UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 3/7/2008

MEMORANDUM

SUBJECT: Chlorantraniliprole (DPX-E2Y45): Human Health Risk Assessment for Proposed Uses on Pome fruit, Stone fruit, Leafy vegetables, *Brassica* leafy vegetables, Cucurbit vegetables, Fruiting vegetables, Cotton, Grapes, Potatoes, Turf and Ornamentals. PC Code: 090100, Petition #7F7181 DP Barcode: D336983, D338120, D348103, D346324, Section 18 Registration # 08LA01 (Rice), D346324.

Regulatory Action: Section 3 and Section 18 registration actions
Risk Assessment Type: Single Chemical Aggregate

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Introduction

This document addresses three different actions submitted to the Agency regarding chlorantraniliprole. The primary action (Section 3, food-uses, Petition #7F7181) was conducted as part of a global project with the Organization for Economic Cooperation and Development (OECD). The goals of the project were to work-share among participating countries and harmonize on maximum residue levels (MRLs) to attenuate potential trade issues. To facilitate the project a common dossier was submitted, and a common OECD monograph is expected as an output. The United States (US) was the lead country for the mammalian toxicology database assessment.

As part of the OECD work-share project, E. I. DuPont de Nemours and Company, DuPont Crop Protection (referred to as DuPont or the registrant throughout the rest of the document) proposed product registrations and exemptions for the requirement of tolerances (for the US only) for the new active ingredient (ai) chlorantraniliprole. The common name, chlorantraniliprole, was officially granted following the generation and submission of the supporting datasets. Therefore, although chlorantraniliprole is used on product labels and government forms, the company name, DPX-E2Y45 is used in the technical reports (both names are used synonymously in this document). This action involves the registration of one technical product (DuPont™ Rynaxypyr™ Technical Insecticide) and two agricultural end-use products (DuPont™ Coragen™ SC Insecticide and DuPont™ Altacor™ WG Insecticide) for use on pome fruit, stone fruit, leafy vegetables, *Brassica* leafy vegetables, cucurbit vegetables, fruiting vegetables, cotton, grapes and potatoes.

Additionally, DuPont submitted 13 product registration applications to the US EPA, to consider the use of chlorantraniliprole on terrestrial non-food crops (*i.e.*, landscape ornamentals and turf grass). One is a soluble concentrate (18.4% ai), but the remaining 12 end-use products are formulated as granulars (all contain less than 1% ai). Also, the registrant has submitted a product registration for a manufacturing concentrate (a dry powder formulation, 35% ai) used to generate the granular formulations. The end-use products are for use on turf grasses and ornamental plants growing in residential, commercial, and public landscaped areas; on golf courses and athletic fields; and to turf grasses grown on commercial sod farms.

Lastly, the Louisiana Department of Agriculture and Forestry has requested an exemption under Section 18 of FIFRA for the use of chlorantraniliprole (DuPont™ Dermacor X-100 Seed Treatment, 51.85% ai) for the purpose of controlling rice water weevils in drill-seeded rice fields in Louisiana (treated seeds are not to be used as part of water-seeded cultivation practices). Associated with this action, is another Section 18 for exemption from tolerances from inadvertent residues on crayfish, resulting from the use on rice seed (residue data in crayfish were not required for the Section 18 request, and therefore are not addressed in this document).

Although maximum residue limits are proposed for food uses outside of the US, based on toxicity considerations, DuPont requests an exemption from the requirement of tolerances for residues resulting from the application of chlorantraniliprole formulations to the crops or crop groups grown in/imported to the US, as well as for residues of chlorantraniliprole which may be

found on rotational crops planted to areas previously treated with chlorantraniliprole; and finally, for residues of chlorantraniliprole on the meat, milk, poultry, and eggs which are derived from animals which consume feed commodities which have been treated with chlorantraniliprole formulations. On the other hand, the Louisiana Department of Agriculture and Forestry has proposed temporary tolerances of 0.05 ppm in rice grain (kernels plus hulls) and 0.25 ppm in rice straw.

Pending submission of a revised Section B (label modifications –see Section 10.2 and 10.3 of this document), the submission of extensive field rotational crop data (see Section 10.2), and the submission of a revised Section F (below), there are no residue chemistry, toxicology and/or exposure issues that would preclude granting a conditional registration for the requested uses of chlorantraniliprole on the crops and/or crop groups addressed herein. Registration should be made conditional pending adequate resolution of the data gaps listed.

The Agency has determined that the request for exemption from tolerances for chlorantraniliprole is not appropriate due to identified toxicity in the submitted mammalian toxicology database and identified exposure potential based on submitted exposure data. The proposed uses and the submitted data support the following tolerances for residues of 3-bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxamide (*i.e.*, chlorantraniliprole) in/on the following raw agricultural or processed commodities or crop groups, at the following levels:

Apple, wet pomace	0.60 ppm
Brassica, head and stem, subgroup 5A	4.0 ppm
Brassica, leafy greens, subgroup 5B	11 ppm
Cotton, gin byproduct	30 ppm
Cotton, hulls	0.40 ppm
Cotton, undelinted seed	0.30 ppm
Fruit, pome, group 11	0.30 ppm
Fruit, stone, group 12	1.0 ppm
Grape	1.2 ppm
Grape, raisin	2.5 ppm
Potato	0.01 ppm
Vegetable, cucurbit, group 9	0.25 ppm
Vegetable, fruiting, group 8	0.70 ppm
Vegetable, leafy, except *Brassica*, group 4	13 ppm
Milk	0.01 ppm
Meat*	0.01 ppm
Meat byproducts*	0.01 ppm
Fat*	0.01 ppm

*of cattle, goats, horses, sheep

And for the Section 18 use on rice, HED recommends the following temporary tolerances or time-limited tolerances in/on the following commodities:

Rice, grain	0.10 ppm
Rice, straw	0.25 ppm

This HED document provides a summary of the findings from the data evaluation and subsequent assessment of human health risk resulting from these requests. The hazard assessment and characterization was conducted by Mary Manibusan; the occupational exposure data review was conducted by Jack Arthur; the residue chemistry data was reviewed by Leung Cheng, and he also conducted the dietary exposure assessment; and the human health risk assessment was conducted by Sarah Winfield (RAB3); additionally, the drinking water assessment was conducted by James Hetrick of OPP's Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Chlorantraniliprole, or DPX-E2Y45, is a novel anthranilic diamide insecticide that belongs to a class of compounds that acts on the ryanodine receptor (Group 28 based on the target site of action). 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 of two agricultural end-use products (Dupont™ Coragen™ SC Insecticide and Dupont™ Altacor™ WG Insecticide) and 13 products for use on turf and ornamentals (Dupont™ E2Y45 SC Insecticide, and 12 granular formulations of varying concentrations ai). Additionally the Louisiana Department of Agriculture has applied for a Section 18 exemption for the use of Dupont™ Dermacor X-100 Seed Treatment on rice seeds. These actions require the establishment of tolerances for resulting residues of 3-bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxamide in/on pome fruit, stone fruit, leafy vegetables, *Brassica* leafy vegetables, cucurbit vegetables, fruiting vegetables, cotton, grapes and potatoes and rice.

Use Profile

For agricultural crops (pome fruit, stone fruit, leafy vegetables, *Brassica* leafy vegetables, cucurbit vegetables, fruiting vegetables, cotton, grapes, potatoes and rice) application rates range from about 0.03 to 0.1 lb ai/A, re-treatment intervals range from 5-10 days, and, pre-harvest intervals (PHIs) range from 1-21 days (except for rice, which is a seed-treatment use). Crops can be treated from 2-6 times per season; as the maximum seasonal application rate is 0.2 lb ai/A (except for rice, which is 0.13 lb ai/A/yr). Application is expected via aerial and ground equipment, as well as chemigation. For turf, application rates range from 0.013 to 0.33 lb ai/A, and the maximum application rate is 0.5 lb ai/A (if the minimum application rate is used, turf can be treated up to 38 times per year). Dupont™ E2Y45 SC Insecticide for use on turf can be applied by ground equipment, and the granular formulations are applied by drop-type, rotary-type or hand-held equipment. Ornamental use directions are highly variable, but maximum seasonal rates range from 0.33 to 0.5 lb ai/A (see Section 2.0 for more specifics on use patterns for each use site). Turf and ornamental use sites include industrial facilities, residential dwellings, business and office complexes/buildings/interior plantscapes, recreational areas of all sorts (parks, playgrounds, golf courses, athletic fields) and sod farms. The labels associated with the Section 3 action propose a restricted entry interval (REI) of 2 hours (agricultural crops, turf and ornamentals).

Toxicity/Hazard Assessment

Chlorantraniliprole/DPX-E2Y45 has no significant acute toxicity *via* the oral, dermal, and inhalation routes of exposure. The LD_{50} for oral and dermal acute exposure is ≥5000 mg/kg/day and the LC_{50} for acute inhalation exposure is ≥5.1 mg/L. This substance is not an eye or skin irritant and does not cause skin sensitization. In short-term studies, the most consistent effects are those associated with non adverse pharmacological response to the xenobiotic, induction of liver enzymes and subsequent increase in liver weights. DPX-E2Y45 is not genotoxic, neurotoxic, immunotoxic, carcinogenic, or teratogenic. Furthermore, it is not uniquely toxic to the conceptus as there were no maternal or fetal effects in studies conducted in rats and rabbits.

Based on the results of a 28-day dermal study in rats, as well as the dermal LD_{50} study, DPX-E2Y45 has relatively low dermal toxicity.

Overall, chlorantraniliprole exhibits minimal mammalian toxicity after long-term exposure. The only consistent observation in the mammalian toxicology studies is an increased degree of microvesiculation of the adrenal cortex after dermal or dietary administration of chlorantraniliprole. Based on the lack of adverse effect on the function of the adrenal gland, this observation was considered treatment related, but not "adverse."

In addition to the adrenal effects, liver effects (*e.g.*, increased liver weight and induction of Cytochrome P450 enzymes) were reported in the 90-day oral subchronic studies across species and only at the highest dose tested (>1000 mg/kg/day). While in the subchronic studies, these effects were considered adaptive, the liver effects were more pronounced in the 18-month chronic mouse study at the highest dose tested. Increased eosinophilic foci (preneoplastic foci) were noted in male mice at 935 mg/kg/day and liver hypertrophy and weight increase were evident at the next lower dose (158 mg/kg/day), but progression to tumors was not apparent for these effects. Therefore, the eosinophilic foci appear to be an adverse effect only seen in the highest dose tested and was graded minimal in severity.

Dietary Exposure (food/water)
The residue of concern in drinking water, plants and livestock for risk assessment and tolerance enforcement is chlorantraniliprole (although drinking water is not subject to tolerance enforcement). If new uses are proposed that significantly impact the dietary burden for livestock, the residue of concern decision for livestock may need to be reevaluated. LC/MS/MS methods are available for measuring chlorantraniliprole in plants, livestock (although tolerances in poultry and eggs are not required), and processed commodities. Adequate methods and concurrent recovery data were provided, and the fortification levels used in the methods and concurrent validations were adequate to bracket the residue levels determined in the proposed crops (and secondary 'crops'). The validated limit of quantitation (LOQ) in plant and livestock matrices is 0.01 ppm. The LC/MS/MS methods have been validated in EPA laboratories. Although data from testing multiresidue methods were submitted, chlorantraniliprole was not recovered by these methods.

Crop field trials were conducted on crops or representative commodities of crop groups. There are adequate field residue data for these crops based on geographic representation and number of field trials. The residue field trials were conducted using either the WG or SC formulation to the proposed crops at the maximum proposed use patterns [residues ranged from <0.01 ppm in many field trial samples to 15 ppm (cotton gin byproducts) and 9.7 ppm (spinach)]. Acceptable processing studies were conducted on apple, cotton, grape, plum, potato, and tomato. The results of these studies show that chlorantraniliprole, upon processing, concentrates in some processed commodities, but not in others. Acceptable limited field rotational crop studies were submitted. The data suggest that rotational crop tolerances are required, and that the petitioner needs to conduct extensive field rotational crop trials. Until the requested data are submitted, a restriction should be imposed on the proposed labels to prohibit the rotation to any crop not on the label. The data that were submitted are supported by adequate storage stability data which indicate that

chlorantraniliprole is stable under frozen conditions and during storage intervals. When applicable, the Agency's standard operating procedures, along with the tolerance spreadsheet, were used for calculating recommended tolerances.

The laboratory environmental fate data indicate chlorantraniliprole is persistent and mobile in terrestrial and aquatic environments. Although degradation products of chlorantraniliprole (in particular, the major environmental degradates IN-EQW78 and IN-LBA24) are found in environmental fate studies, their persistence and mobility in soil and water are not expected to be substantially different than parent chlorantraniliprole. Therefore, the environmental fate properties of chlorantraniliprole were used to model protective estimated drinking water concentrations (EDWCs) in surface water and groundwater (the models PRZM-EXAMS and SCI-GROW, respectively). The modeled EDWCs ranged from 1 µg/L in groundwater (based on the highest use rate, for ornamental plants) to 85 µg/L (an acute estimate based on the rice use).

Because long-term oral exposure was the only route and duration where chlorantraniliprole demonstrated toxicity (an adverse effect), only chronic dietary (food and drinking water) exposure assessments were conducted (using the dietary model DEEM-FCID). The modeled exposure estimates are based on tolerance level residues, assuming 100% of crops associated with the Section 3 and 18 requests are treated, and include the highest modeled EDWC relevant to the scenario. Despite the conservative assumptions on the exposure side, the resulting chronic dietary exposures for all population subgroups were less than 1% of the cPAD.

Residential Exposure
Residential exposure to chlorantraniliprole is expected. 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 (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.

Aggregate Exposure
Although there is potential residential exposure, there is no residential hazard/risk associated with the route/duration of the proposed uses; therefore, aggregate exposure is comprised of food and water only, and is considered in the dietary section of this document.

Occupational Exposure
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 an REI based on the acute toxicity of chemicals. Technical chlorantraniliprole is in Category IV for acute dermal toxicity and Category IV for primary eye and skin irritation. Per the WPS, a 12-hr REI is

required for chemicals classified under Toxicity Category III or IV. However, all the labels submitted for chlorantraniliprole indicate a proposed REI of 2 hours (except the Dermacor label associated with the rice seed use). According to Pesticide Registration (PR) Notice 95-3, EPA permits registrants to reduce REIs from 12 to 4 hours for certain low risk pesticides that meet certain criteria, but not to 2 hours. Chlorantraniliprole meets all of the criteria listed in PR Notice 95-3, and therefore, is a candidate for a reduced REI of 4 hours. The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

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," http://www.eh.doe.gov/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, 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 USDA under the Continuing Survey of Food Intake by Individuals (CSFII) 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, 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. Whenever appropriate, nondietary 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 postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research
This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

Recommendations for Tolerances and Registration
The residue chemistry, toxicological and exposure databases support the establishment of tolerances outlined in the introduction of this document. Pending submission of a revised Section B (label modifications –see Section 10.2 and 10.3 of this document), the submission of extensive field rotational crop data (see Section 10.2), and the submission of a revised Section F (described in the introduction), there are no residue chemistry, toxicology and/or exposure issues that would preclude granting a conditional registration for the requested uses of chlorantraniliprole on the crops and/or crop groups addressed herein. The conditional

registration can be converted to unconditional registration when the remaining deficiencies cited in Section 10.0 of this document are resolved.

2.0 Ingredient Profile

Chlorantraniliprole is an insecticide that was developed by DuPont for control of lepidopteran pests. It belongs to the anthranilic diamide class of insecticides. Despite its structural similarity to some of the phenylpyrazole insecticides, this compound has a different pesticidal mode of action (ryanodine receptor activator), which it shares with phthalic acid diamides. It is a Group 28 insecticide based on the target site of action. Chlorantraniliprole controls many insects (moths, beetles, worms, caterpillars, *etc*.) primarily via interruption of normal muscle contraction pathways, which leads to paralysis and if sustained, leads to the eventual death of the pest. Chlorantraniliprole is formulated as a suspension concentrate (SC) and a water dispersible granule (WG) for agricultural end-use products; and as a SC and granular formulations (G) for use on turf and ornamental plants.

2.1 Summary of Proposed Uses

DuPont is proposing a total of two technical grade/manufacturing formulations and 15 end-use products for use in the US. Two end-use products are intended for agricultural use sites; 13 end-use products are intended for residential and recreational use sites (for use by commercial applicators only). Louisiana is requesting use of Dermacor™ X-100 Seed Treatment formulation [a formulation not proposed by (but manufactured by) DuPont] to treat rice seeds intended for drill-seeded rice fields in Louisiana.

Table 2.1a. Chlorantraniliprole Proposed End-Use Products

Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
DuPont™ Coragen™ SC	352-XXX	18.4% (1.667 lb ai/gallon)	Suspension concentrate (SC)	*Brassica* leafy vegetables, Cucurbit vegetables, Fruiting vegetables, Leafy vegetables (non-*Brassica*)	Broad spectrum systemic insecticide (controls many important insects); some contact activity	Applications may be conducted by ground (chemigation, groundboom, airblast) or aerial equipment. All rotation crops may be planted immediately following the last application. REI 2 hours
DuPont™ Altacor™ WG	352-XXX	35%	Water dispersible granule (WG)	Cotton, Grape, Pome Fruits, Potato, Stone Fruits		Applications may be conducted by ground (groundboom, airblast) or aerial equipment. Do not apply ALTACOR™ through any type of irrigation system. All rotation crops may be planted immediately following the last application. REI 2 hours

Table 2.1a. Chlorantraniliprole Proposed End-Use Products						
Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
DuPont™ Dermacor™ X-100 Seed Treatment	352-XXX	50%	SC	Rice seeds	For control of rice water weevil, *Lissorhoptrus oryzophilus*	For use in drill-seed rice fields (not for use in water-seeded rice fields)
DuPont™ E2Y45 SC Insecticide	352-XXX	18.4% (1.67 lb ai/gallon)	SC	Turf, Ornamental plants	For control of white grubs and other pests infesting landscape and recreational turfgrass (including golf courses and sod farms) as well as caterpillars, clearwing borers and other pests of landscape ornamentals	For use by commercial applicators only. Do not apply through any type of irrigation system, nor with aerial equipment. Do not apply in commercial nurseries and greenhouses. Do not apply more than 38.3 fluid ounces (0.5 lb ai) of product per acre per year in broadcast applications to turfgrass. Minimum retreatment interval – 7 days. REI 2 hours
DuPont™ E2Y45 0.33G Insecticide (I)	352-XXX	0.33%	Granular (G)	Turf, Ornamental plants	For systemic control of white grubs and other pests infesting landscape and recreational turfgrass (including golf courses as well as landscape ornamentals, interior plantscapes and sod farms	For use by commercial applicators only Apply via drop-type, rotary-type or hand-held equipment Apply up 0.5 lb ai/A/yr to turfgrass. Do not apply more than 0.2 lb ai/A in a single application on sod farms Do not apply via air Do not use in commercial nurseries and greenhouses Not for use on plants being grown for sale or other commercial use, or for commercial seed production Minimum retreatment interval – 7 days REI 2 hours
DuPont™ E2Y45 0.25G I	352-XXX	0.25%				
DuPont™ E2Y45 0.167G I	352-XXX	0.167%				
DuPont™ E2Y45 0.16G I	352-XXX	0.16%				
DuPont™ E2Y45 0.133G I + Fertilizer (F)	352-XXX	0.133%				
DuPont™ E2Y45 0.125G I	352-XXX	0.125%				
DuPont™ E2Y45 0.12G I	352-XXX	0.12%				

Table 2.1a. Chlorantraniliprole Proposed End-Use Products						
Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
DuPont™ E2Y45 0.1G I + F	352-XXX	0.1%				
DuPont™ E2Y45 0.067G I + F	352-XXX	0.067%				
DuPont™ E2Y45 0.08G I	352-XXX	0.08%				
DuPont™ E2Y45 0.05G I + F	352-XXX	0.05%				
DuPont™ E2Y45 0.05G I	352-XXX	0.05%				

The summary of the proposed use patterns presented in Table 2.1b is based on information in the labels and from in the document "Good Agricultural Practice for DPX-E2Y45 35WG and DPX-E2Y45 20SC in the United States" provided by the registrant.

Table 2.1b. Summary of Directions for Use of Chlorantraniliprole.						
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)**	**Use Directions and Limitations**
Cotton						
Postemergence Broadcast by ground or air	35% WG	0.044-0.099	Not specified***	0.2 [221]	21	Minimum spray volumes are 5 gal/A (ground) or 5 gal/A (aerial); 5-day minimum RTI
***Brassica* Vegetables** [Broccoli, Broccoli (Chinese), Broccoli Raab, Brussels Sprouts, Cabbage, Cabbage (Chinese, Bok Choy), Cabbage (Chinese, Napa), Cabbage (Chinese Mustard, Choy), Cauliflower, Cavalo Broccolo, Collards, Kale, Kohlrabi, Mizuna, Mustard Greens, Mustard Spinach, and Rape Greens]						
Postemergence Broadcast by ground, drip chemigation, or air	1.67 lb ai/gal SC	0.0261-0.0976	6	0.2 [219]	3	Minimum spray volumes are 10 gal/A (ground) or 5 gal/A (aerial); 3-day minimum RTI for foliar and 10-day RTI for drip chemigation.

Table 2.1b. Summary of Directions for Use of Chlorantraniliprole.						
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)**	**Use Directions and Limitations**
Cucurbit Vegetables [Chayote (Fruit), Chinese Waxgourd, Citron Melon, Cucumber, Gherkin, Gourd Edible (includes Hyotan, Cucuzza, Hechima, Chinese Okra), Momordica, Muskmelon, Pumpkin, Squash, and Watermelon]						
Postemergence Broadcast by ground, drip chemigation, or air	1.67 lb ai/gal SC	0.0261-0.0976	Not specified***	0.2 [219]	1	Minimum spray volumes are 10 gal/A (ground) or 5 gal/A (aerial); 5-day minimum RTI for foliar and 10-day RTI for drip chemigation
Fruiting Vegetables [Eggplant, Groundcherry, Pepino, Pepper (Includes Bell Pepper, Chili Pepper, Cooking Pepper, Pimento, Sweet Pepper), Tomatillo, and Tomato]						
Postemergence Broadcast by ground, drip chemigation, or air	1.67 lb ai/gal SC	0.0261-0.0976	Not specified***	0.2 [219]	1	Minimum spray volumes are 10 gal/A (ground) or 5 gal/A (aerial); 5-day minimum RTI for foliar and 10-day RTI for drip chemigation
Grapes						
Postemergence Broadcast by ground or air	35% WG	0.044-0.099	Not specified***	0.2 [221]	14	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 7-day minimum RTI
Leafy Vegetables (Non-*Brassica*) [Amaranth (Leafy), Arugula, Cardoon, Celery, Celery (Chinese), Celtuse, Chevril, Chrysanthemum (Edible Leaved), Chrysanthemum (Garland, Corn Salad, Cress (Garland), Cress (Upland), Dandelion Leaves, Dock, Endive, Florence Fennel, Lettuce (Head & Leaf), Orach, Parsley Leaves, Purslane (Garden), Purslane (Winter), Radicchio, Rhubarb, Spinach, Spinach (Vine), Spinach (New Zealand, and Swiss Chard]						
Postemergence Broadcast by ground, drip chemigation, or air	1.67 lb ai/gal SC	0.0261-0.0976	6	0.2 [219]	1	Minimum spray volumes are 10 gal/A (ground) or 5 gal/A (aerial); 3-day minimum RTI for foliar and 10-day RTI for drip chemigation
Pome Fruits [Apple, Crabapple, Loquat, Mayhaw, Pear, Pear (Oriental), and Quince]						
Postemergence Broadcast by ground or air	35% WG	0.044-0.099	4	0.2 [221]	21*	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 10-day minimum RTI.
Potato						
Postemergence Broadcast by ground or air	35% WG	0.044-0.066	Not specified***	0.2 [222]	14	Minimum spray volumes are 10 gal/A (ground) or 5 gal/A (aerial); 5-day minimum RTI.
Stone Fruits [Apricot, Cherry (Sweet), Cherry (Tart), Nectarine, Peach, Plum, Plum (Chicksaw, Damson, Japanese), Plumcot, and Prune]						
Postemergence Broadcast by ground or air	35% WG	0.044-0.099	4	0.2 [221]	10	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 7-day minimum RTI

Table 2.1b. Summary of Directions for Use of Chlorantraniliprole.						
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)**	**Use Directions and Limitations**
Section 18/Rice						
At seeding: drill-seeded	Dermacor X-100 50% SC	2.5-5.0 fl oz per 100 lbs seed (0.098-0.20 lb ai/100 lbs seed)**	1	0.13 (based on label, which provides seed treatment + seeding rates)	NA	Treated seed must not be used for or mixed with food or animal feed, or processed for oil. All rotation crops may be planted immediately following last application. Treated seed not to exceed 120 lb/A seeding rate.
Turf						
G formulations: drop-type, rotary-type or hand-held equipment	DuPont™ E2Y45 G (0.05-0.33%)	0.06-0.33	Not specified***	0.5	N/A	For use by commercial applicators only. No aerial, no chemigation application
SC formulation: broadcast application equipment	DuPont™ E2Y45 SC Insecticide	0.013-0.313 (1 to 24 fl oz/A)	Not specified***	0.5 (38.3 fl oz./A)	N/A	For use by commercial applicators only. No aerial, no chemigation application.
Ornamentals						
G formulations	DuPont™ E2Y45 G (0.05-0.33%)	Highly variable	Not specified***	0.33	N/A	For use by commercial applicators only. No aerial, no chemigation application.
SC formulation: broadcast application; soil injection, drenches	DuPont™ E2Y45 SC Insecticide	Highly variable	Not specified***	0.5 (38.3 fl oz./A)	N/A	For use by commercial applicators only. No aerial, no chemigation application.

*Although the proposed Section 3 label states a PHI of 21 days for pome fruits, the proposed label for the Experimental Use Permit label proposed a PHI of 14 days, and the residue chemistry data reflect a PHI of 13/14 days.

**Seed treatment rates in lb ai/lbs seed are calculated assuming Dermacor X-100 contains 5 lbs ai/gal formulation – which was back-calculated using the seed treatment rate + seeding rate table provided in the label.

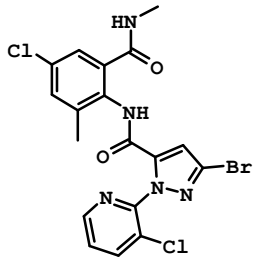
***Although the maximum number of applications is not specified for all the agricultural crops on the DPX-E2Y45 35WG and DPX-E2Y45 20SC labels, if the minimum application rate is 0.044 lb ai/A, to reach the maximum seasonal application rate, about 4 applications can be made per season; and if the minimum application rate is 0.026 lb ai/A, to reach the maximum seasonal application rate, about 6 applications can be made per season. On the E2Y45 SC Insecticide label for use on turf and ornamentals, if the minimum turf application rate of 0.013 lb ai/A is used, the product could be applied 38 times per year (to result in a maximum seasonal rate of 0.5 lb ai/A/yr).

HED Conclusion: Since the residue data (*i.e.*, field studies) for pome fruit reflect spray volumes of 100 gallons per acre, the use directions for pome fruit should be revised to state "minimum spray volume of 100 gal/A (ground)." Also, as there are inadequate residue data that reflect addition of adjuvants in end-use products in the field studies, the proposed labels should be revised to delete the use of adjuvants in all crops except *Brassica* crops. In the absence of residue data on crops grown in greenhouses, the label should prohibit use on crops grown in

greenhouses. Given the results of the confined accumulation and limited field accumulation in rotational crops study, a restriction should be imposed on the proposed labels to prohibit the rotation to any crop not on the label. The proposed REI of 2 hours on most labels should be amended

2.2 Structure and Nomenclature

The chemical nomenclature for chlorantraniliprole is presented in Table 2.2. The chemical names and structures of chlorantraniliprole and its transformation products, reported from metabolism studies, are presented in Appendix B.

Table 2.2. Chlorantraniliprole Nomenclature.	
Chemical structure	
Common name	Chlorantraniliprole
Company experimental name	DPX-E2Y45
IUPAC name	3-Bromo-*N*-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-1-(3-chloro-2-pyridine-2-yl)-1H-pyrazole-5-carboxamide
CAS name	3-Bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxamide
CAS registry number	500008-45-7
End-use product (EP)	Coragen™ SC (18.4% ai, 1.67 lb/gal; EPA Reg. No. 352-XXX) Altacor™ WG (35% ai; EPA Reg. No. 352-XXX) DuPont™ E2Y45 SC Insecticide (18.4% ai, 1.67 lb/gal; EPA Reg. No. 352-XXX) DuPont™ E2Y45 G (0.05-0.33%) – 12 products of varying concentrations Dermacor X-100 (an SC, 50% ai, Section 18)

2.3 Physical and Chemical Properties

The physicochemical properties of DPX-E2Y45 are reported in Table 2.3. The vapor pressure is low, so inhalation exposure is only expected during application, and not via volatilization of deposited residues.

Table 2.3. Physicochemical Properties of Technical Grade of Chlorantraniliprole.		
Parameter	Value	Reference
Melting point/range (°C)	200-202 (95.9%)/208 – 210 (99.2%)	DuPont-13180 MRID 46889033
pH	5.77 ± 0.087 at 20°C	DuPont-13176 MRID 46889031
Relative Density	1.5189 (95.9%)/1.507 (99.2%) at 20°C	DuPont-13180 MRID 46889033

Table 2.3. Physicochemical Properties of Technical Grade of Chlorantraniliprole.		
Parameter	Value	Reference
Water solubility (20°C)	Deionized Water 1.023 mg/L pH 4 0.972 mg/L pH 7 0.880 mg/L pH 9 0.971 mg/L	DuPont-13169 MRID 46889026
Solvent solubility (20°C)	Acetone 3.446 ± 0.172 g/L Acetonitrile 0.711 ± 0.072 g/L Ethyl Acetate 1.144 ± 0.046 g/L Dichloromethane 2.476 ± 0.058 g/L Dimethylformamide 124 ± 4 g/L n-Octanol 0.386 ± 0.01 g/L Methanol 1.714 ± 0.057 g/L n-Hexane <0.0001 g/L o-Xylene 0.162 ± 0.01 g/L	DuPont-13173 MRID 46889030
Vapor pressure	6.3×10^{-12} Pa @ 20°C, 2.1×10^{-11} Pa @ 25°C	DuPont-16517 MRID 46889130
Dissociation constant, pK_a	10.88 ± 0.71	DuPont-13254 MRID 46889034
Octanol/water partition coefficient, K_{OW} (20°C)	Deionized Water 589 pH 4 588 pH 7 721 pH 9 654	DuPont-13177 MRID 46889032
UV/visible absorption (max)	pH <2 no absorption max >200 nm, at 290 ε = 3941 pH 7 no absorption max >200 nm, at 290 ε = 4185 pH >10 absorption max at ~320 nm which may be due to decomposition of DPX-E2Y45, at 290 ε = 6082	DuPont-13167 MRID 46991001

3.0 Hazard Characterization/Assessment

Reference: *Chlorantraniliprole (DPX-E2Y45) Toxicology Assessment*, Mary Manibusan, TXR #0054555, D336940, D337737, D343520, D345100, 11/17/2007.

3.1 Hazard and Dose-Response Characterization

OECD Global Review Process

Chlorantraniliprole is the subject of a global work-share registration with several partnering countries. To this end, the toxicology assessment, lead by the United States, has undergone extensive technical external peer review. Written comments were submitted from Ireland, Canada, Italy, Germany, UK, Australia and the Netherlands. A peer review teleconference was also conducted to achieve harmonization on the endpoint selection. This toxicology assessment reflects the collective views of the US and our global partners.

3.1.1 Toxicology Database Summary

The toxicology database for chlorantraniliprole is considered adequate for risk assessment.

Toxicity studies that have been submitted in support of this registration include: 1) acute oral, dermal, inhalation, primary eye irritation, dermal irritation and dermal sensitization toxicity studies in rats, mice and rabbits, 2) absorption, distribution, metabolism, and excretion in male and female rats (single and multiple dose administration), 3) 28-day dermal study in rats, 4) 90-day subchronic oral toxicity studies in rats, dogs, and mice 5) combined chronic toxicity/oncogenicity study 2- year feeding study in rats, 6) oncogenicity eighteen-month feeding study in mice, 7) developmental toxicity studies in rats and rabbits, 8) 2-generation reproduction study in rats, 9) 28-day immunotoxicity feeding study in rats and mice, 10) acute oral neurotoxicity study in rats, 11) subchronic oral neurotoxicity study in rats, 12) 2-week gavage study in rats with metabolism and genetic toxicology, 13) a full battery of required genetic toxicology assays, and 14) mechanistic studies designed to evaluate the adrenal cortical function in rats. A brief summary of the findings and a toxicology profile table is attached in Appendix A.

3.1.1.2 Biochemical Mode of Action

Chlorantraniliprole is an anthranilic diamide insecticide that operates via a unique biochemical mode of action. Chlorantraniliprole binds and activates ryanodine receptors (RyRs), located in the sarcoendoplasmic reticulum, to release stored intracellular calcium into the cytoplasm of the cell. Calcium is a universal intracellular second messenger, which mediates many cellular and physiological activities; its flux is modulated by several specific calcium channels such as voltage-gated and the ryanodine calcium channels. Calcium ions mediate many cellular and physiological activities, *e.g*., neurotransmitter release, hormone secretion, gene expression and for the purposes of this insecticide, muscle contraction. In muscle cells, chlorantraniliprole locks RyR channels in a subconductance state without prior activation by plasma membrane voltage-gated calcium channels. Ryanodine channels remain opened, internal calcium stores become depleted, triggering capacitative calcium entry upon depletion of internal calcium stores. Sustained exposure to chlorantraniliprole leads to impaired regulation of the muscle excitation, contraction and relaxation cycle; this in turn, leads to complete muscle contraction, paralysis and the ensuing death of the organism (Cordova *et al.*, 2006). This mode of action has been shown to be highly selective for insect ryanodine receptors, but not for mammalian ryanodine receptors, typically exhibiting several hundred fold lower potency to mammalian ryanodine receptors. Comparative studies with mammalian cell lines that endogenously express RyRs demonstrate that the most potent anthranilic diamide tested exhibits greater than a 500-fold differential selectivity for insect receptors relative to mammalian receptors (Cordova *et al*., 2006). For chlorantraniliprole, the differential selectivity is greater than approximately 350-fold (Cordova *et al.,* 2007).

This difference in selectivity may be explained by the considerable variability in the amino acid sequences of specific N-terminal domains between insect and mammalian ryanodine receptors. Mammals express three isoforms of ryanodine receptors: RyR1 and RyR2, distributed predominately in skeletal and cardiac muscle, respectively, and RyR3 distributed more heterogeneously. While these three isoforms are reasonably similar in structure, there are known differences. For example, under three-dimensional cryo-microscopy, it is revealed that RyR3 is similar in its overall three-dimensional architecture to the other RyR isoforms but there is at least

one significant difference that is attributed provisionally to a particular region of the amino acid sequence of the receptor. There are also several structural differences at diverse locations between two conformational states of RyR3 that likely correspond to "open" and "closed" states of the receptor (Manjuli *et al*., 2000). To what extent each isoform contributes to the overall calcium response in mammals is not yet clear. Insects, on the other hand, express a single form of the receptor, sharing only a 47% amino acid sequence homology with mammalian ryanodine receptors. (Takeshima *et al*., 1994; Cordova *et al*., 2006). Sequence analysis for the amino acid region corresponding to the chlorantraniliprole binding site has been conducted for various species. Sequence comparisons for the corresponding RyR isoforms in humans, rats, mice, and dogs show similarities of 85% or greater in these mammalian species. However, the sequence similarity between mammals and insects for this region is no greater than 21%. Consequently, there is a high degree of divergence between mammalian and insect amino acids for the region associated with the chlorantraniliprole binding site.

The ryanodine receptor is present across species, its role is similar across species, but primary sequence diversity indicates differences between the isoforms within and across species. The level of activation of this receptor, and the subsequent release of intracellular calcium stores via the binding of chlorantraniliprole to the cytoplasmic face of the receptor, accounts for the difference in specificity between insect and mammalian species. Differences in specificity and potency of effects distinguish the mammalian ryanodine receptor response from that of the insect and these differences appear to be the major contributing factors to the low mammalian toxicity exhibited for chlorantraniliprole.

3.1.2 Toxicological Effects

DPX-E2Y45 has no significant acute toxicity via the oral, dermal, and inhalation routes of exposure. The LD_{50} for oral and dermal acute exposure is ≥5000 mg/kg/day and the LC_{50} for acute inhalation exposure is ≥5.1 mg/L. This substance is not an eye or skin irritant and does not cause skin sensitization. The acute inhalation study did not report any portal of entry effects or acute irritation via the inhalation route of exposure. In short-term studies, the most consistent effects are those associated with non adverse pharmacological response to the xenobiotic, induction of liver enzymes and subsequent increase in liver weights. DPX-E2Y45 is not genotoxic, neurotoxic, immunotoxic, carcinogenic, or teratogenic. Furthermore, it does not exhibit pre- or postnatal toxicity as there were no maternal or fetal effects in studies conducted in rats and rabbits. Based on the results of a 28-Day dermal study in rats, as well as the dermal LD_{50} study, DPX-E2Y45 has relatively low dermal toxicity.

The only consistent effects associated with DPX-E2Y45 exposure were those associated with the adrenal cortex (mild microvesiculation of the *zona fasciculata*) and liver toxicity. These effects were not considered adverse because the effect in the adrenal cortex was minimal, the adrenal cortical morphology was generally within the range of what was observed in the control rats and there was no cytotoxicity or abnormal cellular structures observed by light or electron microscopy. Furthermore, no adverse effects indicative of an adverse impact on the function of the adrenal cortex was found in the numerous toxicological studies available (*e.g*., 90-day rat, mouse, dog studies, prenatal toxicity studies, two-generation reproductive study, dermal toxicity

study) or in special adrenal functionality studies evaluating corticosterone concentrations in serum and urine (under both basal and stimulated conditions). There was also an absence of adrenal tumors or tumors of any organ in the 18-month mouse and 2-year rat cancer bioassay. Therefore, the mild microvesiculation reported in the male rat adrenal cortex is not considered of toxicological significance.

Table 3.1.2 Incidence of Microvesiculation of Adrenal Cortex in Rats					
Parameter	0 ppm	200 ppm	1000 ppm	4000 ppm	20,000 ppm
90-day Subchronic Feeding Rat Study (MRID 46889010)					
Males	0	NC	NC	NC	2/10 (2)
Two Generation Reproduction Rat Study (MRID 46889107)					
P1 males	3/30 (1)	2/30 (1)	8/30 (1)	13/30 (1)	16/30 (1-2)
F1 males	2/30 (1)	7/30 (1)	12/30 (1)	16/30 (1-2)	16/30 (1-2)
F1 females	1/30 (1)	1/30 (1)	0	0	3/30 (1)
Two Year Chronic Rat Study (MRID 46979719)					
1-year males	0	2/10 (1)	5/10 (1)	5/10 (1-2)	5/10 (1-2)
2-year males	4/20 (1)	14/23 (1-2)	17/26 (1-2)	14/21 (1-2)	19/27 (1-3)
28-day Dermal Rat Study (MRID 46889128)					
	0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg	
Males	0	2/10 (1)	2/10 (1)	5/10 (1)	

NC = microscopic evaluation not conducted at this dose
() = Grade of increased degree of microvesiculation. Histologic grading is based on a scale of 0-4 (0= change not present, 1=minimal, 2=mild, 3=moderate, 4=severe)

While the adrenal cortex effects were considered non-adverse, the liver effects form the bases for establishing the no observed adverse effect level (NOAEL) of 158 mg/kg bw/day on the mean daily intake in male mice in an eighteen month chronic toxicity/carcinogenicity study. A lowest observed adverse effect level (LOAEL) was established in the same study at 935 mg/kg/day for male mice based on eosinophilic foci of cellular alteration accompanied by hepatocellular hypertrophy and increased liver weight. While in the shorter-term toxicity studies, the slight liver weight increase in the 90-day studies were considered pharmacological effects and not adverse, the weight of evidence from the combined liver weight increase, liver hypertrophy and eosinophilic foci in the 18-month mice study shifts these effects to be considered adverse.

3.1.3 Dose-response

Overall, chlorantraniliprole exhibits minimal mammalian toxicity after exposure. The only consistent observation in the mammalian toxicology studies is an increased degree of microvesiculation of the adrenal cortex after dermal or dietary administration of chlorantraniliprole. This histologic change was observed in several rat studies including a 28-day dermal, 90-day study, a multigeneration reproduction study and at the 1-and 2-year intervals of a 2-year chronic study. The histologic grading of increased microvesiculation in affected groups ranged from grade 0-2 (mild) on a scale ranging from 0-4, with one microvesiculation graded 3 (moderate) in the high dose group of the 2-year rat study (see Table 3.1.2). Increased microvesiculation of the *zona fasciculata* was considered to be treatment-related as the incidence and histologic grade increased above that observed in controls in a dose-related pattern. Based on the lack of adverse effect on the function of the adrenal gland, this observation was considered treatment related, but not “adverse.”

In addition to the adrenal effects, liver effects (*e.g.*, increased liver weight and induction of Cytochrome P450 enzymes) were reported in the 90-day oral subchronic studies across species and only at the highest dose tested (>1000 mg/kg/day). While in the subchronic studies, these effects were considered adaptive, the liver effects were more pronounced in the 18-month chronic mouse study at the highest dose tested. Increased eosinophilic foci (preneoplastic foci) were noted in male mice at 935 mg/kg/day and liver hypertrophy and weight increase were evident at the next lower dose (158 mg/kg/day), but progression to tumors was not apparent for these effects. Therefore, the eosinophilic foci appear to be an adverse effect only seen in the highest dose tested and was graded minimal in severity.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The absorption of ^{14}C-DPX-E2Y45 was rapid with peak concentrations occurring at 5-12 hours after low or high (10 or 200 mg/kg bw) oral single dose administration. Absorption at the low dose (10 mg/kg bw) was determined to be 72.9-85.2% compared with 11.8-13.3% at the high dose (200 mg/kg bw) using bile duct cannulated rats. The plasma elimination half-lives ranged from 38-82 hours. Tissue distribution of the absorbed dose was extensive and indicated low potential for accumulation. The tissue residues were higher in female rats than in male rats, which is consistent with female rats having a longer elimination half-life and higher area under the curve (AUC) in plasma. Excretion in both high- and low-dose groups was substantially complete by 48-72 hours after dosing. Fecal excretion was the primary route of elimination followed by the urine with no significant excretion occurring by exhalation. Metabolism of the absorbed dose was extensive and involved sex (greater hydroxylation in males) differences primarily in initial tolyl methyl and N-methyl carbon hydroxylation. Further metabolism of the hydroxylated metabolites included N-demethylation, nitrogen-to-carbon cyclisation with loss of a water molecule resulting in the formation of the pyrimidone ring, oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis, and O-glucuronidation. Most of the administered dose (88-97%) was eliminated in the excreta. Tissue:plasma concentration ratios (<1) indicated low potential for accumulation. Metabolites represented in the rat metabolism cascade were: IN-K9T00, IN-HXH44, IN-KAA24, IN-H2H20, and IN-GAZ70.

Following 14 days of oral dose administration (10 mg/kg), steady-state kinetic behaviour was apparent in male rats. The slight increase in plasma and tissue concentrations through the 14 days of oral dosing indicated that female rats were near steady state. After cessation of dosing, the ^{14}C residues were readily eliminated from the plasma and tissues. The overall tissue distribution in male and female rats at 1 and 7 days after dosing was similar to that found after single dose administration and confirmed minimal potential for accumulation. Cumulative excretion in feces was the predominate route of elimination. The profile of metabolites in urine and feces indicated extensive metabolism consistent with that observed for the single dose study.

In addition to the rat metabolism studies conducted with ^{14}C-labelled DPX-E2Y45, analysis of plasma for parent and primary metabolites was conducted during the 90-day rats, mice and dogs dietary administration studies and the rat 14-day oral gavage study. DPX-E2Y45 and primary metabolites observed above the limit of quantification of 0.005 ug/mL plasma were reported.

14-day oral gavage rat

In the 14-day oral gavage study, a toxicokinetic assessment was performed. The area under the plasma concentration versus time curve (AUC) was not proportional with the dose of DPX-E2Y45 indicating decreased absorption at higher doses. The half-lives were estimated to be 3.4, 3.4 and 4.0 hours for 25, 100 and 1000 mg/kg/day groups, respectively. The time of maximum concentration (T_{max}) was 0.25, 0.42, and 2.75 hours in the 25, 100, and 1000 mg/kg/day groups, respectively. The maximum concentrations (C_{max}) were similar at all dose levels, with the highest concentration (0.48 ug/mL) occurring in the 25 mg/kg/day group. The half life for DPX-E2Y45 was sufficiently short that a significant portion of the parent compound will be cleared from the plasma after 24 hours, even following two weeks of repeated dosing at 1000 mg/kg/day indicating low potential for bioaccumulation.

90-day oral rat

In the 90-day oral rat study, DPX-E2Y45 and the metabolites IN-GAZ70 and IN-H2H2O were identified quantitatively. The concentration of IN-GAZ70 in plasma from male and female rats on Day 59 was considerably greater than the plasma concentration of DPX-E2Y45. In males, this difference was approximately 10-fold, but in females, the difference was 100-fold. The concentration of each analyte was greater in females than in males. With the exception of the plasma concentration of IN-H2H2O in male rats dosed at the highest dose being statistically different from the 2000 ppm dose, the plasma concentration of DPX-E2Y45, IN-GAZ70 and IN-H2H2O were not statistically different from one another in the three highest dose concentrations in either sex.

90-day oral mouse

In the 90-day oral mouse study, DPX-E2Y45 and the metabolite IN-GAZ70 were quantified. The concentration of the parent DPX-E2Y45 was below the limit of quantification in all mouse samples analyzed. The metabolite IN-GAZ70 was the only significant analyte present in plasma from male mice on day 92 and female mice on day 93. The plasma concentration of IN-GAZ70 in plasma from female mice dosed at the highest dietary concentration was statistically different from the 700 ppm dose. In male mice, the plasma concentration in mice dosed at the 2000 and 7000 ppm dose concentrations were both statistically different from the 700 ppm dose concentration.

90-day oral dog

In the 90-day dog study, DPX-E2Y45 and metabolite IN-HXH44 were quantified. The concentration of parent DPX-E2Y45 for both male and female dogs in plasma was approximately five times the concentration of the metabolite IN-HXH44. The plasma concentration of DPX-E2Y45 in male dogs dosed at the high dose (40,000 ppm) was not statistically different from the 4000 ppm dose. The plasma concentration of the IN-HXH44 was not statistically different at any dose concentration in either sex.

Conclusions:

These results demonstrate systemic uptake and metabolism of DPX-E2Y45 during dietary and oral gavage administrations. These results also suggest possible species differences in the primary metabolites formed in all three species, rats, mice and dogs. The concentration of DPX-E2Y45 in plasma was dog>rat>mouse. The primary methylphenyl ring hydroxylated metabolite (IN-HXH44) was quantified only in dog plasma, while the N-methyl hydroxylated metabolite (IN-H2H2O) was quantified only in rat plasma. The cyclization product of IN-H2H20 with loss of a water molecule or N-demethylation product of IN-EQW78 (IN-GAZ70) was quantified in both mouse and rat, but not dog plasma. Mouse plasma contained more IN-GAZ70 than rat plasma in these studies. In all three species, the relatively constant analyte concentrations at the higher dose levels suggested decreased absorption with increasing dose, confirming the previously described rat metabolism studies. The slight decrease in the plasma DPX-E2Y45 concentrations with increasing dose in the 14-day oral gavage rat study also provided evidence for decreased absorption. A significant sex difference was observed in rats with female rats showing higher concentrations of DPX-E2Y45, IN-H2H20, and IN-GAZ70 than male rats. No sex difference was noted in the dog or mouse. Overall, the results in rats for the 90-day and 14-day studies were consistent with the plasma concentrations of ^{14}C residues, decreased absorption, and proposed metabolic pathway from the single and multiple oral gavage studies with ^{14}C-DPX-E2Y45 in rats.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicity database for this chemical is complete for the purposes of this risk assessment and considered adequate for the characterization of potential pre- and postnatal risks to infants and children. Acceptable developmental and 2-generation reproduction studies have been submitted and reviewed.

In addition, a developmental neurotoxicity is not required based on the lack of any clinical signs indicative of potential neurotoxicity in either acute or subchronic oral neurotoxicity studies in rats, lack of any substance related developmental toxicity tested at 1000 mg/kg/day (limit dose), and no indications of increased quantitative or qualitative susceptibility to fetuses and pups following pre-and/or postnatal exposure to chlorantraniliprole as reported in the rat and rabbit developmental toxicity studies and the rat 2-generation reproduction study. There is no concern for developmental neurotoxicity associated with chlorantraniliprole exposure; therefore, a developmental neurotoxicity study is not being requested. The current toxicity database is considered adequate for risk assessment.

3.3.2 Evidence of Neurotoxicity

No evidence of neurotoxicity was observed in studies conducted with DPX-E2Y45 in rats. The NOAEL in an acute, oral gavage neurotoxicity study was 2000 mg/kg bw and was the highest dose administered in the study. In a subchronic neurotoxicity study, the NOAEL was 1313 and

1586 mg/kg bw/day in males and females, respectively, the maximum dietary concentration administered. The NOAELs were based on the absence of treatment related effects on systemic toxicity and neurotoxicity parameters, including microscopic neuropathology. Neurological assessments conducted in conjunction with the 18-month oncogenicity study in mice following 45, 60, and 90 days of dietary administration of DPX-E2Y45 confirmed the lack of potential neurotoxicity. Further, no treatment related clinical signs indicative of potential neurotoxicity were observed in short-term and long-term exposure studies in rats, mice, or dogs. Therefore, it is concluded that DPX-E2Y45 is not a neurotoxicant.

3.3.3 Developmental Toxicity Studies

For both the rat and rabbit developmental studies, no adverse, test substance-related effects on maternal clinical observations, body weight, weight gain, food consumption, or gross post-mortem observations were detected at any dose. The mean number of corpora lutea, implantation sites, resorptions, live fetuses, fetal weight, and sex ratio were comparable across all groups. There were no abortions, premature deliveries, or complete litter resorptions and no effects of treatment on the numbers of litters, post-implantation loss, or on gravid uterine weights. The maternal systemic toxicity is ≥1000 mg/kg/day and the maternal systemic toxicity LOAEL is greater than 1000 mg/kg/day (the limit dose). There were no test substance-related fetal external, visceral, skeletal malformations, variations, adverse effects on fetal skeletal ossification observed at any dose. The developmental toxicity is ≥1000 mg/kg/day and the developmental toxicity LOAEL is greater than 1000 mg/kg/day (the limit dose).

3.3.4 Reproductive Toxicity Study

There were no adverse, test substance-related effects on body weight, body weight gain, food consumption, or food efficiency, clinical signs of toxicity, or mortality in P and F1 males during pre-mating and in P and F1 females during pre-mating, gestation, or lactation. An increase in mean liver weights was observed in P and F1 females at 238/318.9 mg/kg/day, respectively and above and was attributed to a pharmacological increase in metabolism. In addition, a slight, yet statistically significant, increase in mean adrenal weight (absolute and/or relative to body weight) was observed at 4000 and 20,000 ppm P and F1 males and females. There were no adverse test substance-related effects on any gross or microscopic pathology endpoint. The parental systemic toxicity NOAEL is ≥ 1199/1594 mg/kg/day males/females, respectively and the parental systemic toxicity LOAEL is greater than 1199/1594 mg/kg/day males/females, respectively based on the absence of adverse effects in P and F1 males and females (above the limit dose).

There were no test substance-related effects on sperm motility, morphology, epididymal sperm or testicular spermatid numbers in either the P or F1 males at any dietary concentration. Similarly, there were no effects produced by chlorantraniliprole on the mean percent days in estrus, diestrus or proestrus mean cycle length, or mean precoital interval in either the P or F1 females. Mating, fertility, gestation length, number of implantation sites, and implantation efficiency in either P or F1 generation were unaffected at any dietary concentration. The reproductive toxicity NOAEL is ≥ 20,000 ppm (1199/1594 mg/kg/day males/females, respectively) based on the absence of adverse effects in P and F1 males and females (above the

limit dose).

Mean body weight of the 20,000 ppm F1 pups was slightly reduced (7-8%) when compared to controls on lactation days 7, 14, and 21. The slightly lower 20,000 ppm pup weights were considered not adverse as they were transient, small in magnitude, and F1 offspring weights were similar to controls by Day 35 postweaning. In addition, there were no effects on F2 offspring weights during lactation. The offspring/developmental toxicity NOAEL is ≥ 1199/1594 mg/kg/day males/females, respectively based on the absence of adverse effects in F1 and F2 pups during lactation.

3.3.5 Additional Information from Literature Sources

No additional information relevant to the toxicity of chlorantraniliprole was identified.

3.3.6 Pre-and/or Postnatal Toxicity

There were no effects on prenatal fetal growth or postnatal development up to the limit dose of 1000 mg/kg/day in rats or rabbits. There were no treatment related effects on the numbers of litters, fetuses (live or dead), resorptions, sex ratio, or post-implantation loss. There were no effects on fetal body weights, skeletal ossification, and external, visceral, or skeletal malformations or variations.

3.3.6.1 Determination of Susceptibility

Based on the dataset submitted in support of this registration, there appears to be no increased quantitative or qualitative susceptibility to fetuses and pups following pre-and/or postnatal exposure to chlorantraniliprole as reported in the rat and rabbit developmental toxicity studies and the rat 2-generation reproduction study.

3.4 FQPA Safety Factor for Infants and Children

The chlorantraniliprole risk assessment team evaluated the quality of the toxicity and exposure data and, based on these data, recommended that the FQPA Safety Factor be reduced to 1x. The recommendation is based on the following:

- 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.
- No susceptibility was identified in the toxicological database, and there are no residual uncertainties re: 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)]. Therefore, a degree of concern analysis for pre- and/or postnatal susceptibility is not necessary.
- There are no treatment-related neurotoxic findings in the acute and subchronic oral neurotoxicity studies in rats.

- Additionally, 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 2 estimates) utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations. By using these screening-level exposure assessments, the chronic dietary (food and drinking water) risk is not underestimated.
- 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.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Dietary (All populations, including Females 13-49 years old)

No acute hazard, attributable to a single dose, was identified; therefore, an acute dietary endpoint was not selected for quantitative risk assessment.

3.5.2 Chronic Dietary (All populations)

Establishment of a Chronic Dietary Reference Dose (cRfD)

The relevant NOAEL from chronic toxicity studies is derived from the oncogenicity eighteen month feeding toxicity study in male Crl:CD1(ICR) mice at 158 mg/kg/day based on the presence of eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight observed at the next highest dose (935 mg/kg/day). These liver effects are considered minimal in severity, low in incidence and do not display progression to tumors in the 18-month chronic mouse study. In addition, the 24-month rat cancer study also does not show evidence for an active substance related increase in liver tumors. The eosinophilic foci were observed in one gender only (males), categorized as minimal, and there was no increase in severity (*i.e.*, dose response); the foci were observed only at the highest dose tested and a monotonic dose response was not evident. Examination of the microscopic results presented in the original study showed no evidence of increased degenerative changes to hepatocytes with increasing dose. There is no increase in necrotic cells, fatty change, hyperplastic nodules, inflammation, mitotic figures, or evidence of Mallory bodies relative to controls and low dose groups. However, despite the lack of general histopathology and progression to tumors, these eosinophilic foci are not considered an adaptive response because they are not reversible nor are they commonly associated with a normal liver response to high dose xenobiotics (historical control range 0-1.92% for Crl:CD-1(ICR) mice). Based on this understanding, it is considered a prudent public health protective decision to base the chronic reference dose on the liver effects observed at the highest dose in the 18-month chronic mouse study as treatment related and adverse.

A composite uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variability is applied to the NOAEL to derive a cRfD/cPAD[*] of 1.58 mg/kg/day.

[*] The chronic Population Adjusted Dose (cPAD) is equivalent to the chronic Reference Dose (cRfD) divided by the FQPA Safety Factor, which in the case of chlorantraniliprole, is 1x.

158 mg/kg bw/day = 1.58 mg/kg bw/day (cRfD/cPAD)
100 (UF)

3.5.3 Incidental Oral Exposure (Short- and intermediate-term)

Establishment of a short- and intermediate-term reference dose for incidental oral exposure is not justified for chlorantraniliprole (DPX-E2Y45) based on the lack of identified hazard over the short- and intermediate-term: only a slight increase in liver weight at the highest dose tested (HDT) in the 90-day rat, mouse and dog oral toxicity studies, at doses up to 1000 mg/kg/day (limit dose) was observed. The liver weight increases (approximately 20%) were considered a pharmacological response to the xenobiotic and not an adverse effect. Therefore, no short- and/or intermediate-term incidental oral endpoint was selected for quantitative risk assessment.

3.5.4 Dermal Exposure (Short- and intermediate-term)

A 28-day dermal toxicity study was performed on rats at doses of 0, 100, 300, or 1000 mg/kg/day (MRID 46889128). The NOAEL was the HDT (1000 mg/kg/day). The only effect was a reduction in overall body weight gain (22% and 19% males and females, respectively) with a corresponding decrease in food efficiency (17% and 19% males and females, respectively). There was no effect on absolute body weights in males or females. Additionally, there were no identified developmental reproductive effects in the database, nor neurotoxic effects. Because there was no hazard identified, no dermal endpoint was selected for quantitative risk assessment.

3.5.5 Inhalation Exposure (Short- and intermediate-term)

For chlorantraniliprole, the requirement for a longer term, repeat inhalation study may be waived based on its lack of acute irritation and extremely low oral toxicity, even at the limit dose of 1000 mg/kg/day. The acute 4-hour inhalation study determined an LC_{50} of >5.1 mg/L for both male and female rats, and did not report any portal of entry effects or acute irritation via the inhalation route of exposure. Based on this weight of evidence in support of the longer term inhalation study waiver and the lack of hazard identified in the acute inhalation study, no inhalation endpoint was selected for quantitative risk assessment.

There is no short-term oral toxicity, and the chronic liver effect is only at the limit dose in the cancer study (and late in the study), these effects observed in oral studies are not relevant to extrapolate to short- and intermediate-term inhalation exposure scenarios.

3.5.6 Recommendation for Aggregate Exposure Risk Assessments

Dietary exposure via residues in/on food and drinking water are aggregated in the chronic dietary assessment. Aggregating routes and/or pathways of exposure are not relevant for all other scenarios due to lack of observed hazard for all other durations and exposure routes.

3.5.7 Classification of Carcinogenic Potential

No treatment-related tumors have been reported in the submitted chronic and oncogenicity studies in rats and mice, subchronic studies in mice, dogs and rats and no mutagenic concern was reported in the genotoxicity studies. The most consistent effect across durations and species tested is a slight increase in liver weight due to induction of cytochrome P450 activity that is reflective of a pharmacological response to the xenobiotic and not considered adverse. In the 18-month chronic/oncogenicity oral mice study, however, the increase in liver weight was accompanied by hepatocellular hypertrophy and a slight increase in eosinophilic foci of cellular alteration, which in combination formed the bases of establishing the LOAEL at the highest dose tested (935 mg/kg/day) and the NOAEL at 158 mg/kg/day for male mice. Eosinophilic foci are preneoplastic lesions, but in neither the 24-month oral rat cancer bioassay nor the 18-month oral mouse study were treatment-related rodent liver tumors reported. In addition, the possibility of rodent liver tumors formed via the activation of the peroxisome proliferator-activated receptor (PPARa) was negated through the 14-day oral gavage rat study that measured for peroxisomal beta-oxidation activity using ^{14}C-palmitoyl CoA as the substrate and did not find an association. DPX-E2Y45 did not alter beta-oxidation activity.

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".

3.5.8 Summary of Toxicological Doses and Endpoints for Chlorantraniliprole for use in Human Health Risk Assessment

Table 3.5.8a 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.
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 3.5.8b 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. 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

3.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

4.0 Public Health and Pesticide Epidemiology Data

Chlorantraniliprole is an unregistered, new ai, and therefore, no public health, epidemiologic data, and/or incident reports are available.

The following information was provided by DuPont: 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.

No specific human symptoms of DPX-E2Y45 toxicity are known.

5.0 Dietary Exposure/Risk Characterization

Reference: The residue chemistry summary document was reviewed by the Chemistry Science Advisory Council: *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 and Summary of Analytical Chemistry and Residue Data, Section 18 Exemption 08LA01 for Use on Rice*, D336941, Leung Cheng, 2/25/08. Note: Under international agreements the Australian Pesticide and Veterinary Medicines Authority was designated as the lead for residue chemistry data review. The US did review North American field trials, analytical methods, storage stability data and processing studies.

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The nature of the residue in plants is adequately understood. Studies have been conducted depicting the metabolism of chlorantraniliprole in apple, cotton, lettuce, rice, and tomato. In the apple, cotton, lettuce and tomato studies, the plants were treated at 3 x 100 g ai/ha by foliar application (~ 0.5 proposed maximum application rate), and rice was treated at 1 x 150 g ai/ha by soil drench (0.68x, based on the proposed Section 18 use). Total radioactive residues were measured in apples (0.092-0.138 ppm at 15 and 30 day PHI, respectively), lettuce (0.301 and 0.372 ppm at 7 and 15 day PHI, respectively), cotton seed (<0.01 ppm at 126 day PHI), tomato (0.056 and 0.013 ppm at 7 and 15 day PHI, respectively), and rice (0.155 ppm at 132 day PHI). For apple, lettuce and tomato, the majority of the residues were surface residues. In all these crops, unchanged chlorantraniliprole was the major residue (57-92% TRR).

Very little degradation of chlorantraniliprole was observed in apple, cotton, lettuce and tomato. Many metabolites were found in rice commodities and the metabolism in rice generally involves: (i) hydroxylation of the N-methyl group (to IN-H2H20) or hydroxylation of the tolyl methyl group (to IN-HXH44); (ii) cyclization with loss of water to a quinazolinone derivative (IN-EQW78); and similar condensation of IN-H2H20 with an additional loss of CH_2O (to IN-GAZ70); and (iii) N-demethylation via IN-H2H20 to IN-F9N04. HED concludes that the nature of the residue in primary crops is parent chlorantraniliprole. For the chemical names and structures of identified metabolites, see Appendix B and Table 5.1.7.

5.1.2 Metabolism in Rotational Crops

The submitted confined rotational crop studies have been reviewed and deemed adequate to satisfy data requirements. Unchanged parent was the major identified residue in all rotational crop commodities (1 x 300g ai/ha) including lettuce (64-85% TRR), wheat grain (48% TRR from an exaggerated rate at 120 DAT), wheat forage (54-84% TRR), wheat hay (51-73% TRR),

and wheat straw (37-69% TRR); TRR were <0.01 ppm in wheat grain, beet root, and beet foliage. HED concludes that the nature of the residue in rotational crops is parent chlorantraniliprole.

5.1.3 Metabolism in Livestock

The nature of the residue in livestock is adequately understood based on highly exaggerated acceptable goat and hen metabolism studies. The ruminant metabolism study was conducted at 10 ppm (5.6x for beef cattle and 40x for dairy cattle) in the diet; the poultry metabolism study was conducted at 10 ppm (111x) in the diet.

The metabolism of chlorantraniliprole in livestock was extensive and followed the major steps similar to those observed in rice: (i) hydroxylation of the N-methyl group (to IN-H2H20) or hydroxylation of the tolyl methyl group (to IN-HXH44); (ii) cyclization with loss of water to a quinazolinone derivative (IN-EQW78); and (iii) N-demethylation via IN-H2H20 to IN-F9N04.

The residue of concern in ruminants for tolerance enforcement and for risk assessment is the parent compound. The residue of concern in poultry in connection with the proposed Section 18 use on rice is the parent compound for tolerance enforcement and risk assessment (even though, at this time, poultry is considered a category 180.6(a)(3) situation, based on the current dietary burden).

5.1.4 Analytical Methodology

The registrant has proposed LC/MS/MS methods for enforcing residues of the parent compound in plants and livestock commodities. The enforcement method for plant commodities, Analytical Method for the Determination of DPX-E2Y45 in Crops Using LC/MS/MS, DuPont-11374, and Analytical Method for the Determination of DPX-E2Y45 and Degradation Products in Crop Process Fractions Using LC/MS/MS, DuPont-14314, involves extracting chlorantraniliprole in aqueous acetonitrile. The extracts are filtered through SPE cartridges and the residue is analyzed by LC/MS/MS operating in the positive ionization mode: m/z 484 → 453, 484 → 286, 284 → 112, 284 → 177. The validated limit of quantification is 0.01 ppm. The method has undergone a successful independent laboratory validation and has been validated with the analysis of numerous field trial samples. The method is adequate for tolerance enforcement purposes for plant commodities.

The enforcement method for livestock commodities, Analytical Method for the Determination of DPX-E2Y45 and Metabolites in Bovine Tissues, Milk, and Eggs Using LC/MS/MS, is described in DuPont-14314. Milk and cream samples and tissue and egg samples are extracted and partitioned with hexane and water/acetonitrile. A homogenizing probe followed by centrifugation is used with the tissue and egg samples. Proteins are expected to precipitate from milk during the partitioning. An aliquot of the water/acetonitrile phase is diluted with water and purified by solid phase extraction. Extracts are placed on a Varian SAX SPE cartridge in series with a Water Oasis HLB SPE cartridge. Analytes are eluted with acetonitrile, followed by acidified (0.5% formic acid) ethyl acetate. The eluate separates into two layers, and the lower

water layer (pH 2) is removed (and discarded) to obtain consistent recoveries of IN-K9T00. The organic eluate is evaporated to dryness and reconstituted in acetonitrile.

Reversed-phase liquid chromatography (C18 column for dairy, muscle, liver, and fat samples; phenyl-hexyl column for kidney and whole egg samples) is used to separate parent and metabolites. Detection is by Atmospheric Pressure Chemical Ionization (APCI) MS/MS operated in the positive ion mode. The validated LOQ is 0.01 ppm chlorantraniliprole. The method is adequate for tolerance enforcement purposes for livestock commodities.

The proposed plant and animal methods have been reviewed by Agency chemists in ACB/BEAD (D340358, C. Stafford, 2/6/08).

5.1.5 Environmental Degradation

Reference: *Drinking Water Assessment for Chlorantraniliprole*, D348133, James A. Hetrick, *et.al.*, January 10, 2008. Under international agreements the Agency was not responsible for conducting environmental fate data reviews. Data review was conducted for use by all parties to the international agreement by the Pesticide Control Service, Department of Agriculture and Food, Ireland. The Agency is using the results of the PSD review as they appear in the dossier for registration in Europe except for the aerobic soil metabolism half-lives, which EFED recalculated to be representative of the total extractable fraction in soil.

Chlorantraniliprole is persistent and mobile in terrestrial and aquatic environments. Extended chlorantraniliprole use is expected to cause accumulation of residues in soil from year to year. Laboratory studies indicate the major routes of dissipation are expected to be alkaline-catalyzed hydrolysis (predominant degradate IN-EQW78), photodegradation in water (predominant degradate IN-LBA24), leaching, and runoff. Soil metabolism is minimal, although higher temperatures are expected to reduce half-lives. Field studies support the findings in the laboratory studies, where half-lives of chlorantraniliprole range from 52 to 1130 days in both radiolabeled and non-radiolabeled studies. For a more detailed description of the fate studies, as well as a summary table of structures and study results, see Appendix B.

In addition to the environmental fate and effects studies, there were three dislodgeable foliar residue (DFR) studies submitted on cabbage plants (in New York, Georgia and California), tomato plants (in New York, Georgia and California), and apple trees (in New York, Minnesota and Idaho). These studies show similar findings as in the fate database, indicating chlorantraniliprole is persistent. As shown below, the DFR studies indicate that chlorantraniliprole dissipates slowly, however, it does not necessarily following a pattern of steady decline. The studies also indicate rain events aid dissipation.

Table 5.1.5 Dislodgeable Foliar Residue Studies Summary				
Crop	**Site**	**Half-life (days)**	**R^2**	**Comments**
Cabbage	NY	14	0.807	Residue levels declined, increased, and then declined again
	GA	13	0.897	
	CA	19	0.251	Residue levels declined, increased, and then declined again; R^2 value particularly low
Tomato	NY	18	0.641	
	GA	15	0.798	
	CA	21	0.393	Residues declined until day 14, and then increased until day 35; R^2 value particularly low
Apple	NY	25	0.541	Not certain that the sampling duration was sufficient to thoroughly characterize the dissipation
	MN	5	0.947	Higher than average rainfall
	ID	30	0.573	Not certain that the sampling duration was sufficient to thoroughly characterize the dissipation

5.1.6 Comparative Metabolic Profile

In plants where DPX-E2Y45 is applied to the foliage, although metabolites are identified, they are at such low levels, metabolism is not considered significant. However, in animal matrices (such as livestock, rats, mice, dogs) and rice (where DPX-E2Y45 is in contact with soil), DPX-E2Y45 does get metabolized and follows similar patterns. Either the tolyl methyl or N-methyl carbon gets hydroxylated (IN-HXH44, IN-H2H20) – then, further metabolism results in N-demethylation (IN-F9N04) and nitrogen to carbon cyclization with loss of a water molecule resulting in the formation of the pyrimidone ring (IN-EQW78). The mammalian metabolism studies further describe oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis and O-glucuronidation. It is not clear if environmental degradation follows the same breakdown pattern – although DPX-E2Y45 resists degradation in environmental matrices as well. Laboratory studies indicate degradation is expected via alkaline-catalyzed hydrolysis (predominant degradate IN-EQW78) and photodegradation in water (predominant degradate IN-LBA24, which was not identified in plant or animal metabolism studies). Also, degradation could occur through soil metabolism (although only minimally; degradates include IN-F6L99, IN-EVK64, IN-EQW78, IN-ECD73 and IN-GAZ70).

Although metabolism pathways/patterns are similar across matrices, there are differences. Within the metabolism studies/assessments from the toxicology database, the results suggest possible species and sex differences in the primary metabolites formed in all three species: rats, mice and dogs. And even though IN-EQW78 is postulated as an intermediary metabolite in the rat metabolism pathway, it was not quantified in the study in urine and/or feces (tissues were not analyzed for metabolites). These studies discuss these differences further: the primary methylphenyl ring hydroxylated metabolite (IN-HXH44) was quantified only in dog plasma, while the N-methyl hydroxylated metabolite (IN-H2H2O) was quantified only in rat plasma. The cyclization product of IN-H2H20 with loss of a water molecule or N-demethylation product of IN-EQW78 (IN-GAZ70) was quantified in both mouse and rat, but not dog plasma. Mouse plasma contained more IN-GAZ70 than rat plasma in these studies. A significant sex difference was observed in rats with female rats showing higher concentrations of DPX-E2Y45, IN-H2H20, and IN-GAZ70 than male rats. No sex difference was noted in the dog or mouse. Overall, the

results in rats for the 90-day and 14-day studies were consistent with the plasma concentrations of carbon-labeled (^{14}C) residues, decreased absorption, and the proposed metabolic pathway from the single and multiple oral gavage studies with carbon-labeled (^{14}C)-DPX-E2Y45 in rats.

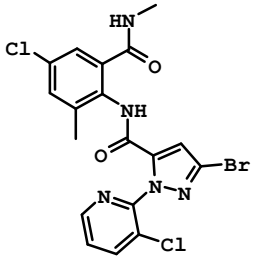
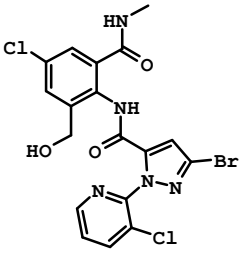
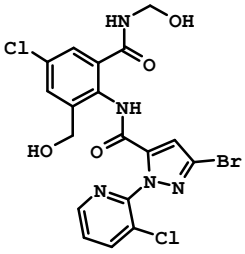
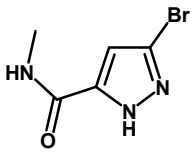
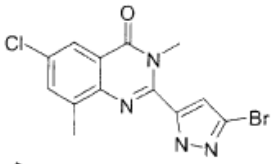
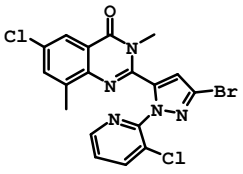
However, despite the metabolic differences between species and sexes, there is a consistent effect on the liver, indicating that the differences in metabolism do not appear to be the primary driver of mammalian toxicity for DPX-E2Y45.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

Limited information is available on the toxicity of the major DPX-E2Y45 metabolites/degradates that were not tested in the mammalian toxicology database (*i.e.*, compounds that were not identified as metabolites in the rat, mouse or dog, and therefore not tested). The only major degradate expected to be encountered via drinking water exposure is IN-LBA24 (due to rice cultivation having the potential for degradation via aquatic photolysis). However, IN-LBA24 is expected to be of equivalent or lesser toxicity than DPX-E2Y45 based on submitted acute oral and genotoxicity studies of LBA-24. Additionally, it is not clear whether IN-EQW78 was tested in the mammalian toxicology database, however, again – because it is structurally similar to parent (and metabolites that are seen in the rat metabolism cascade), it is expected to be of equivalent or lesser toxicity than DPX-E2Y45 (which is considered in light of the extremely low toxicity of DPX-E2Y45).

The only other major metabolites are IN-K9T00 and IN-HXH44, bis- or monohydroxylated on the methyl groups, identified in milk. These species were considered in the mammalian toxicology database.[†] Also, since the hydroxylated metabolites are very similar to DPX-E2Y45 (and expected to be readily excreted) they are not anticipated to pose increased toxicity over the parent compound.

[†] **IN-HXH44** – in the single oral gavage rat metabolism study, only 2% and 5% were excreted in the urine, female and male respectively; and in 3% and 7% in female and male feces, respectively. In the repeat dose rat metabolism study, the % excreted decreased over time. This particular metabolite is found mostly in dog plasma and evaluations of the dog studies have indicated no toxicological effects associated with short- or long-term exposures at doses that exceed the limit dose (1000 mkd)
IN-K9T00 – in the single oral gavage rat metabolism study, only 2% and 7% were excreted in the urine, female and male respectively; and in 5% and 10% in female and male feces, respectively. In the repeat dose rat metabolism study, the % excreted decreased over time. While this metabolite is included in the rat metabolism cascade, it has not been specifically identified in any one species tested. Its structure is similar to IN-H2H20 which is a single hydroxylated metabolite found only in rat plasma. The short-term and long-term rat studies have shown liver induction effects, but no other frank toxicities, even at doses that exceed the limit dose (1000 mkd)

Table 5.1.7. Major Metabolites and Degradates		
Common name/code ID No.	Chemical name	Chemical structure
Chlorantraniliprole, DPX-E2Y45	3-Bromo-*N*-[4-chloro-2-methyl-6-[(methylamino) carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
IN-HXH44	3-Bromo-*N*-[4-chloro-2-(hydroxymethyl)-6-[(methylamino) carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
IN-K9T00	3-Bromo-*N*-[4-chloro-2-(hydroxymethyl)-6-[[(hydroxymethyl) amino)carbonyl] phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
IN-F6L99	5-Bromo-N-methyl-1H-pyrazole-3-carboxamide	
IN-LBA24		
IN-EQW78	2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-6-chloro-3, 8-dimethyl-4(3H)-quinazolinone	

5.1.8 Pesticide Metabolites and Degradates of Concern

Reference: the risk assessment team consulted the Residues of Concern Knowledgebase Subcommittee (ROCKS), the meeting is captured in the following memo: *Chlorantraniliprole (DPX-E2Y45). Report of the Residues of*

HED is including the residues of only the parent compound in its risk assessments for chlorantraniliprole as well as for tolerance-enforcement purposes, (although drinking water is not subject to tolerance enforcement). See Table 5.1.8 below.

Table 5.1.8. 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	Chlorantraniliprole	Chlorantraniliprole
	Rotational Crop	Chlorantraniliprole	Chlorantraniliprole
Livestock	Ruminant	Chlorantraniliprole	Chlorantraniliprole
	Poultry*	N/A	N/A
Drinking Water		Chlorantraniliprole	N/A

N/A = not applicable

* At this time the risk assessment team believes that poultry can be considered a category 180.6(a)(3) situation that based on the current dietary burden, tolerances are not needed for poultry commodities.

Plants: The parent compound was the major residue found in the nature of the residue studies and the confined rotational crop studies. One metabolite, IN-F6L99, was found at 11% of the total radioactive residues (TRR) in beet tops in the rotational crop studies. Since this metabolite was not a major residue in any other study, and there were no specific toxicity concerns with this metabolite, it need not be included in the risk assessment or tolerance expression.

Ruminants: The parent compound was a major residue in the ruminant metabolism and feeding studies, and a reliable method is available for analysis. Although two metabolites (IN-K9T00 and IN-HXH44, structures in Table 5.1.7), were major residues in the milk for both the ruminant metabolism and feeding studies (only when dosed at levels greater than 100 times the expected dietary burden) – both are hydroxylated metabolites, and as such are likely to be more readily excreted than the parent. The feeding studies are considered more representative and reliable since a large number of animals were employed in the study and pooled samples of morning and afternoon milk were collected over a 28-day period at four different dose levels. Generally the levels found for the individual metabolites were comparable to, or less than, the parent. Toxicity data and QSAR (quantitative structure activity relationship) information are not available for the metabolites. However, both metabolites are included in the rat metabolism cascade, and therefore the *in vivo* rat studies provide insight on the low relative toxicity of these metabolites. Considering that the estimated combined levels of the parent and metabolites would be much less than the proposed tolerance levels in livestock commodities, only the parent compound need be included in the risk assessment at this time. In the future if the anticipated dietary burden increases significantly, the decision to exclude the hydroxylated metabolites as residues of concern for risk assessment should be reconsidered.

Poultry: At this time poultry can be considered a category 40 CFR 180.6(a)(3) situation – based on the current dietary burden, tolerances are not needed for poultry commodities.

Water: The environmental fate data suggest that chlorantraniliprole is persistent, and that microbial-mediated degradation is likely the major degradation pathway for the proposed terrestrial agricultural uses. IN-EQW78 is the primary environmental degradation product of chlorantraniliprole. It is a major degradation product [>10% of (*e.g.*, 86.7% of applied at pH 9) applied chlorantraniliprole @ 120 days post-treatment] in hydrolysis studies only at elevated temperatures and/or under alkaline conditions. IN-EQW78 was the major degradation product (9 to 46 % of applied) in field dissipation studies in California, Texas, New Jersey, and Georgia. Leaching was detected as a route of dissipation for IN-EQW78; it was found at a maximum soil depth of 36 inches. Degradation of IN-EQW78 was not observed in laboratory and field studies because levels were generally still increasing or reached a steady-state condition at the termination of the studies. The average half-life of IN-EQW78 is 703 days in aerobic soil metabolism studies. Under standard test conditions (25°C) in aerobic soils, the 90th percentile of mean half-life for total soil extractable chlorantraniliprole is 632 days. However, chlorantraniliprole can be as persistent as IN-EQW78 (the aerobic soil metabolism half-life was as long as 924 days, and in the field dissipation study in Georgia, 1130 days).

Because the parent is so persistent, modeling EDWCs based on parent and IN-EQW78 with current aquatic models in EFED would not give estimates substantially different than modeling parent alone. Therefore, only the parent need be included in the human health drinking water risk assessment.

It is noted that a Section 18 registration has been proposed for the use of chlorantraniliprole on rice. Unique photochemical degradation products (IN-LBA22, IN-LBA23, and IN-LBA24) of chlorantraniliprole were detected in laboratory aquatic photolysis studies. IN-LBA22 and IN-LBA23 were sequentially and rapidly photolyzed to form IN-LBA24. IN-LBA24 (structurally similar to IN-EQW78, but without the chloropyridine ring attached to the pyrazole ring at the 1-position) was a major degradation product (>80% of applied chlorantraniliprole) in photolysis studies in natural water and pH 7 buffer solution. The estimated photolytic half-life of IN-LBA24 was stable in pH 7 buffer solution and 129 days in natural water. IN-LBA24 has the potential to be present in drinking water sources when chlorantraniliprole is applied to agricultural crops that are cultivated via flooding.

Because the parent is substantially more persistent than IN-LBA24, modeling EDWCs based on parent alone is more protective than modeling parent and IN-LBA24 with current aquatic models in EFED. Therefore, for this screening level Section 18 action, only the parent need be included in the human health drinking water risk assessment.

5.1.9 Drinking Water Residue Profile

Chlorantraniliprole is persistent and mobile in terrestrial and aquatic environments. These fate properties suggest that it has a potential to move into surface water and shallow groundwater.

The Environmental Fate and Effects Division (EFED) has completed a drinking water assessment for chlorantraniliprole (James Hetrick, D348133, 1/10/2008). At this time, the Agency lacks sufficient monitoring exposure data for use in risk assessments, as this is a new ai. Because the Agency does not have comprehensive monitoring data, drinking water concentration estimates are made by reliance on simulation or modeling, taking into account data on the physical characteristics and fate characteristics of chlorantraniliprole.

Surface Water. A Tier 2 PRZM/EXAMS assessment based on a number of different crops was used to estimate drinking water concentrations derived from surface water sources. For the 1 in 10 year peak, the highest PRZM/EXAMS estimated drinking water concentration (EDWC) for chlorantraniliprole was 26.862 µg/L based on nursery applications in Tennessee. For the 1 in 10 year annual average, the highest PRZM/EXAMS EDWC was 3.650 µg/L, also based on nursery applications in Tennessee. For the 30 year annual average, the highest EDWC was 1.721 µg/L based on nursery applications in Florida.

Groundwater. In lieu of sufficient groundwater monitoring data for chlorantraniliprole, the Tier 1 groundwater screening model SCI-GROW was used to estimate concentration of chlorantraniliprole in shallow groundwater sources. Ornamental plants, which represent the highest registered annual use rate (0.4992 lbs ai/A) was used for the modeling, and resulted in a groundwater EDWC of 1.06 µg/L.

Table 5.1.9a Summary of Estimated Surface Water and Groundwater Concentrations for Chlorantraniliprole.

	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	26.862	1.06
Chronic (non-cancer, 1 in 10 year annual average)	3.650	
Chronic (cancer, 30-year annual average)	1.721	

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on nursery applications in Tennessee, AR 0.4992 lb ai/A.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.4992 lb ai/A, a K_{oc} of 272, and a half-life of 509 days from the aerobic soil metabolism study.

Tier 1 modeling for rice was conducted to provide EDWCs for the proposed rice seed treatment use of chlorantraniliprole. The proposed label (Dermacor X-100) for rice allows chlorantraniliprole treated rice seed use with only drill seeded and broadcast rice planting techniques. Water seeded rice is not allowed on the proposed label. Because the Tier 1 rice model assumes a 1 cm sediment depth interaction zone, the model was modified to account for 1 inch (2.54 cm) seed incorporation depth. Table 5.1.9b shows the peak concentration of chlorantraniliprole in rice paddy water. This concentration is expected to provide conservative EDWC because it represents edge-of-paddy concentrations. No dilution or aerobic aquatic metabolism is considered in the modeling. The maximum application rate of chlorantraniliprole (0.202 lbs ai/A) was assumed in the modeling.

Table 5.1.9b. Acute Chlorantraniliprole Concentrations in Rice Paddy Water		
Residue	**Chorantraniliprole Estimated Concentration (µg/L)**	**IN-LBA24 Estimated Concentration (µg/L)**
Chlorantraniliprole (@ 0.202 lbs ai/A)	84.495	61.766

Further refinement of the rice paddy EDWC was conducted to assess the annual average concentration. Although degradation routines in the Tier 1 rice model are not standard policy, photodegradation is an important degradation pathway ($t_{1/2}$=0.31 days) of chlorantraniliprole in aquatic environments. A first-order decay model ($y= 60.27*e^{-2.359*time}$) was used to estimate the average annual concentration in the rice paddy water. Table 5.1.9c shows the estimated annual average concentration of chlorantraniliprole.

Table 5.1.9c. Annual Average Chlorantraniliprole Concentrations in Rice Paddy Water		
Residue	**Chorantraniliprole Estimated Concentration (µg/L)**	**IN-LBA24 Estimated Concentration (µg/L)**
Chlorantraniliprole (@ 0.202 lbs ai/A)	0.257	0.188

5.1.10 Food Residue Profile

Most residues are found on the surface of plants. Residues ranged from less than the LOQ (<0.01 ppm) to up to 15 ppm (cotton gin byproducts) and 9.7 ppm (spinach). Residue levels varied depending on the crop. Residues in livestock are expected due to residues in feedstuff. Residues of detected metabolites seem to partition into milk fat – which is supported by the rat metabolism study. There is a high level of confidence in the field trial data, from which the tolerance levels were determined (and subsequently used in the dietary exposure assessment) – as field trials were conducted on a wide variety of crops, generally at maximum application rates and re-treatments, and minimal re-treatment intervals and PHIs.

5.1.11 International Residue Limits

There are no international residue limits that affect HED's recommendations at this time. There are no Canadian, CODEX or Mexican maximum residue limits (MRLs) for chlorantraniliprole. The new tolerances recommended by HED have been derived using the NAFTA Tolerance Harmonization Spreadsheet. As this is a global review, considerable effort was devoted to harmonizing the MRLs. Although the tolerance expression achieved harmonization, due predominantly to differences in crop grouping and what crops are considered representative of a group – harmonized MRLs were only achieved for potatoes and possibly cotton (MRL decisions still pending).

Secondary reasons that contribute to harmonization difficulties include use pattern differences (for one crop, application rates and formulations may be different in different countries due to different pest pressures/conditions).

5.2 Dietary Exposure and Risk

Reference: The dietary exposure and risk assessment was reviewed by the Dietary Exposure Science Advisory Council. *Chlorantraniliprole Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessments for the Section 3 Registration Action to Support New 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, Potatoes, and Section 18 Exemption on Rice*, D346596, Leung Cheng, 2/19/2008

The dietary exposure assessment considers only chronic exposure, since chlorantraniliprole was determined to be toxic only via the chronic oral exposure duration.

5.2.1 Chronic Dietary Exposure/Risk

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to evaluate Section 3 requests for new uses of chlorantraniliprole on leafy vegetables (except *Brassica*), *Brassica* leafy vegetables, fruiting vegetables, cucurbit vegetables, pome fruit, stone fruit, cotton, grapes, potatoes and rice (a Section 18 request).

The chronic assessments assumed that 100% of crops with requested uses of chlorantraniliprole are treated, and that all treated crops contain residues at tolerance level. In addition, the assessments include the maximum modeled EDWC (3.650 µg/L – the maximum value relevant to chronic exposure).

These assumptions result in conservative, health-protective estimates of exposure (Table 5.2). These estimates are well below HED's level of concern (100% of the cPAD). The maximum estimate is less than 1% of the cPAD for all population subgroups. These analyses indicate that there are no dietary exposure considerations that would preclude registration of chlorantraniliprole for the requested uses (*i.e.*, dietary risk is not of concern).

Table 5.2. Results of Chronic Dietary Exposure and Risk Estimates for Chlorantraniliprole

Population Subgroup	cPAD, mg/kg/day	Chronic Estimates (Food only)		Chronic Estimates (Food and Drinking Water)	
		Exposure, mg/kg/day	Risk, % cPAD	Exposure, mg/kg/day	Risk, % cPAD
U.S. Population	1.58	0.007679	<1	0.007756	<1
All infants		0.007856	<1	0.008108	<1
Children 1-2 yrs		**0.014855**	**<1**	0.014969	**<1**
Children 3-5 yrs		0.012043	<1	0.012150	<1
Children 6-12 yrs		0.007999	<1	0.008073	<1
Youth 13-19 yrs		0.005850	<1	0.005906	<1
Adults 20-49 yrs		0.007082	<1	0.007154	<1
Adults 50+ yrs		0.007613	<1	0.007689	<1
Females 13-49 yrs		0.007215	<1	0.007286	<1

The population subgroup with the highest estimated exposure/risk is bolded.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The dietary assessment is a screening-level assessment using residues at tolerance levels and assuming that 100% of requested crops are treated.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

DuPont is applying to register thirteen end-use products for use by commercial applicators on turfgrass and ornamental plants. One end-use product is a suspension concentrate, and all others are formulated as granulars. Although the percent ai in each formulation varies, the use-sites and application rates are comparable.

Although there are only two use sites (turfgrass and ornamental plants), as indicated on the DuPont™ E2Y45 0.33G Insecticide label, these use sites encompass a multitude of places that may be treated: home lawns, commercial lawns, industrial facilities, residential dwellings, business and office complexes, shopping complexes, multi-family residential complexes, institutional buildings, airports, cemeteries, interior plantscapes, ornamental gardens, parks, wildlife plantings, playgrounds, schools, daycare facilities, golf courses (tee box areas, roughs, fairways, greens, collars, *etc*.), athletic fields, sod farms and other landscaped areas. The multitude of use sites, in addition to the persistence of chlorantraniliprole, indicates there is potential for short- and intermediate-term postapplication dermal (adults and children) and incidental oral (children only) exposure to chlorantraniliprole (inhalation exposure is not expected due to low vapor pressure). However, due to the lack of toxicity over the acute, short- and intermediate-term via the oral and dermal routes – no risk is expected from these exposures.

Long-term (greater than 6 months) dermal exposure to turfgrass is not expected because the use pattern suggests a seasonal window of application, and DFR data indicate a maximum half-life of only 30 days on foliage. While chlorantraniliprole's persistence in soil (half-life up to 1130 days in dissipation studies on bareground plots) increases the possibility of long-term exposure for toddlers via incidental ingestion, the daily quantity of soil a toddler would need to eat to reach the cPAD is not feasible (more than 4 lbs/day, even when accounting for accumulation).

It should also be noted that spray drift is always a potential source of exposure to residents nearby to 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 groundboom and airblast application 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. 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 US 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 and risks associated with aerial as well as other application types where appropriate.

Again, it should be noted that due to the lack of toxicity resulting from chlorantraniliprole exposure (other than chronic oral ingestion), spray drift is not expected to pose a risk to residents near spraying operations.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (*e.g.*, a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For this action, although there is potential exposure to chlorantraniliprole from food, drinking water and residential use sites, 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).

7.1 Long-Term Aggregate Risk

Refer to Section 5.2, which discusses dietary exposure (food and water) in detail. The dietary route alone is relevant for long-term/chronic exposure and risk assessment; and the chronic dietary exposure and risk assessment conducted for chlorantraniliprole is screening-level (the assessment assigns tolerance level residue values to all food commodities proposed to be treated with chlorantraniliprole; and modeled residue values to all drinking water).

8.0 Cumulative Risk Characterization/Assessment

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

9.0 Occupational Exposure/Risk Pathway

As mentioned in Section 6.0, DuPont has applied to register thirteen end-use products for use by commercial applicators on turfgrass and ornamental plants. There is one end-use product that is a suspension concentrate, and all others are formulated as granulars. Additionally, DuPont is applying to register two chlorantraniliprole end-use products (one suspension concentrate and one water dispersible granule) for use on pome fruit, stone fruit, leafy vegetables, *Brassica* leafy vegetables, cucurbit vegetables, fruiting vegetables, cotton, grapes and potatoes. The Section 18 use on rice seed involves a 50% ai SC formulation.

For agricultural crops the maximum application rate is about 0.1 lb ai/A, re-treatment intervals range from 5-10 days, and, PHIs range from 1-21 days. Application is expected via aerial and ground equipment, as well as chemigation for the SC and WG formulations. The 50% ai SC formulation for use on rice seed is to be used with commercial seed treaters only. For turf and ornamentals, the maximum application rate is 0.3 lb ai/A. The SC formulation can be applied by ground equipment, and the granular formulations are applied by drop-type, rotary-type or hand-held equipment (see Section 2.0 for more specifics on use patterns for each use site). 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.

In addition to systemic hazard, the Worker Protection Standard (WPS) sets a restricted entry interval (REI) based on the acute toxicity of chemicals. Technical chlorantraniliprole is in Category IV for acute dermal toxicity and Category IV for primary eye and skin irritation. Per the WPS, a 12-hr REI is required for chemicals classified under Toxicity Category III or IV. However, all the labels submitted for chlorantraniliprole indicate a proposed REI of 2 hours.

REIs of 2 hours are not an option under the WPS.

According to Pesticide Registration (PR) Notice 95-3, EPA permits registrants to reduce REIs from 12 to 4 hours for certain low risk pesticides that meet certain criteria. The criteria are

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 (NMethyl 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. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the Worker Protection Standard (WPS).

Three dislodgeable foliar residue (DFR) studies were submitted by the registrant. DFR studies are generally used to refine postapplication activity exposure estimates. Since no risk is expected, the DFR results are not used in that way. Regardless, it is interesting to note that the dissipation pattern on the surface foliage of plants (tomatoes, cabbage and apples, in this case) do not follow a uniform pattern. In some cases the residues decline and then increase. It is possible that climate/weather plays a significant role in the dissipation pattern – with rainfall aiding dissipation. Although the DFR studies are quite different from the fate studies (fate studies investigate residues remaining within a 3-dimensional volume, rather than the residue that can be dislodged on a 2-dimensional plant surface), they both indicate that chlorantraniliprole is persistent.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

There are no data gaps in the toxicology database.

10.2 Residue Chemistry

860.1200 Directions for Use

Since the residue data for pome fruit reflect spray volumes of 100 gallons per acre, the use directions for pome fruit should be revised to state “minimum spray volume of 100 gal/A (ground).” Also, as there are inadequate residue data that reflect use of adjuvants in end-use products in the residue field trials, the proposed labels should be revised to delete the use of adjuvants on all crops except *Brassica* crops. In the absence of residue data on crops grown in greenhouses, the label should prohibit use on crops grown in greenhouses. Given the results of the confined accumulation and limited field accumulation in rotational crops study, a restriction should be imposed on the proposed labels to prohibit the rotation to any crop not on the label.

860.1400 Water, fish, and irrigated crops

Residue data in crayfish will not be required for the Section 18 request, but may be required for a Section 3 registration.

860.1900 Field Accumulation In Rotational Crops

The petitioner is required to conduct extensive field rotational crop trials. The requirement for number of trials would be the same as that to establish primary tolerances on all crops or crop groups which the petitioner intends to have as rotational crops on the label. If a registrant desires to allow the universe of crops to be rotated, magnitude of the residue data are required on representative crops for *all* crop groups which could be planted in a typical crop rotation sequence.

10.3 Occupational and Residential Exposure

REIs of 2 hours are not an option under the WPS, but are listed on most of the proposed labels. Chlorantraniliprole meets all of the criteria listed in Section 9.0, and therefore, is a candidate for a reduced REI of 4 hours according to PR Notice 95-3.

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Appendix A: Toxicology Assessment

Reference: *Chlorantraniliprole (DPX-E2Y45) Toxicology Assessment*, Mary Manibusan, TXR #0054555, D336940, D337737, D343520, D345100, 11/17/2007.

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for a food use for chlorantraniliprole are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	no	-
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5385 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Micronucleus	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
Special Studies		
28-day immunotoxicity (rat)		yes
28-day immunotoxicity (mouse)		yes

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity of Technical DPX-E2Y45 (Chlorantraniliprole)				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral toxicity	46889112	LD50 = >5000 mg/kg bw	IV
870.1200	Acute dermal toxicity	46889113	LD50 = >5000 mg/kg bw	IV
870.1300	Acute inhalation toxicity	46889121	LC50 = >5.1 mg/L	IV
870.2400	Acute eye irritation	46889115	Iritis score of 1 in 1/3 rabbits, conjuctival redness score of 1 in 2/3 rabbits. All eyes returned to normal after 72 hours.	IV
870.2500	Primary skin irritation	46889114	No dermal irritation, clinical signs or body weight loss	IV
870.2600	Dermal sensitization	46889221	Not a dermal sensitizer	Negative

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile				
STUDY/ SPECIES	**DOSES (mg/kg/day)**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**EFFECTS**
14-day Oral Gavage/ rat	0, 25, 100, 1000	1000	Not established	No adverse effects. Weak inducer of cytochrome P450 3A at all dose levels, with statistical significance at 100 and 1000 mg/kg/day.
28-Day Oral (feed)/rat	0, 20.7, 106 and 584 (male); 0, 24, 128 and 675 (female)	584 (male) and 675 (female)	Not established	No adverse effects. Slight increase in liver weight at 128 and 675 mg/kg/day in females and minimal hepatocellular hypertrophy at 675 mg/kg that is attributed to enzyme induction characterized by increased amount of eosinophilic cytoplasm with hepatocytes but no histomorphologic evidence of hepatocellular damage. In 128 and 675 mg/kg females, a statistically significant increase in UDP-GT activity was observed in HDT female rats, with a similar increase in males. These changes are consistent with a pharmacological response and were not considered adverse.
28-Day Oral (feed)/mouse	0, 52, 182, 538 and 1443 (male); 0, 64, 206, 658 and 1524 (female)	1443 (male) and 1524 (female)	Not established	No adverse effects. Slight increase in liver wt. in 658 and 1524 mg/kg/day females corresponded with a mild increase in cytochrome P450 enzyme activity. No histopathological evidence of liver toxicity was observed. A reduction in body weight gain was observed in HDT males (52%) but not in females. No statistically significant decrease in absolute body weight was observed therefore, this effect was not considered adverse.
28-day Oral (capsule)/ Dog	0, 300, 1000	1000	Not established	No adverse effects. Induction of cytochrome P450 enzyme activity (58%) in both males and females at 1000 mg/kg/day, specifically 1A1 and 2B1/2 at 300 and 1000 mg/kg/day.
28-day Oral (feed)/dog – Palatability study	0, 26, 138, 266, 797 and 1302 (male); 0, 28, 138, 298, 888, and 1240 (female)	1302 (male) and 1240 (female)	Not established	No adverse effects. Food consumption generally increased as the study progressed with males generally demonstrating the highest food consumption when fed the HDT.
28-day Dermal/rat	0, 100, 300 and 1000	1000	Not established	No adverse effects. Reductions in mean body weight gain (22% and 19% for males and females) and food efficiency (19% and 17% for males and females) over the 28-day at the HDT.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile				
STUDY/ SPECIES	**DOSES (mg/kg/day)**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**EFFECTS**
				Increased microvesiculation of adrenal cortex in males only, with no light or electronic microscopic evidence of adrenal cellular degeneration or toxicity. No effect on the capacity of the adrenal gland to produce corticosterone under either basal or following ACTH stimulation. Therefore, these effects were not considered adverse.
90-day Oral (feed)/rat	0, 36.9, 120, 359, 1188 (male); 0, 47, 157, 460, 1526 (female)	1188 (male) and 1526 (female)	Not established	No adverse effects. A slight increase in liver weight at HDT females and reduction in bilirubin in females at ≥157 mg/kg/day, with no corresponding histopathological evidence of liver toxicity.
90-day Oral (feed)/mouse	0, 32.6, 115, 345, 1135 (male); 0, 40.7, 158, 422, 1529 (female)	1135 (male) and 1529 (female)	Not established	No adverse effects. Hyperactivity and hyperreactivity in females were observed near the end of the study and one male in the upper mid dose had convulsions, but these effects were considered spurious as they were not reproducible in the 18-month mouse study with a FOB. A slight increase in liver weight at the HDT males and females, with no corresponding histopathological evidence of liver toxicity.
90-day Oral (feed)/dog	0, 32.2, 119, 303, 1163 (male); 0, 36.5, 133, 318, 1220 (female)	1163 (male) and 1220 (female)	Not established	No adverse effects. A mild increase in liver weight was observed in males at 1163 mg/kg/day, with no corresponding histopathological evidence of liver toxicity.
52-week Oral (feed)/dog	0, 32, 112, 317, 1164 (male); 0, 34, 113, 278, 1233 (female)	1164 (male) and 1233 (female)	Not established	No adverse effects. A mild increase in liver weight in HDT males and females, and increase in alkaline phosphatase in HDT males, with no corresponding histopathological evidence of liver toxicity. Body weight gain increase in HDT males for weeks 8-9 compared to controls, with an increase in food efficiency in week 9.
2-Year Oral (feeding)/rat	0, 7.71, 39, 156, 805 (male); 0, 10.9, 51, 212, 1076 (female)	805 (male) and 1076 (female)	Not established	No evidence of carcinogenicity and no adverse findings. Increased adrenal cortical microvesiculation due to lipid was present in the zona fasciculata region of the adrenal gland of some male rats in all dose groups in both the one-year and main studies. This finding was considered test substance related but was not considered adverse as the adrenal morphology was generally in the range of what was observed in control rats, and the finding was not associated with any indication of cytotoxicity or other evidence of structural or functional impairment of the adrenal gland.
18-Month Oral (feeding)/ Mouse	0, 2.6, 9.2, 26.1, 158, 935 (male); 0, 3.34, 11.6, 32.9, 196, 1155 (female)	158 (male) and 1155 (female)	935 (male), no LOAEL established for female	No evidence of carcinogenicity. Eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight form the bases for the male LOAEL of 935 mg/kg/day.
Two-generation oral study/rat	0, 200, 1000, 4000, 20000 ppm, mg/kg bw/d equivalents:	1199 (male) and 1594 (female)	Not established	A slight increase in mean liver weights in P1 and F1 males and females at 238/318.9 mg/kg/day and above, slight increase in mean adrenal weight at 238/318.9 mg/kg/day and 1199/1594 mg/kg/day P1 and F1 males and

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile				
STUDY/ SPECIES	**DOSES (mg/kg/day)**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**EFFECTS**
	pre-mating: P1 m: 0, 12, 60, 238, 1199 F1 m: 0, 18, 89, 370, 1926 P1 f: 0, 16, 78, 318, 1594 F1 f: 0, 20, 104, 406, 2178 gestation: P1 f: 0, 14, 68, 278, 1373 F1 f: 0, 14, 71, 272, 1465 lactation: P1 f: 0, 32, 162, 654, 3118 F1 f: 0, 35, 183, 696, 3641			females. Mean body weight of 1199/1594 mg/kg/day F1 pups was slightly reduced on lactation days 7, 14 and 21. No effects on F2 offspring weights during lactation. Minimal to mild increase in adrenal cortical microvesiculation in P1 adult males and F1 adult males and females. P1 adult at 60.4/77.8 mg/kg/day and greater. F1 adult males at 12 mg/kg/day and greater. These effects were not observed in weanlings. No cytotoxicity or abnormal cellular structures were observed under light or electron microscopy.
Develop mental study/rat	0, 20, 100, 300, 1000	1000	Not established	No adverse effects.
Develop mental study/rabbit	0, 20, 100, 300, 1000	1000	Not established	No adverse effects.
Acute oral neuro-toxicity/rat	0, 200, 700, 2000 in 0.5% methyl cellulose	2000	Not established	No evidence of neurotoxicity was observed at any dose
Subchronic oral neuron-toxicity/rat	0, 12.7, 64.2, 255, 1313 (male); 0, 15.1, 77.3, 304, 1586 (female)	1313 (male) and 1586 (female)	Not established	No evidence of neurotoxicity was observed at any dose.
28-day Immuno-toxicity/rat	0, 74, 363, 1494 (male); 0, 82, 397, 1601 (female)	1494 (male) and 1601 (female)	Not established	No evidence of treatment-related effects on the sheep red blood cells specific antibody (IgM) responses in either male or female rats at any dietary concentration tested.
28-day Immuno-toxicity/ Mouse	0, 48, 264, 1144 (male); 0, 64, 362, 1566 (female)	1144 (male) and 1566 (female)	Not established	No evidence of treatment-related effect on the sheep red blood cells specific antibody (IgM) responses in either male or female mice at any dietary concentration tested.

A.3 Toxicity Summaries

Acute Toxicity – Technical Chlorantraniliprole

DuPont has submitted three six-packs of acute toxicity studies (eighteen studies total) in support of this registration for three products: DPX-E2Y45 technical (Table 3.1.1), and two formulations DuPont Altacor™ WG Insecticide (35% ai) and DuPont Coragen™ SC Insecticide (18.4% ai). The acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation and dermal sensitization studies submitted for each product have been reviewed and all are

classified as acceptable. Chlorantraniliprole (technical) and the two formulations (DuPont Altacor™ WG and DuPont Coragen™ SC) are in Toxicity Category IV for all routes of exposure and are non-sensitizers. **No acute hazard has been identified.**

Table 3.1.1. Acute Toxicity of Technical DPX-E2Y45 (Chlorantraniliprole)

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral toxicity	46889112	LD50 = >5000 mg/kg bw	IV
870.1200	Acute dermal toxicity	46889113	LD50 = >5000 mg/kg bw	IV
870.1300	Acute inhalation toxicity	46889121	LC50 = >5.1 mg/L	IV
870.2400	Acute eye irritation	46889115	Iritis score of 1 in 1/3 rabbits, conjuctival redness score of 1 in 2/3 rabbits. All eyes returned to normal after 72 hours.	IV
870.2500	Primary skin irritation	46889114	No dermal irritation, clinical signs or body weight loss	IV
870.2600	Dermal sensitization	46889221	Not a dermal sensitizer	Negative

Metabolism Studies (MRID 46979330)

Rate and extent of oral absorption	Absorption was 73-85% within 48 hours after a single low dose (10 mg/kg/day) and 12-13% after a single high dose (200 mg/kg/day) based on the sum in bile, urine, and carcass (except GI contents). Peak plasma concentrations occurred at 5-12 hours after low and high single dose administration. Plasma ^{14}C residue concentrations showed steady-state kinetics in male rats and near steady-state kinetics in female rats after multiple low dose administration (10 mg/kg/day x 14 days).
Distribution	Uniformly distributed with maximum concentrations observed in plasma relative to other tissues. Female rats had higher tissue residues than male rats.
Potential for accumulation	Very low potential for accumulation based on tissue to plasma ratios substantially less than one after single or multiple oral dosing.
Rate and extent of excretion	Elimination half-lives for ^{14}C residues from plasma through 5 days after single low dose administration were shorter in male ($T_{1/2}$ = 1.7 days) than female rats ($T_{1/2}$ = 3.3 days), increased to $T_{1/2}$ = 7.2 days through 13 days after multiple oral dosing. Rapid excretion observed via bile (49-53%) within 48 hours. Extensive excretion (98-97%) within 7 days after single or multiple dose administration mainly via feces (62-92%) compared with urine (3.7-29%). Urinary excretion for the low dose at 48 hour ranged from 18-30%.
Metabolism in animals	Metabolism of the absorbed dose was fairly extensive* and involved sex differences primarily in initial tolyl methyl and N-methyl carbon hydroxylations. Further metabolism of the hydroxylated metabolites included N-demethylation, nitrogen to carbon cyclization with loss of a water molecule resulting in the formation of the pyrimidone ring, oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis, and O-glucuronidation. Metabolism was similar after multiple low dose (10 mg/kg/day x 14 days) or single high dose (200 mg/kg/day) administration.
Toxicologically relevant compound	Parent compound (DPX-E2Y45)

***Note:** The majority of the administered dose is excreted as the unchanged parent molecule with little of the truncated species arising from cleavage of the central carboximide link.

In addition to the rat metabolism studies conducted with ^{14}C-labelled DPX-E2Y45, analysis of plasma for parent and primary metabolites was conducted during the 90-day rats, mice and dogs

dietary administration studies and the rat 14-day oral gavage study. DPX-E2Y45 and primary metabolites observed above the limit of quantification of 0.005 ug/mL plasma were reported.

14-day oral gavage rat (MRID 46979935)
In the 14-day oral gavage study, a toxicokinetic assessment was performed. The area under the plasma concentration versus time curve (AUC) was not proportional with the dose of DPX-E2Y45 indicating decreased absorption at higher doses. The half-lives were estimated to be 3.4, 3.4 and 4.0 hours for 25, 100 and 1000 mg/kg/day groups, respectively. The time of maximum concentration (T_{max}) was 0.25, 0.42, and 2.75 hours in the 25, 100, and 1000 mg/kg/day groups, respectively. The maximum concentrations (C_{max}) was similar at all dose levels, with the highest concentration (0.48 ug/mL) occurring in the 25 mg/kg/day group. The half life for DPX-E2Y45 was sufficiently short that a significant portion of the parent compound will be cleared from the plasma after 24 hours, even following two weeks of repeated dosing at 1000 mg/kg/day indicating low potential for bioaccumulation.

90-day oral rat
In the 90-day oral rat study, DPX-E2Y45 and the metabolites IN-GAZ70 and IN-H2H2O were identified quantitatively. The concentration of IN-GAZ70 in plasma from male and female rats on Day 59 was considerably greater than the plasma concentration of DPX-E2Y45. In males, this difference was approximately 10-fold, but in females, the difference was 100-fold. The concentration of each analyte was greater in females than in males. With the exception of the plasma concentration of IN-H2H2O in male rats dosed at the highest dose being statistically different from the 2000 ppm dose, the plasma concentration of DPX-E2Y45, IN-GAZ70 and IN-H2H2O were not statistically different from one another in the three highest dose concentrations in either sex.

90-day oral mouse
In the 90-day oral mouse study, DPX-E2Y45 and the metabolite IN-GAZ70 were quantified. The concentration of the parent DPX-E2Y45 was below the limit of quantification in all mouse samples analyzed. The metabolite IN-GAZ70 was the only significant analyte present in plasma from male mice on day 92 and female mice on day 93. The plasma concentration of IN-GAZ70 in female mice dosed at the highest dietary concentration was statistically different from the 700 ppm dose. In male mice, the plasma concentrations at the 2000 and 7000 ppm dose concentrations were both statistically different from the 700 ppm dose concentration.

90-day oral dog
In the 90-day dog study, DPX-E2Y45 and metabolite IN-HXH44 were quantified. The concentration of parent DPX-E2Y45 for both male and female dogs in plasma was approximately five times the concentration of the metabolite IN-HXH44. The plasma concentration of DPX-E2Y45 in male dogs dosed at 40,000 ppm (high dose) was not statistically different from the 4000 ppm dose. The plasma concentration of the IN-HXH44 was not statistically different at any dose concentration in either sex.

Conclusions:
These results demonstrate systemic uptake and metabolism of DPX-E2Y45 during dietary and

oral gavage administrations. These results also suggest possible species differences in the primary metabolites formed in all three species, rats, mice and dogs. The concentration of DPX-E2Y45 in plasma was dog>rat>mouse. The primary methylphenyl ring hydroxylated metabolite (IN-HXH44) was quantified only in dog plasma, while the N-methyl hydroxylated metabolite (IN-H2H2O) was quantified only in rat plasma. The cyclization product of IN-H2H20 with loss of a water molecule or N-demethylation product of IN-EQW78 (IN-GAZ70) was quantified in both mouse and rat, but not dog plasma. Mouse plasma contained more IN-GAZ70 than rat plasma in these studies. In all three species, the relatively constant analyte concentrations at the higher dose levels suggested decreased absorption with increasing dose, confirming the previously described rat metabolism studies. The slight decrease in the plasma DPX-E2Y45 concentrations with increasing dose in the 14-day oral gavage rat study also provided evidence for decreased absorption. A significant sex difference was observed in rats with female rats showing higher concentrations of DPX-E2Y45, IN-H2H20, and IN-GAZ70 than male rats. No sex difference was noted in the dog or mouse. Overall, the results in rats for the 90-day and 14-day studies were consistent with the plasma concentrations of ^{14}C residues, decreased absorption, and proposed metabolic pathway from the single and multiple oral gavage studies with ^{14}C-DPX-E2Y45 in rats.

28-day Dermal Toxicity Study (MRID 46889128)

In the 28-day dermal toxicity study, chlorantraniliprole was applied to shaved dorsal skin of male and female CrL:CD(SD)IGS BR rats (10/sex/dose). Exposure doses were 0, 100, 300, or 1000 mg/kg/day. Test substance related reductions in mean body weight gain (↓22% and ↓19% males and females, respectively) and corresponding food efficiency values (19% and 17% for males and females, respectively) were observed over the 28-day period in both males and females at the highest dose, 1000 mg/kg/day. No statistically significant change in absolute body weight was reported. Mean body weight on test day 28 in the male and female 1000 mg/kg/day group was ↓6% and ↓5% from control for both males and females, respectively.

A minimal increase in microvesiculation in the *zona fasciculata* region of the adrenal cortex was observed in some treated males at 100 (2/10), 300 (2/10) and 1000 (5/10) mg/kg/day, with histologic grade of 1 (minimal), but not in the control or female rats. The increased microvesiculation was not considered adverse because the increase was within the range of normal adrenal morphology; and under both light and electron microscopy, there was no evidence of adrenal cellular degeneration or toxicity, and no effect on the adrenal gland was observed in a functionality test (MRID 46889215). No other effects were noted in the study. **Based on the absence of treatment related adverse effects, the NOAEL was established at 1000 mg/kg/day [limit dose and highest dose tested (HDT)].**

90-day Subchronic Feeding Rat Study (MRID 46889010)

In a 90-day feeding study, chlorantraniliprole was administered to male and female Crl:CD(SD)IGS BR rats (10 rats/sex/concentration) at concentrations of 0, 600, 2000, 6000, or 20,000 ppm, which correspond to overall mean daily intakes of 0, 36.9, 120, 359, or 1188 mg/kg/day for males and 0, 47, 157, 460, or 1526 mg/kg/day for females. No test substance related effects on mean body weight, body weight gain, food consumption or food efficiency were observed in any male or female dose groups.

A slight increase in mean liver weight (18% from control) at 1526 mg/kg/day and a reduction in bilirubin (↓36-43% from controls on day 49 and ↓25-35% on day 98) at ≥157 mg/kg/day was observed in female rats, but not in males. The increase in liver weight and reduction in bilirubin did not correlate with any liver microscopic changes, but could be attributed to the induction of hepatic metabolic enzymes.

Urine volume was increased by 95-100% in the ≥460 mg/kg/day males at test day 48 and 65-75% at test day 97. Urine osmolality was minimally decreased in males at 1188 mg/kg/day at test day 97, but in the absence of corroborating gross or histologic findings in the kidneys, this finding was not considered adverse.

A minimal increase in microvesiculation (vacuolation) in the *zona fasciculata* region of the adrenal cortex was observed in some treated males at 1188 mg/kg/day (2/10 rats) pathology grade of 2 (mild); similar effects were not reported in other treated males and females at any dose. This finding in isolation, without functional impact on the adrenal cortex (MRID 46889215) or any evidence of adrenal cellular degeneration or toxicity is not considered adverse. **Based on the absence of treatment related adverse effects, the NOAEL is established at 1188 and 1526 mg/kg/day for males and females, respectively [the highest doses tested (HDTs)]. These levels exceed the limit dose (1000 mg/kg) for subchronic studies.**

90-day Subchronic Feeding Mouse Study (MRID 46889013)

In the 90-day feeding study, chlorantraniliprole was administered to male and female Crl:CD-1(ICR)BR mice (15 mice/sex/concentration) at concentrations of 0, 200, 700, 2000, or 7000 ppm, which correspond to mean daily intakes of 0, 32.6, 115, 345, or 1135 mg/kg/day for males, and 0, 40.7, 158, 422, or 1539 mg/kg/day for females. No test substance related effects on mean body weight, body weight gain, food consumption or food efficiency were observed in any male or female dose groups.

A slight increase (13% and 10% for males and females, respectively) in liver weight at 1135 mg/kg/day males and 1539 mg/kg/day females was not associated with any gross or microscopic liver pathology, but could be attributed to a pharmacological response of hepatic cytochrome P450 enzyme induction. No liver enzyme measurements were provided, but changes are not expected due to the minor increase in liver weight and lack of liver histopathology.

Increased incidences (see Table 3, section 3.3.2) of hyper-reactive behavior in the ≥700 ppm females and hyperactive behavior in the ≥2000 ppm females were observed. In these animals, hyperactivity and hyper-reactivity were most commonly observed between Day 56 and 70 or thereafter. One 2000 ppm male had convulsions on Day 91, but no other instance of convulsions was observed in any animal.

A functional observational battery was included in the 18-month mouse feeding study. Dietary concentrations, animal source, and approximate age of the mice at study start were the same as in this 90-day study, but no treatment-related effects on any neurobehavioral parameters were reported during the first 180 days. The author of the study stated that over the entire 18-month

mouse study, the incidence of convulsions, hyperactivity, and hyper-reactivity did not exhibit a dose-response. Therefore, these findings in the 90-day study were considered incidental and not treatment related. **Based on the absence of treatment related adverse effects, the NOAEL is established at 1135 and 1539 mg/kg/day for males and females, respectively (HDTs). These levels exceed the limit dose (1000 mg/kg) for subchronic studies.**

90-day Subchronic Feeding Dog Study (MRID 46889012)

In the 90-day feeding study, chlorantraniliprole was administered to male and female beagle dogs (4 dogs/sex/concentration) at concentrations of 0, 1000, 4000, 10,000, and 40,000 ppm, which correspond to mean daily intakes of 0, 32.2, 119, 303, and 1163 mg/kg/day for males and 0, 36.5, 133, 318, and 1220 mg/kg/day for females, respectively. No test substance related effects on mean body weight, body weight gain, food consumption or food efficiency were observed in any male or female dose groups.

A slight increase in absolute liver with gallbladder weight (6-23% of control) was observed in all treated male dogs, with statistical significance at 40,000 ppm (23% of control) (1163 mg/kg/day); this finding was not associated with any liver histopathology, but may be due to a pharmacologic response to metabolism of a xenobiotic. **Based on the absence of treatment related adverse effects, the NOAEL is established at 1163 and 1220 mg/kg/day for males and females, respectively (HDTs). These levels exceed the limit dose (1000 mg/kg) for subchronic studies.**

52-week Chronic Feeding Dog Study (MRID 46979718)

In a 1-year feeding study, DPX-E2Y45 (Batch #177; 96.45% a.i.) was administered to male and female beagle dogs (4 dogs/sex/concentration) at 0, 1000, 4000, 10,000, or 40,000 ppm. The mean daily intakes for male dogs were 0, 32, 112, 317, and 1164 mg/kg bw/day. The mean daily intakes for female dogs were 0, 34, 113, 278, and 1233 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical and neurobehavioral signs, clinical pathology (hematology, clinical chemistry, urinalysis), ophthalmology, organ weights, gross and microscopic pathology.

No test substance-related effects were observed on survival, clinical and neurobehavioral signs, or ophthalmology, body weight and nutritional parameters, clinical pathology, or gross or microscopic pathology. Test substance-related increases in liver weight (absolute and relative) were observed in 40,000 ppm male and female dogs, but were not associated with any microscopic pathology changes. These weight effects were considered non-adverse and due to induction of liver metabolic enzymes. One male dog in the 40,000 ppm group demonstrated clinical signs, clinical pathology, and anatomic pathology changes consistent with canine juvenile polyarteritis syndrome, a naturally occurring vasculitis and perivasculitis of unknown etiology (Snyder *et. al.* 1995); these effects were not considered to be test substance related.

The no observed adverse effect level (NOAEL) was 40,000 ppm (1164 mg/kg bw/day for males and 1233 mg/kg bw/day for females). The NOAEL was based on a lack of adverse effects in males or females at 40,000 ppm, the highest concentration tested.

Combined chronic toxicity/oncogenicity study 2- year feeding study in rats (MRID 46979719) and Eighteen month chronic feeding study in mice (46979720)

DPX-E2Y45 was not carcinogenic in rats or mice. The NOAEL for chronic toxicity in rats was 20000 ppm (805/1076 mg/kg/day, M/F) and was based on the absence of any treatment-related toxicity at any dietary concentration evaluated in the study. Mild increases in liver weight occurred in the 4000 (156/212 mg/kg/day, M/F) and 20000 ppm female rats at 1 year. These changes were not associated with other changes indicative of liver toxicity, but were consistent with the non-adverse pharmacological response to metabolism that was observed in short-term feeding studies with DPX-E2Y45. A minimal to mild increase in the degree of microvesiculation in the adrenal cortex was present in some male rats at 1 and 2 years. Based on mechanistic studies, this finding was determined to have no toxicological impact on adrenal cortical cell function and was not considered toxicologically relevant.

In mice, there were treatment-related effects in males at the highest dose tested, but not females administered DPX-E2Y45 up to and including a maximum dietary concentration of 7000 ppm (1155 mg/kg/day). Increased liver weights in males and females and small increases in the incidence of hepatocellular hypertrophy in males were observed at the two highest concentrations tested (158 mg/kg/day and 935 mg/kg/day). The liver changes at the mid dose (158 mg/kg/day) were consistent with the non-adverse induction of liver enzymes observed in short-term feeding studies with DPX-E2Y45. However, the slight increase in the incidence of eosinophilic foci (5/70) of cellular alteration in the livers of high dose male mice was considered outside the historical control range (0-1.92%) for this strain of mice and therefore, treatment related and adverse.

The LOAEL in male mice is 935 mg/kg bw/day based on the slightly increased, minimal eosinophilic foci of cellular alteration accompanied by hepatocellular hypertrophy and increased liver weight in male mice. The NOAEL in male mice was taken as the next highest dose tested, 158 mg/kg bw/day. The NOAEL for female mice was 1155 mg/kg bw/day due to the lack of adverse treatment-related effects on any parameter at any dietary level of DPX-E2Y45 evaluated.

The NOAEL in the 2-year rat study is 805 and 1076 mg/kg/day (M/F, HDT) based on the lack of adverse treatment related findings.

Based on the results of chronic feeding studies in rats and mice, DPX-E2Y45 is not carcinogenic at the durations and doses tested in these animal toxicity studies.

Developmental Rat Study (MRID 46889108)
Developmental Rabbit Study (MRID 46889109)

In the rat developmental toxicity study, chlorantraniliprole was administered by oral gavage to time mated Crl:CD(SD)IGS BR female rats (22/dose group) on gestation days 6-20 at dose levels of 0, 20, 100, 300 or 1000 mg/kg/day (dose volume was 4 mL/kg); and in the rabbit developmental toxicity study, chlorantraniliprole was administered by oral gavage to time-mated Hra:(NZW)SPF female rabbits (22/dose group) on gestation days 7-28 at dose levels of 0, 20, 100, 300, and 1000 mg/kg/day. No test substance related effects on maternal clinical

observations, body weight, weight gain, food consumption, or gross post-mortem observations were detected at any dose. The mean number of corpora lutea, implantation sites, resorptions, live fetuses, fetal weight, and sex ratio were comparable across all groups. There were no abortions, premature deliveries, or complete litter resorptions and no effects of treatment on the numbers of litters, post-implantation loss, or on gravid uterine weights. No test substance-related fetal external, visceral, skeletal malformations, variations, and adverse effects on fetal skeletal ossifications were observed at any dose.

Based on the absence of treatment related adverse effects the maternal systemic toxicity and developmental toxicity NOAEL is greater than 1000 mg/kg/day (limit dose and HDT).

Two Generation Reproduction Rat Study (MRID 46889107)
In the two-generation reproduction study, Crl:CD(SD)IGS BR rats were administered chlorantraniliprole in the diet at dose levels of 0, 200, 1000, 4000, or 20,000 ppm, which is equivalent to 0, 12, 60.4, 238 and 1199 mg/kg/day in males and 0, 15.5, 77.8, 318.9 and 1594 mg/kg/day for females, respectively. There was an increase (10-19% from controls) in liver weights observed in P and F1 females at 4000 ppm and above, which was attributed to a pharmacological increase in metabolism. A statistically significant increase in mean adrenal weight (8-22% from controls absolute and/or relative to body weight) was observed in 4000 and 20,000 P and F1 males and females. No adverse test substance related effects on any gross or microscopic pathology endpoint were observed. Mean body weight of the 20,000 ppm F1 pups was slightly reduced when compared to controls on lactation days 7, 14 and 21. The slightly lower 20,000 ppm pup weights were considered not adverse as they were transient, small in magnitude, and F1 offspring weights were similar to controls by Day 35 postweaning. In addition, there were no effects on F2 offspring weights during lactation.

An increased incidence in microvesiculation of the adrenal cortex for P and F1 parental rats were reported. The minimal to mild (pathology grade 1-2) vacuolations were treatment-related in P and F1 males for all dose groups and F1 females treated only at the high dose. Although treatment related, this finding in isolation, with no functional impact on the adrenal cortex or any evidence of adrenal cellular degeneration or toxicity, is not considered adverse. Electron microscopy of the adrenal gland, conducted on two control P males and two P males in the 20,000 ppm group, did not reveal any adverse, test-substance related effects.

Based on the absence of treatment related adverse effects, the parental systemic toxicity, reproductive toxicity and offspring/developmental toxicity NOAEL is ≥20,000 ppm (1199/1594 mg/kg/day (M/F) (above the limit dose and HDTs).

28-day Immunotoxicity Studies in Rats and Mice (MRID 46979344 and MRID 46979343)
Exposure to DPX-E2Y45 produced no effects on thymus or spleen weights or on the antibody response to sheep red blood cells in rat and mouse 28-day immunotoxicity studies. No evidence of systemic toxicity was noted during the studies. The NOAELs in the studies were the highest dietary concentrations evaluated, corresponding to 20000 ppm in rats and 7000 ppm in mice. In addition, no indications of the potential of DPX-E2Y45 to adversely affect the immune system were noted in 90-day and chronic/oncogenicity studies conducted in rats, mice, or dogs. Based

on these results, DPX-E2Y45 does not pose an immunotoxic hazard. **The NOAEL is >1000 mg/kg/day (limit dose).**

Acute Oral Neurotoxicity in Rats (46979312) and Subchronic Oral Neurotoxicity in Rats (4697921)

No evidence of neurotoxicity was observed in studies conducted with DPX-E2Y45 in rats. The NOAEL in an acute, oral gavage neurotoxicity study was 2000 mg/kg bw and was the highest dose administered in the study. In a subchronic neurotoxicity study, the NOAEL was 20000 ppm (equivalent to 1313 and 1586 mg/kg bw/day in males and females, respectively), the maximum dietary concentration administered. The NOAELs were based on the absence of treatment related effects on systemic toxicity and neurotoxicity parameters, including microscopic neuropathology. Neurological assessments conducted in conjunction with the 18-Month oncogenicity study in mice following 45, 60, and 90 days of dietary administration of DPX-E2Y45 confirmed the lack of potential neurotoxicity. Further, no treatment related clinical signs indicative of potential neurotoxicity were observed in short-term and long-term exposure studies in rats, mice, or dogs. Therefore, it is concluded that DPX-E2Y45 is not a neurotoxicant. **The NOAEL is >1000 mg/kg/day (limit dose).**

Genotoxicity Summary (MRID 46889103, 46889104, 46889105, 46889106)

Chlorantraniliprole has been evaluated for mutagenicity in the standard battery of Genetic Toxicology studies. Results indicate that the test material is not mutagenic in bacteria (*Salmonella typhimurium* or *Escherichia coli*) or in mammalian cells (Chinese hamster ovary, CHO cells). It was also not clastogenic *in vitro* in human lymphocytes or *in vivo* in mouse bone marrow. The submitted studies satisfy the FIFRA test guidelines for mutagenicity, and there is no concern for mutagenicity at this time. Summarized findings from these studies are presented below:

GENE MUTATION

Bacterial Reverse Gene Mutation Assay: In a S.typhimurium TA1535, TA1537, TA98 and TA100 and *E.coli* WP2 *uvrA* reverse gene mutation assay (MRID 46889103), DPX-E2Y45 technical (chlorantraniliprole) was not mutagenic up to insoluble concentrations (≥ 1800 μg/plate +/-S9).

Mammalian Cell Forward Gene Mutation Assay: In a Chinese hamster ovary (CHO) cell forward gene mutation assay (MRID 46889106), DPX-E2Y45 Technical (Chlorantraniliprole) was tested up to and beyond the limit of solubility (≥250 μg/mL) and did not induce a mutagenic effect at the HGPRT locus.

CHROMOSOME ABERRATIONS

Mammalian Cell Cytogenetic Assay: In a cytogenetic assay (MRID 46889105), primary human lymphocyte cultures were exposed to DPX-E2Y45 Technical (chlorantraniliprole) at concentrations up to precipitating levels (≥750 μg/mL) and there were no statistically significant increases in the percentages of cells with structural aberrations or in polyploidy.

Micronucleus Assay: In a mouse micronucleus assay (MRID 46889104), Crl:CD-1®(ICR)BR male and female mice were treated once by oral gavage with DPX-E2Y45 Technical (chlorantraniliprole) at levels up to the limit dose (2000 mg/kg). No significant increase in the frequency of micronucleated polychromatic erythrocytes was seen in bone marrow at either

sacrifice time.

Development of Methods for the Evaluation of Adrenal Cortical Function in Rats (MRID 46889215)

The functional impact of the increased degree of microvesiculation in the adrenal cortex of chlorantraniliprole was evaluated by measuring corticosterone concentrations under non-stressed (i.e., basal) conditions and conditions of simulated physiologic stress (i.e., ACTH-induced). The conduct of these tests was based on clinical tests normally conducted in human and veterinary medicine for evaluation of adrenal cortical function.

Corticosterone Under Basal Conditions

Basal corticosterone synthesis in rats administered chlorantraniliprole was determined by measuring total corticosterone excreted overnight in urine (corticosterone concentration x urine volume; DuPont 14123). Urine corticosterone excretion was measured approximately 1 week prior to sacrifice for all male and female rats designated for the 1-year interim sacrifice on the 2-year chronic study. These rats had been fed dietary concentrations of chlorantraniliprole at 0, 200, 1000, 4000 and 20,000 ppm (intakes up to approximately 880 mg/kg/d at 1 year), with increased microvesiculation in the adrenal cortex observed in males fed ≥200 ppm. There were no treatment related effects of chlorantraniliprole on urine corticosterone excretion in male and female rats. Chlorantraniliprole does not affect basal corticosterone synthesis in rats with histologic evidence of minimal to mild increases in the degree of microvesiculation of the adrenal cortical *zona fasciculata*.

Corticosterone Under Simulated Physiologic Stress – ACTH Stimulation Test

The utility of an ACTH stimulation test is dependent on its ability to detect suppression of serum corticosterone concentrations. The rat ACTH stimulation test was assessed using a known adrenal toxicant and inhibitor of corticosterone production, aminoglutethimide. The sensitivity of the rat ACTH stimulation test was confirmed by demonstrating that it would detect suppression of ACTH-stimulated corticosterone synthesis at aminoglutethimide doses that did not inhibit basal corticosterone production.

The effect of chlorantraniliprole on corticosterone production in ACTH-stimulated rats was evaluated in male rats dosed via the dermal route with 1000 mg/kg/day chlorantraniliprole for 1 month. In addition to the control group, a group of unshaved, nonwrapped and unwashed male control rats were included in the study to account for any possible stress due to physical manipulations during dermal dosing. The dermal route was chosen because in short term toxicity studies, an increased degree of microvesiculation was observed most consistently in male rats treated via the dermal route. ACTH (12.5 µg) was administered to all rats on the morning following the last day of dosing with chlorantraniliprole. One hour after ACTH administration, blood was collected for corticosterone measurements and adrenal glands were fixed, processed, and underwent histologic examination. Chlorantraniliprole did not decrease corticosterone production under conditions of simulated physiologic stress.

Based on these findings, the capacity of the adrenal gland to synthesize corticosterone (primary hormonal product of the *zona fasciculata*) under either non-stimulated (basal) or ACTH-

stimulated (physiologic stress) conditions was not affected by administration of chlorantraniliprole at doses that caused increased microvesiculation.

Appendix B: Metabolism Assessment

B.1 Metabolism Guidance and Considerations

Table B.2. Tabular Summary of Metabolites and Degradates

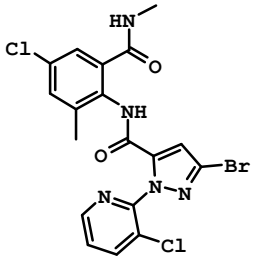
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
3-Bromo-*N*-[4-chloro-2-methyl-6-[(methylamino) carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (Chlorantraniliprole, DPX-E2Y45)	Apple	Fruit – 83.2-83.5 (0.077-0.089)		
		Leaves – 91.6-93.7 (3.803-3.180)		
	Cotton	Foliage/hulls – 24.7-68.1 (<0.01-0.04)		
		Lint/seed – 56.9 (<0.01)		
	Lettuce	Leaves – 88.7 (0.268)		
	Rice	Grain – 51.4 (0.08)		
		Hulls – 66.3 (0.117)		
		Leaves – 52.3 (2.118)		
		Sheaths – 64.9 (0.086)		
		Straw [1] – 53.8 (0.486)		
	Tomato	Fruit – 92.2 (0.012)		
		Leaves – 98.1 (1.340)		
	Rotational Crops	Lettuce – 63.9-85.2 (0.020-0.032)	Beet tops – 0.9-4.8 (<0.002-0.005)	
		Radish tops – 53.8 (0.016)		
		Radish root – 68 (0.05)		
		Soybean fodder – 45.4-63.6 (0.07-0.08)		
		Wheat forage – 53.5-84.1 (0.050-0.198)		
		Wheat hay – 50.6-73.1 (0.224-0.797)		
		Wheat grain – 85.9 (0.02)		
		Wheat straw – 36.6-73.2 (0.079-1.34)		
		Wheat chaff – 87.3 (0.39)		
	Ruminant	Milk – 23.6 (0.016)	Liver – 0.72-4.45 (0.005-0.029)	
		Kidney – 18.92 (0.016)		
		Muscle – 41.01 (0.007)		
		Fat – 34.72-75.29 (0.024-0.051)		
	Poultry	Egg yolk – 11.9-22.65 (0.059-0.106)	Liver – 2.21-3.75 (0.012-0.017)	
		Egg white – 26.18-31.62 (0.355-0409)	Muscle – 3.54 (<0.001)	
		Skin w/fat – 17.87 (0.009)		
	Rat	38.6% of administered dose in repeated dosing rat metabolism study at day 14		

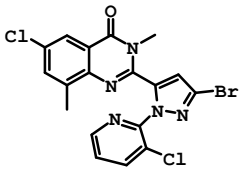
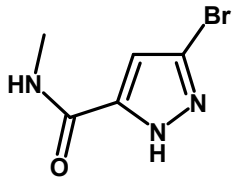
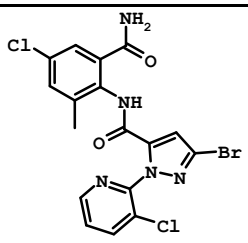
Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-chloro-3, 8-dimethyl-4(3*H*)-quinazolinone (IN-EQW78)	Rice		Grain – 1.3 (0.002)	
			Hulls – 3.2 (0.006)	
			Leaves – 4.2 (0.167)	
			Sheaths – 5.3 (0.007)	
			Straw [1] – 4.3 (0.039)	
	Rotational crops		Radish tops – 1.5 (<0.01)	
			Radish root – 1.4 (<0.01)	
			Soybean fodder – 0.6-1 (<0.01)	
			Wheat forage – 0.8-1.4 (0.001-0.002)	
			Wheat hay – 1.1-2.9 (0.005-0.022)	
			Wheat straw – 1-2.6 (0.005-0.054)	
	Ruminant	Fat – 6.35-10.99 (0.004-0.007)	Liver – 6.2 (0.040)	
			Muscle – 2.0 (<0.001)	
	Poultry		Egg white – 3.25-6.4 (0.042-0.087)	
			Muscle – 6.79 (0.002)	
			Skin w/fat – 3.10 (0.002)	
5-Bromo-*N*-methyl-1*H*-pyrazole-3-carboxamide (IN-F6L99)	Rice		Grain – 1.5 (0.002)	
			Leaves – 2.7 (0.107)	
			Sheaths – 1.2 (0.002)	
			Straw [1] – 2.5 (0.023)	
	Rotational crops	Beet tops – 0.2-10.8 (<0.001-0.013)	Lettuce – 1.4 (0.001)	
			Wheat hay – 0.2-2.4 (0.001-0.038)	
			Wheat straw – 0.5-2.6 (<0.002-0.013)	
N-[2-(Aminocarbonyl)-4-chloro-6-methylphenyl]-3-bromo-1-(3-chloro-2-pyridinyl)1*H*-pyrazole-5-carboxamide (IN-F9N04)	Rice		Leaves – 3.2 (0.134)	
			Straw [1] – 2.8 (0.025)	
	Rotational crops		Lettuce – 1.6-5.2 (0.001-0.002)	
			Beet tops – 4.1-6.2 (0.003-0.007)	
			Radish tops – 1.1 (<0.01)	
			Radish root – 2.9 (<0.01)	
			Soybean fodder – 1.8-2.0 (<0.01)	
			Wheat forage – 1.4-3.2 (0.002-0.004)	
			Wheat hay – 0.8-2.1 (0.003-0.032)	
			Wheat straw – 1.2-2.0 (0.006-0.028)	
	Poultry		Egg white – 4.37-9.23 (0.055-0.119)	
			Liver – 1.17-5.37 (0.007-0.028)	
			Skin w/fat – 8.82 (0.005)	

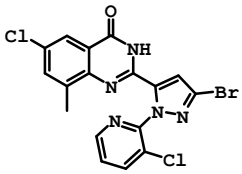
Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-chloro-8-methyl-4(3*H*)-quinazolinone (IN-GAZ70)	Rice		Leaves – 6.1 (0.244)	
			Straw [1] – 5.4 (0.049)	
	Rotational Crops		Lettuce – 0.8-1.9 (<0.001-0.001)	
			Beet tops – 1.6 (0.002)	
			Wheat hay – 0.4-2.5 (0.002-0.039)	
			Soybean fodder – 3.0-6.4 (<0.01-0.01)	
	Ruminant		Liver – 3.12 (0.020)	
			Fat – 4.86 (0.002)	
	Poultry	Egg white – 32.57-40.44 (0.421-0.548)	Egg yolk – 4.25-6.57 (0.020-0.034)	
			Skin w/fat – 1.11 (0.001)	
	Rat	In the female rat, 1.41% of administered dose in repeated dosing rat metabolism study at day 14		

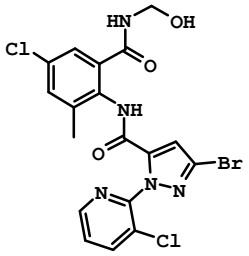
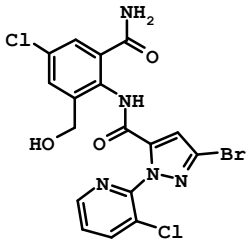
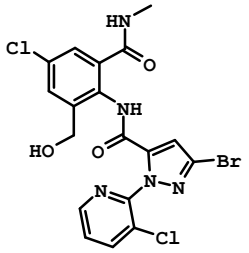
Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
3-Bromo-*N*-[4-chloro-2-[[(hydroxymethyl) amino]carbonyl]-6-methylphenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (IN-H2H20)	Rice		Leaves – 2.5 (0.101)	
			Straw [1] – 2.2 (0.02)	
	Rotational crops		Beet tops – 0.9-2.8 (0.001-0.002)	
			Wheat hay – 1.5 (0.009)	
			Wheat straw – 2-2.5 (0.007-0.009)	
	Ruminant		Kidney – 2.54 (0.002)	
			Liver – 0.65-1.21 (0.004-0.008)	
			Muscle – 5.8 (0.001)	
			Fat – 1.20 (<0.001)	
	Poultry	Egg yolk – 10.76-16.58 (0.054-0.078)	Egg white –3.49 (0.045)	
	Rat	In female rat feces, 15% of administered dose in repeated dosing rat metabolism study at day 14		
(*N*-[2-Aminocarbonyl]-4-chloro-6-(hydroxymethyl) phenyl]-3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (IN-HXH40)	Rice		Leaves – 3.7 (0.153)	
			Straw [1] – 3.4 (0.031)	
	Rotational crops		Beet tops – 5.7-9.7 (0.004-0.012)	
			Wheat forage – ≤5.7 (≤0.005)	
			Wheat hay – 2.2 (0.009)	
			Wheat straw – 1.1-1.2 (0.004)	
	Ruminant		Milk – 5.9 (0.004)	
			Liver – 0.65-2.1 (0.004-0.014)	
			Fat – 1.18 (<0.001)	
	Poultry		Liver – 2.92-3.20 (0.015-0.016)	
			Muscle – 1.10 (<0.001)	
			Skin w/fat – 1.31 (0.001)	
3-Bromo-*N*-[4-chloro-2-(hydroxymethyl)-6-[(methylamino) carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (IN-HXH44)	Rice		Leaves – 2.3 (0.088)	
			Straw [1] – 2.0 (0.018)	
	Rotational crops		Beet tops – 2.7-7.5 (0.003-0.008)	
			Wheat forage – ≤5.7 (≤0.005)	
			Wheat hay – 0.5-3.1 (0.007-0.013)	
			Wheat straw – 0.7-2.6 (0.002-0.054)	
	Ruminant	Milk – 26.9 (0.018)	Kidney – 3.35 (0.003)	
		Muscle – 10.98 (0.002)	Liver – 0.95-4.16 (0.006-0.026)	
			Fat – 1.40-1.75 (0.001-0.002)	
	Poultry		Egg yolk – 1.96 (0.011)	
			Egg white – 2.86 (0.037)	
			Liver – 1.65-2.03 (0.009-0.010)	
	Rat	10.04% of administered dose in repeated dosing rat metabolism study at day 14		

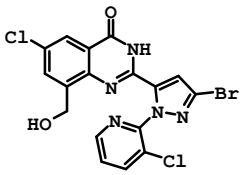
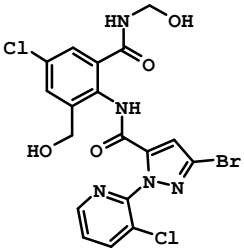
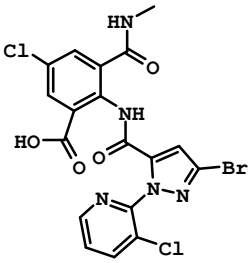
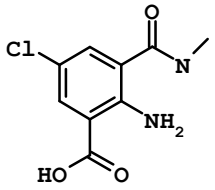
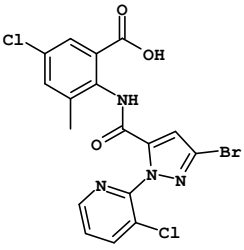
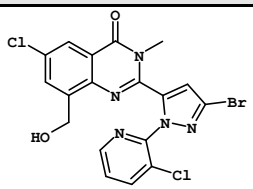
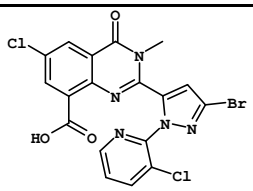
Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-chloro-8-(hydroxymethyl)-4(3*H*)-quinazolinone (IN-K7H29)	Rice		Grain – 1 (0.001)	
	Rotational crops		Wheat forage – 0.2-2.2 (<0.001-0.002)	
			Wheat straw – 0.6-1.8 (0.003-0.012)	
	Ruminant		Fat – 1.52-1.75 (<0.001-0.001)	
	Poultry	Egg yolk – 13.14-24 (0.066-0.112)	Egg white – 3.13-3.52 (0.042-0.046)	
			Liver – 2.27 (0.011)	
			Muscle – 1.03 (<0.001)	
			Skin w/fat – 3.19 (0.002)	
3-Bromo-*N*-[4-chloro-2-(hydroxymethyl)-6-[[(hydroxymethyl) amino)carbonyl] phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide (IN-K9T00)	Ruminant	Milk – 26.1 (0.017)	Kidney – 2.85 (0.002)	
	Rat	11.28% of administered dose in repeated dosing rat metabolism study at day 14		
2-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-chloro-3-[(methylamino carbonyl]benzoic acid (IN-KAA24)	Rice		Leaves – 4.3 (0.171)	
			Straw [1] – 3.9 (0.035)	
	Rotational crops		Beet tops – 1-3.2 (0.001-0.004)	
			Wheat forage – 0.1-2.1 (<0.001-0.002)	
			Wheat straw – 2.3 (0.048)	
	Ruminant		Liver – 0.64-2.6 (0.004-0.017)	
	Poultry		Egg yolk – 1.92 (0.009)	
	Rat	7.65% of administered dose in repeated dosing rat metabolism study at day 14		
2-Amino-5-chloro-3-[(methylamino) carbonyl]benzoic acid (IN-L8F56)	Rice		Grain – 1.8 (0.003)	
			Leaves – 3.3 (0.135)	
			Straw [1] – 2.9 (0.026)	
	Ruminant		Liver – 4.5-8.23 (0.028-0.052)	
			Kidney – 1.35 (0.001)	
	Poultry		Liver – 0.41-1.20 (0.002-0.006)	
(IN-GKQ52)	Ruminant		Liver – 1.3 (0.008)	
	Poultry		Egg yolk – 3.68 (0.019)	
			Liver – 1.79-5.05 (0.009-0.026)	

Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM)		Structure
		Matrices – Major Residue (≥10%TRR)	Matrices – Minor Residue (<10%TRR)	
(IN-K3X21)	Poultry		Egg white – 2.07 (0.027)	
			Muscle – 1.49 (<0.001)	
			Skin w/fat – 5.86 (0.003)	
(IN-LEM10)	Rotational crops		Beet tops – 1.3 (0.002)	
	Ruminant		Kidney – 5.24 (0.005)	
			Liver – 2.87 (0.018)	
			Fat – 1.16-6.94 (<0.001-0.005)	
Apple; 46889004; 0.268 lb ai/A (300 g ai/ha); 1.36x; 3 foliar apps. at BBCH 71, 75, and 77; 30 days. Cotton; 46979310; 0.134 lb ai/A (150 g ai/ha); 0.68x; 1 foliar app. with 0.5% surfactant to 41-day-old plants; 86 days (foliage, hulls, and lint/seed), and 126 days (foliage/hulls, lint, and seed); **or** 1 foliar app. without surfactant to 57-day-old plants; 48 days (foliage). Lettuce; 46889005; 0.268 lb ai/A (300 g ai/ha); 1.37x; 3 foliar apps. at BBCH 13, 19, and 19; 15 days. Rice; 46979738; 0.268 lb ai/A (300 g ai/ha); 1 soil drench app. at BBCH 11-12; 132 days. Tomato; 46889006; 0.268 lb ai/A (300 g ai/ha); 1.37x; 3 foliar apps. at BBCH 19-61, 19-73, and 19-81; 15 days. Rotational lettuce, beet, and wheat; 46895501; 0.268 lb ai/A (300 g ai/ha); applied to bare soil; 0-, 30-, 120, and/or 365-day PBIs. Rotational radish, soybean, and wheat; 46979311; 0.134 lb ai/A (150 g ai/ha); applied to bare soil; 30-day PBI. Goat; 46889116; 10 ppm; (5.6x for beef, 40x for dairy); orally for 7 days; 23-hour PSI. Hen; 46979424; 10 ppm; 91x; orally for 14 days; 23-hour PSI.				

Environmental Fate and Effects

Laboratory Studies Summary

Hydrolysis

Chlorantraniliprole is stable to hydrolytic degradation in pH 5 and 7 buffer solutions. It does, however, undergo rapid hydrolysis in pH 9 buffer solution. The major hydrolysis degradation product is IN-EQW78.

Photodegradation

Photodegradation of chlorantraniliprole is a predominant degradation pathway. Chlorantraniliprole has a half-life of 0.37 days in pH 7 buffer solution and 0.31 days in natural water irradiated with a Xenon arc lamp. In a water/sediment system, chlorantraniliprole had photodegradation half-lives of 22 days in loamy sand sediment and 9.9 days in sandy loam sediment system. The major photodegradation products are IN-EQW78, IN-LBA22, IN-LBA24, and IN-LBA23. A minor photodegradation product was identified as IN-ECD73.

Soil metabolism

Chlorantraniliprole is stable ($t_{1/2}$ = 228 to 924 days) in aerobic soils incubated at 25^0C. It degrades faster at higher soil temperatures of 34-35^0C and 49^0C. Major degradation products were identified as IN-F6L99, IN-EVK64, IN-EQW78, IN-ECD73, IN-GAZ70. Minor degradation products were identified IF-F9N04 and IN-EVK64. Chlorantraniliprole is also persistent ($t_{1/2}$= 231 and 125 days) under stratified redox test conditions in a sand and loam sediment/water systems. The major degradation product was identified as IN-EQW78. Minor degradations products were identified as IN-F6L99, IN-F9N04, IN-GAZ70, and IN-ECD73.

Mobility

Chlorantraniliprole is expected to be mobile in soil and aquatic environments. It has soil: water Freundlich batch equilibrium adsorption coefficients of 1.22 (K_{oc}=153, 1/n=1.0028) in a loamy sand from Spain, 9.16 (K_{oc}=509, 1/n=1.0434) in a silty clay loam from IA, 1.36 (K_{oc}=272, 1/n=0.8485) in a sandy loam from MS, 1.59 (K_{oc}= 526, 1/n=0.9370) in a loamy sand from GA, 2.34 (K_{oc}=180, 1/n=0.9256) in a loam from Italy. Because there is a positive, linear regression between K_d and soil organic carbon, it is appropriate to use K_{oc} for environmental fate modeling. Field studies support the findings in the laboratory. Radiolabelled chlorantraniliprole (applied at 0.286 lbs ai/A) had half-lives of 181 to 222 days for dissipation studies in California and Texas bareground field dissipation studies. In the Texas study, degradation products include IN-EQW78 (42% of applied @ Day 450), IN-GAZ70 (7% of applied radioactivity), IN-ECD73 (9.5%@ Day 540), IN-F6L99 (5% @ Day 120). Most of radioactivity was detected in the surface 0 to 6 inch soil layer. In the California study, degradation products include IN-EQW78 (29% of applied @ Day 741), IN-ECD73 (6.8% of applied radioactivity@ Day 740), IN-GAZ70 (5.9%@ Day 300), IN-F6L99 (2.1% @ Day 531). The maximum depth of radioactivity detection was 30-36 inches soil layer (2.7% of applied radioactivity @ Day 379).

Nonradiolabelled chlorantraniliprole (formulated as 35WG at 0.286 lbs ai/A) had half-lives of 210 days in a Minnesota study and 274 days in a Prince Edward Island study. In the Minnesota study, degradation products included IN-EQW78 (3.8% of applied @ Day 0), IN-ECD73

(4.1%@ Day 0) and IN-GAZ70 (4.1% @Day 0). Routes of dissipation for chlorantraniliprole were identified as leaching (1% of applied @ 12 to 30 inches) and runoff (<6% of applied). In the Prince Edward study, IN-EQW78 (5.3% of applied @ Day 0), IN-ECD73 (1.3%@ Day 0) and IN-GAZ70 (0.4% @Day 0) were identified. Chlorantraniliprole was detected (<0.5% of applied) at soil depths greater than 30 cm.

Nonradiolabelled chlorantraniliprole (formulated as 20SC at 0.286 lbs ai/A) on bareground plots had half-lives of 52 days in a California study, 206 days in the a Texas study, 697 days in a New Jersey study, and 1130 days in a Georgia study. In the California study, degradation products included IN-EQW78 (21% of applied @ Day 540) and IN-ECD73 (4.0%@ Day 540). Chlorantraniliprole residues were detected at depth 18 inches (45 cm). In the Texas study, degradation products included IN-EQW78 (20% of applied @ Day 540) and IN-ECD73 (2%@ Day 540). Chlorantraniliprole residues were detected at depths > 24 inches (<0.8% of applied). In the New Jersey study, degradation products included IN-EQW78 (9% of applied @ Day 475) and IN-ECD73 (4%@ Day 541). Chlorantraniliprole residues were detected at depths > 24 inches (1% of applied). In the Georgia study, degradation products included IN-EQW78 (12% of applied @ Day 540) and IN-ECD73 (6%@ Day 540). Chlorantraniliprole residues were detected at depths 12 to 18 inches (~0.33 % of applied).

Appendix C: Review of Human Research

No studies were relied on which involved human subjects.