliprole (DPX-E2Y45) is a novel anthranilic diamide insecticide that belongs to a class of compounds that acts on the ryanodine receptor (Group 28). It is an insecticide that was developed by DuPont for control of lepidopteran pests and controls many insects primarily via interruption of normal muscle contraction pathways, which leads to paralysis and eventual death of the pest. DuPont has applied for a Section 3 registration for the use of DuPont™ Coragen® SC Insect Control (EPA Reg. No. 352-729), a 1.67 lb ai/gal suspension concentrate (SC) formulation, on tobacco.

Permanent tolerances are currently established in the 40 CFR §180.628 for chlorantraniliprole in/on a variety of commodities.

Use Profile

Coragen® (1.67 lb/gal SC) is proposed for use on tobacco for multiple foliar spray applications at 0.045-0.098 lb ai/A per application, with a minimum 3-day retreatment interval, a maximum seasonal rate of 0.2 lb ai/A, and a 1-day PHI. Foliar applications may be made using ground equipment in approximately 10-100 gal/A (93-935 L/ha) of finished spray. Use of adjuvants is currently restricted. This use pattern is identical to the use pattern for leafy vegetables (Crop Group 4).

HAZARD CHARACTERIZATION

Chlorantraniliprole (DPX-E2Y45). Human Health Risk Assessment for Proposed Uses on the Tree Nut Crop Group and Pistachios and for Increases in the Established Tolerances for Pome Fruits, Stone Fruits, Grapes, and Raisins due to the Removal of Adjuvant Restrictions from the Label for Pome Fruits, Stone Fruits, and Grapes. DP#357072, N. Tsaur, 03/04/2009.

Chlorantraniliprole (DPX-E2Y45). Human Health Risk Assessment for Section 3 Registration Request to Expand Uses of Coragen®, Altacor®, and Dermacor™ X-100 Labels on Various Field, Vegetable, and Fruit Crops. DP#361397, D. Rate, 01/12/2010.

The ARIA/HED Risk Assessment Team has concluded that sufficient toxicology information exists for chlorantraniliprole for selecting the doses and endpoints needed for assessing its risk to humans when used as an insecticide. Chlorantraniliprole is not genotoxic, neurotoxic, immunotoxic, carcinogenic, or teratogenic. Chlorantraniliprole is classified in Acute Toxicity Category IV for oral toxicity, dermal toxicity, inhalation toxicity, eye irritation, and primary skin irritation. Also, chlorantraniliprole is not a dermal sensitizer. There was only one toxicity study in the toxicology database that indicated chlorantraniliprole yielded an adverse effect (18-month oral/mouse). This study was used to establish a point of departure (POD) based on hepatocellular effects for the chronic dietary exposure scenario.

ARIA/HED recommend that the FQPA SF be reduced to 1X because 1) the toxicology database for chlorantraniliprole is complete for the purposes of this risk assessment and the characterization of potential pre- and postnatal risks to infants and children; 2) no susceptibility was identified in the toxicological database, and there are no residual uncertainties with respect to pre-and/or postnatal exposure [i.e., the developmental and reproduction studies report no

adverse effects related to treatment ≥ 1000 mg/kg/day (limit dose)]; 3) no treatment-related neurotoxic findings in the acute or subchronic oral neurotoxicity studies in rats; 4) the exposure assessment is protective: the dietary food exposure assessment utilizes tolerance level residues and 100% crop treated information for all commodities; the drinking water assessment (Tier II estimates) utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations; and 5) although residential exposure is expected over the short- and intermediate-term (via the dermal and/or incidental oral route), there is no hazard expected via these routes/durations, and therefore no risk associated with these scenarios.

RESIDUE CHEMISTRY

Chlorantraniliprole in/on Tobacco. Summary of Analytical Chemistry and Residue Data. DP#369223, D. Rate, 12/10/2009.

The nature of the residue in plants, rotational crops, ruminants and water is adequately understood. For the purposes of tolerance establishment and enforcement, the residue of concern in plants, livestock, and rotational crops is the parent chlorantraniliprole. For the purposes of dietary risk, the residue of concern is the parent only for plants and poultry (except eggs). The residues of concern for dietary risk assessment are the parent plus metabolites (IN-HXH44 and IN-K9T00) for ruminants and parent plus metabolites (IN-H2H20, IN-K7H29 and IN-GAZ70) for eggs (See Table 5.1.4). In drinking water, the residue of concern is the parent only.

The maximum seasonal application proposed for the new use on tobacco is less than or equal to currently registered use rates. As such, a previously modeled Tier II drinking water assessment for the established chlorantraniliprole uses conducted by Environmental Fate and Effects Division (EFED) was used for the most recent dietary assessment (DP#348133, J. Hetrick, 01/10/2008; DP#361792, D. Rate, 12/09/2009). The drinking water assessment includes the parent residue, chlorantraniliprole. There are no livestock feed items associated with the proposed use on tobacco.

Although no tolerance is required for tobacco, adequate methods are available to determine residues of chlorantraniliprole residues in/on crops including tobacco (liquid chromatography with tandem mass spectrometry (LC/MS/MS) detection, Method DuPont-11374) and livestock (LC/MS/MS; MRID 46889003). The limits of quantitation (LOQs) are 0.01 ppm for chlorantraniliprole in crop and livestock matrices. DuPont-11374 was adequately validated by the petitioner as well as by an independent laboratory. The Agency concluded that the method meets the criteria for an acceptable tolerance enforcement method (DP#340358, C. Stafford, 02/06/2008).

A waiver was granted for magnitude of the residue studies on tobacco. Tobacco residue levels were translated from leafy vegetables (Crop Group 4; 13 ppm) with a maximum theoretical concentration factor of 3.9X factor applied to green and dried tobacco leaves. As this is believed to be a worst-case scenario residue level, these are the residue levels which will be used in any tobacco risk assessments. The proposed use on tobacco is identical to that of leafy vegetables

(Crop Group 4). An adequate pyrolysis study is available for use in assessing exposure to tobacco smoke.

DIETARY, RESIDENTIAL and SMOKER (TOBACCO) EXPOSURE PATHWAYS:

Dietary Risk Estimates (Food + Water)

A conservative chronic dietary risk assessment (DP#361792, D. Rate, 12/09/2009) was recently conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03). DEEM™ 7.81 default processing factors, 100% crop treated (CT), and recommended or tolerance-level residues were assumed for all commodities. Drinking water was incorporated directly into the dietary exposure assessment using the chronic estimated drinking water concentration (EDWC) of 36.5 µg/L for surface water (the non-cancer, 1 in 10 year annual average), based on nursery use in TN at 0.499 lb ai/A. The chronic dietary risk assessment shows that the chronic dietary risk estimates do not exceed ARIA's level of concern [i.e., <100% of the chronic population-adjusted dose (cPAD)]. For the general U.S. population the exposure (0.027054 mg/kg bw/day) for food and water utilized 2% of the cPAD. The chronic dietary risk estimate for the highest exposed population subgroup, children 1-2 years old, is 5% of the cPAD (0.080839 mg/kg bw/day exposure).

Residential Exposure

There are existing residential uses that are considered in this assessment. The multitude of use sites, in addition to the persistence of chlorantraniliprole, indicate there is potential for short- and intermediate-term postapplication dermal (adults and children) and incidental oral (children only) exposure to chlorantraniliprole (postapplication inhalation exposure is not expected due to low vapor pressure). However, due to the lack of toxicity via the dermal route, as well as the lack of toxicity over the acute, short- and intermediate-term via the oral route – no risk is expected from these exposures. Spray drift is a potential source of exposure to residents nearby to spraying operations but it is not expected to pose a risk due to the lack of toxicity resulting from chlorantraniliprole exposure (other than chronic oral ingestion).

Inhalation Risk From Tobacco:

There is a proposed use for chlorantraniliprole on tobacco, and subsequently, a potential for exposure to chlorantraniliprole via tobacco products. Although it is well documented that there are adverse health effects from chronic use of tobacco itself, short-term exposure as well as chronic exposure to pesticide residues in tobacco products will be qualitatively assessed and aggregated. Based on the lack of hazard identified in the acute inhalation study, lack of acute irritation, and extremely low oral toxicity – no acute inhalation endpoint was selected for risk assessment. Based on the chronic oral endpoint a long-term margin of exposure (MOE) for chlorantraniliprole from the use of treated tobacco can be conservatively estimated on a mg/kg bw/day basis. The MOE for tobacco is estimated at ~14,000 (0.011 mg/kg bw/day exposure). The MOE for the use of chlorantraniliprole on tobacco does not exceed ARIA/HED's level of concern.

Aggregate Risk:

The long-term aggregate risk assessment for chlorantraniliprole includes exposure to residues in food and water as well as from residues in tobacco smoke. As described above, no risk is expected from residential exposures or from spray drift. A highly conservative MOE for chlorantraniliprole exposure from the use of treated tobacco has been calculated using the chronic oral NOAEL (158 mg/kg bw/day). To aggregate the exposure and risk from chlorantraniliprole in food, water and tobacco smoke, the MOEs from each route are compared (See Section 8.1.). For the general U.S. population the exposure contribution in tobacco smoke (0.011 mg/kg/day; MOE=14,000) is much less than the exposure in food and water (0.027054 mg/kg/day; MOE=5,800). Thus, aggregation of exposure from tobacco smoke would not appreciably alter the risk estimate for food and water alone. Therefore, the long-term aggregate risk and exposure via chronic exposures to food, water and tobacco smoke do not exceed ARIA/HED's level of concern.

Acute and cancer aggregate risks were not assessed due to the absence of an acute dietary endpoint and to the fact that chlorantraniliprole is not likely to be carcinogenic to humans.

Occupational Risk:

There is a potential for occupational short- and intermediate-term inhalation and dermal exposure to chlorantraniliprole during mixing, loading, application, and postapplication activities. However, the chlorantraniliprole toxicology database indicates there is no systemic hazard associated with short- and intermediate-term dermal and inhalation exposure, and therefore, no occupational exposure and risk assessment was conducted.

In addition to systemic hazard, the Worker Protection Standard (WPS) sets a restricted entry interval (REI) based on the acute toxicity of chemicals. Chlorantraniliprole is classified in Acute Toxicity Category IV for oral toxicity, dermal toxicity, inhalation toxicity, eye irritation, and primary skin irritation. Also, chlorantraniliprole is not a dermal sensitizer. Per the WPS, a 12-hr REI is required for chemicals classified under Toxicity Category III or IV. According to Pesticide Registration (PR) Notice 95-3, EPA permits registrants to reduce REIs from 12 to 4 hours for low risk pesticides that meet certain criteria. Chlorantraniliprole meets all of the criteria listed in PR Notice 95-3 and is, therefore, a candidate for a reduced REI of 4 hours. The minimum level of personal protective equipment (PPE) for handlers is based on acute toxicity for the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with the WPS.

ENVIRONMENTAL JUSTICE CONSIDERATIONS

Potential areas of environmental justice concern, 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," (http://homer.ornl.gov/nuclearsafety/nsea/oepa/guidance/justice/eo12898.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 (as it relates to an imported crop), ARIA estimates risks to population subgroups from pesticide exposures that are

based on patterns of that subgroup's food consumption. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all proposed/registered food uses/tolerances of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure from traditional dietary patterns among specific subgroups.

REVIEW OF HUMAN RESEARCH:

No studies involving human research were relied on in this human health risk assessment.

RECOMMENDATIONS

There are no outstanding residue chemistry data requirements or human health risk issues that would preclude adding tobacco to the current label of DuPont™ Coragen® SC Insect Control (EPA Reg. No. 352-729).

2.0 Ingredient Profile

For a discussion of the physical and chemical properties of chlorantraniliprole see Memo, PP#9F7513, DP#361791, D. Rate, 01/08/2010.

2.1 Summary of Proposed Uses

Table 2.1. Summary of Directions for Use of DuPont™ Coragen® SC on Tobacco.

Applic. Timing, Type, and Equip.	Formulation	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)
Tobacco					
Foliar Broadcast by ground or air	18.4% SC	0.045-0.098	NS	0.2 [221]	1
	Use Directions and Limitations: Minimum interval between treatments is 3 days. Do not use an adjuvant with Coragen applications. Do not apply more than 0.2 lb ai/A per crop cycle. Minimum spray volumes are 100 gal/A (ground) or 10 gal/A (aerial); 4-hour minimum RTI.				

For the Section 3 registration of tobacco, the submitted label is adequate for the proposed use.

3.0 Hazard Characterization/Assessment

Chlorantraniliprole (DPX-E2Y45). Human Health Risk Assessment for Proposed Uses on the Tree Nut Crop Group and Pistachios and for Increases in the Established Tolerances for Pome Fruits, Stone Fruits, Grapes, and Raisins due to the Removal of Adjuvant Restrictions from the Label for Pome Fruits, Stone Fruits, and Grapes. DP#357072, N. Tsaur, 03/04/2009.

Chlorantraniliprole (DPX-E2Y45). Human Health Risk Assessment for Section 3 Registration Request to Expand Uses of Coragen®, Altacor®, and Dermacor™ X-100 Labels on Various Field, Vegetable, and Fruit Crops. DP#361397, D. Rate, 01/12/2010.

ARIA/HED has concluded that sufficient toxicology information exist for chlorantraniliprole for selecting the toxicological endpoints needed for assessing its risks to humans resulting from its use as an insecticide (DP#361397, D. Rate, 01/12/2010). Chlorantraniliprole has been classified as "not likely to be carcinogenic to humans."

For a discussion of the hazard and dose/response assessments of chlorantraniliprole see Memo, PP#9F7513, DP#361397, D. Rate, 01/12/2010. A summary of the toxicological endpoints for use in human risk assessment is given below.

No adverse effects were attributable to a single dose which can be used to assess short-term risk to smokers. However, based on the chronic oral endpoint (1.58 mg/kg bw/day) a long-term MOE for chlorantraniliprole from the use of tobacco has been qualitatively estimated.

Tables 3.0.a and 3.0.b summarize the toxicological doses and endpoints for chlorantraniliprole for use in dietary and occupational human health risk assessments, respectively.

Table 3.0.a. Summary of Toxicological Doses and Endpoints for Chlorantraniliprole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	N/A	N/A	N/A	No acute hazard, attributable to a single dose, was identified; therefore, an acute dietary endpoint was not selected for quantitative risk assessment.
Chronic Dietary (All Populations)	NOAEL= 158 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 1.58 mg/kg/day cPAD = 1.58 mg/kg/day	18-Month Oral (feeding)/mouse LOAEL = 935 mg/kg/day based on eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight (males only)
Incidental Oral Short- /Intermediate-Term	N/A	N/A	N/A	There was no hazard identified via the oral route over the short- and intermediate-term and therefore, no endpoint was selected for quantitative risk assessment.
Dermal Short- /Intermediate-Term	N/A	N/A	N/A	There was no hazard identified via the dermal route (and no concerns for developmental, reproductive or neurotoxic effects) and therefore, no dermal endpoint was selected for quantitative risk assessment.
Inhalation Short- /Intermediate-Term	N/A	N/A	N/A	Based on the lack of hazard identified in the acute inhalation study, lack of acute irritation, and extremely low oral toxicity – no inhalation endpoint was selected for quantitative risk assessment.

Table 3.0.a. Summary of Toxicological Doses and Endpoints for Chlorantraniliprole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation Long-Term	NOAEL= 158 mg/kg/day	N/A	MOE ≤100	18-Month Oral (feeding)/mouse LOAEL = 935 mg/kg/day based on eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight (males only)
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on weight of evidence of data: no treatment-related tumors reported in the submitted chronic and oncogenicity studies in rats and mice, subchronic studies in mice, dogs and rats and that no mutagenic concern was reported in the genotoxicity studies.			

Table 3.0.b. Summary of Toxicological Doses and Endpoints for Chlorantraniliprole for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-/Intermediate-Term	N/A	N/A	N/A	There was no hazard identified via the dermal route (and no concerns for developmental, reproductive or neurotoxic effects) and therefore, no dermal endpoint was selected for quantitative risk assessment.
Inhalation Short-/Intermediate-Term	N/A	N/A	N/A	Based on the lack of hazard identified in the acute inhalation study, lack of acute irritation, and extremely low oral toxicity – no inhalation endpoint was selected for quantitative risk assessment.
Cancer (dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on weight of evidence of data: no treatment-related tumors reported in the submitted chronic and oncogenicity studies in rats and mice, subchronic studies in mice, dogs and rats and that no mutagenic concern was reported in the genotoxicity studies.			

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. MOE = margin of exposure. 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. PAD = population adjusted dose (c = chronic). RfD = reference dose. LOC = level of concern. N/A = not applicable

3.1 Recommendation for Aggregate Exposure Risk Assessments

Under FQPA, the Agency considers and may aggregate pesticide exposures from major exposure pathways. In addition to food, drinking water, and residential exposure pathways, the potential for exposure to chlorantraniliprole residues in tobacco smoke has also been considered. There were no adverse effects identified for short- or intermediate-term dermal and inhalation exposures. Consequently, residential exposure need not be considered as a component of aggregate risk. The adverse effects identified for long-term dietary exposure and inhalation exposure are the same; therefore, it would be appropriate to aggregate exposure/risk from these pathways.

3.2 Classification of Carcinogenic Potential

There were no treatment-related tumors reported in the submitted chronic toxicity and carcinogenicity studies in rats and mice or the subchronic studies in mice, dogs and rats after exposure to chlorantraniliprole. Additionally, there was no mutagenic concern reported in the genotoxicity studies. Based on the weight of evidence of the available scientific data, and in accordance with EPA's Final Guidelines for Carcinogen Risk Assessment (March 2005),

chlorantraniliprole is classified as "Not Likely to Be Carcinogenic to Humans."

4.0 Public Health and Pesticide Epidemiology Data

The following information was provided by DuPont when chlorantraniliprole was first assessed in 2007/2008:

> DPX-E2Y45 has been produced on a pilot scale since 2003 at a contract facility, Albemarle Process Development Center, in Baton Rouge, Louisiana or at the DuPont Experimental Station (Wilmington, Delaware). The formulated preparations have been made at the DuPont Stine Haskell Research Center (Newark, Delaware). DPX-E2Y45 has not been manufactured on an industrial scale for commercial use. A limited number of workers have been involved with the synthesis of this compound to date. No illnesses have been attributed to exposure associated with the handling, testing, or manufacturing of DPX-E2Y45.
>
> Additional workers have been exposed during the regulatory and field biological testing. No illnesses have been attributed to exposure associated with the handling, testing, or manufacturing of DPX-E2Y45.

5.0 Dietary Exposure/Risk Characterization

5.1 Analytical Methodology

Chlorantraniliprole in/on Tobacco. Summary of Analytical Chemistry and Residue Data. DP#369223, D. Rate, 12/10/2009.

Adequate methods are available for the enforcement of tolerances for chlorantraniliprole residues in/on crops (LC/MS/MS Method DuPont-11374) and livestock (LC/MS/MS; MRID 46889003). The LOQs are 0.01 ppm for chlorantraniliprole in crop and livestock matrices. Chlorantraniliprole is not recovered by the US FDA's multi-residue methods. For data collection, LC/MS/MS method DuPont-13294 was used for the analysis of chlorantraniliprole residues in samples from the field trial and processing studies submitted in conjunction with the subject petition. The adequacy of data-collection methods was verified with method recoveries in the acceptable 70-120% range.

5.2 Residue Profile

Chlorantraniliprole in/on Tobacco. Summary of Analytical Chemistry and Residue Data. DP#369223, D. Rate, 12/10/2009.

Chlorantraniliprole (DPX-E2Y45). Section 3 Registration Request for Use on Leafy Vegetables (Except Brassica) (Crop Group 4), Brassica (Cole) Leafy Vegetables (Crop Group 5), Fruiting Vegetables (Crop Group 8), Cucurbit Vegetables (Crop Group 9), Pome Fruits (Crop Group 11), Stone Fruits (Crop Group 12), Cotton, Grapes, and Potatoes. Summary of Analytical Chemistry and Residue Data Section 18 Exemption 08LA01 for Use on Rice. DP#336941, L. Cheng, 2/25/2008.

The petitioner's request for a waiver of tobacco magnitude of residue studies is granted based on the lack of plant metabolism, the short pre-harvest and application intervals, and the lack of phloem mobility. The magnitude of chlorantraniliprole residues are expected to be driven by the rate of application and crop architecture. For the purpose of this petition, ARIA concludes that it is acceptable to translate field trial data from leafy vegetables to tobacco. The currently established tolerance of 13 ppm for Crop Group 4 (leafy vegetables) along with a maximum theoretical concentration factor of 3.9X may be used as estimates of chlorantraniliprole residues in/on green and cured tobacco, respectively, to conduct the necessary risk assessments for tobacco registration. ARIA/HED will re-visit this issue when the results of adjuvant bridging study for leafy vegetables are submitted for review.

5.3 International Residue Limits

As tolerances are not required for the use on tobacco, international harmonization for the proposed use on tobacco is not applicable.

5.4 Dietary Exposure and Risk

Chlorantraniliprole: Chronic Aggregate Dietary (Food plus Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action to Allow use of Chlorantraniliprole on Various Crops. DP#361792, D. Rate, 12/09/2009.

A recent chronic dietary risk assessment was conducted incorporating recommended and tolerance-level residues in/on a wide variety of agricultural commodities using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998 (DP#361792, D. Rate, 12/09/2009). Chronic dietary risk for established and proposed uses of chlorantraniliprole is 2% of the cPAD (0.027054 mg/kg/day exposure; MOE=5800) for the general U.S. population and 5% of the cPAD (0.080839 mg/kg bw/day exposure) for the highest exposed population subgroup, children 1-2 years old. This risk is below the Agency's level of concern.

6.0 Residential and Other Exposures (Spray Drift, etc.)

Although there are existing residential uses for chlorantraniliprole, residential exposure to chlorantraniliprole was not assessed due to the lack of toxicity via the inhalation route, the dermal route, as well as the lack of toxicity over the acute, short- and intermediate-term via the oral route. No risk is expected from residential exposure to chlorantraniliprole.

Spray drift is always a potential source of exposure to residents near spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method (both methods employed for chlorantraniliprole). The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now

requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Smoker Exposure/Risk Characterization

With this petition (PP# 9F7513), there is a proposed use on tobacco, and subsequently, a potential for exposure to chlorantraniliprole via smoking chlorantraniliprole treated tobacco products.

It has been OPP policy to assess adverse health effects from use of pesticide-treated tobacco. Human health risk assessment documents for chemicals which are proposed or currently registered for use on tobacco assess short-term exposure/risk resulting from use of tobacco. Although it is well documented that there are adverse health effects from chronic use of tobacco itself, ARIA/HED has assessed and aggregated chronic exposure/risk to chlorantantiliprole in tobacco smoke with those exposures expected in the food and water pathways.

In assessing exposure through use of tobacco, ARIA has assumed that the greatest exposure to chlorantraniliprole would come from cigarettes. Further, ARIA has assumed that the average U.S. smoker smokes 15 cigarettes per day (Pierce, J. P., et al. 1989. Tobacco Use in 1986 - Methods and Basic Tabulations from Adult Use of Tobacco Survey. U.S. Dept. of Health and Human Services Publication Number OM90-2004. Office on Smoking and Health, Rockville, Maryland). Translated residue levels for tobacco and a tobacco pyrolysis study were provided in PP# 9F7513 (DP#369223, D. Rate, 12/10/2009). The pyrolysis of chlorantraniliprole in cigarettes resulted in unchanged parent (17.4-17.9% of the applied dose) with carbon dioxide being the major identified residue (25.1-32.9% of the applied dose). Three additional metabolites were also identified: IN-ECD73 (15.9%), IN-EQW78 (10.1-14.7%), and IN-F6L99 (9.5%). Tobacco residue levels are translated from leafy vegetables (Crop Group 4), a worst-case scenario. The maximum residue of chlorantraniliprole in tobacco leaves would be 13 ppm with a 3.9X processing factor applied for green and cured leaves, respectively. For this conservative assessment, ARIA has assumed that 100% of the pesticide residue on the tobacco is inhaled and 100% of the residues inhaled are absorbed. These assumptions are conservative and are likely to overestimate potential exposure. With the assumptions regarding smoking frequency and an average body weight of 70 kg (for adults), ARIA estimates that exposure to chlorantraniliprole will not exceed 0.011 mg/kg bw/day for the average adult smoker [50.7 µg/ cigarette x 15 cigarettes/day x 1 mg/1000 µg ÷ 70 kg body weight.]

No short-term inhalation NOAEL has been identified due to the lack of hazard identified in the acute inhalation study, lack of acute irritation, and extremely low oral toxicity. Based on the lack of inhalation endpoints, the short-term MOE for chlorantraniliprole exposure from the use

of tobacco could not be quantified at this time. This route of exposure is not a risk concern.

The chronic inhalation NOAEL is 158 mg/kg bw/day and is based on eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight (males only) from a 18-month oral (feeding) in mice. The use of this endpoint is considered a worst-case scenario for chronic exposure to chlorantraniliprole via smoking treated tobacco. Based on the inhalation NOAEL, the long-term MOE for chlorantraniliprole exposure from the use of tobacco is estimated to be greater than 14,000/day (based on 70 kg body weight), which is higher than the target MOE of 100 for the general U.S. population. This is a highly conservative value for reasons stated above and is not a risk concern.

$$MOE = \frac{NOAEL_{(tobacco)}}{Exposure_{(tobacco)}}$$

MOE = (158 mg/kg bw/day) / (0.011 mg/kg bw/day) = 14,364

8.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

In accordance with the FQPA, ARIA has considered and aggregated pesticide exposures and risks from food and drinking water, and residential uses. In addition to FQPA requirements, exposure from the use of treated tobacco has also be aggregated. 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, ARIA has considered both the route and duration of exposure.

For this action, exposure from smoking chlorantranililprole-treated tobacco is also considered in the aggregate assessment. Although there is potential exposure to chlorantraniliprole from food, drinking water, residential use sites and tobacco smoke, the only identified hazard is via the oral route over a chronic duration. Residential exposures are expected to occur over a short- or intermediate-term duration. Therefore, the aggregate risk assessment considers only exposures from food and drinking water consumed over a long-term duration (greater than 6 months of daily exposure) and exposure from tobacco smoke calculated on a long-term basis.

8.1 Long-Term Aggregate Risk

There is no expected risk from residential exposures to chlorantraniliprole, and therefore aggregate risk is equal to that from consumption of food and water, and tobacco use. As stated earlier, the Agency considers the likely route of exposure from the use of pesticides on tobacco to be neither dietary nor residential. Instead, such exposures are addressed as an inhalation hazard from tobacco smoke. As addressed in Section 7.0, due to the lack of inhalation endpoints, a MOE for chlorantraniliprole exposure from the use of tobacco was conservatively calculated using the chronic oral NOAEL of 158 mg/kg bw/day (18-month oral mouse study). Exposure estimates for tobacco smoke, food and water are based on conservative upper bound assumptions. Neither risk from food and water (registered and proposed uses) nor risk from

tobacco smoke is above the Agency's level of concern (MOE≤100). For the general U.S. population the exposure contribution in tobacco smoke (0.011 mg/kg/day; MOE=14,000) is much less than the exposure in food and water (0.027054 mg/kg/day; MOE=5,800). Thus, aggregation of exposure from tobacco smoke would not appreciably alter the risk estimate for food and water alone.

9.0 Occupational Exposure/Risk Pathway

9.1 Occupational Pesticide Handler Exposure and Risk

DuPont is registering Coragen® SC for use on tobacco. For tobacco, the maximum application rate is 0.10 lb ai/A/application (total rate of 0.2 lb ai/A/season) with a minimum RTI of 3 days and a PHI of 1 days. Application is expected via ground sprays. Subsequently, there is potential for short- and intermediate-term occupational exposure to chlorantraniliprole during both handler [mixing, loading, and application (via the dermal and inhalation routes)] and postapplication activities (via the dermal route) based on the proposed uses. However, the chlorantraniliprole toxicology database indicates there is no systemic hazard associated with short- and intermediate-term dermal and inhalation exposure, and therefore, no occupational exposure and risk assessment was conducted.

9.2 Occupational Post-Application Worker Exposure and Risk

In addition to systemic hazard, the WPS sets an REI based on the acute toxicity of chemicals. Chlorantraniliprole is classified in Acute Toxicity Category IV for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, acute eye irritation, and primary skin irritation. Also, chlorantraniliprole is not a dermal sensitizer. Per the WPS, a 12-hr REI is required for chemicals classified under Toxicity Category III or IV. However, the label submitted for chlorantraniliprole indicates a proposed REI of 4 hours. If a pesticide meets all the criteria in Pesticide Registration (PR) Notice 95-3, EPA permits registrants to reduce REIs from 12 to 4 hours:

1. The active ingredient is in Toxicity category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation.

2. The active ingredient is not a dermal sensitizer (or in the case of biochemical and microbial active ingredients, no known reports of hypersensitivity exist).

3. The active ingredient is not a cholinesterase inhibitor (N-methyl carbamate and Organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.

4. No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the active ingredient.

5. EPA does not possess incident information (illness or injury reports) that are "definitely" or "probably" related to post-application exposures to the active ingredient.

Chlorantraniliprole meets all of the above criteria, and therefore, is a candidate for a reduced REI of 4 hours according to PR Notice 95-3.

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. RD is responsible for ensuring that PPE listed on the label is in compliance with the WPS.

10.0 DATA NEEDS AND LABEL RECOMMENDATIONS

10.1 Toxicology

- None.

10.2 Residue Chemistry

- None.

10.3 Occupational and Residential Exposure

- None.

11.0 References

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