UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES

MEMORANDUM

Date: 04-MAR-2009

SUBJECT: **Chlorantraniliprole (DPX-E2Y45).** Human Health Risk Assessment for Proposed Uses on the Tree Nut Crop Group and Pistachios and for Increases in the Established Tolerances for Pome Fruits, Stone Fruits, Grapes, and Raisins due to the Removal of Adjuvant Restrictions from the Label for Pome Fruits, Stone Fruits, and Grapes.

PC Code: 090100	**DP Barcode:** 357072
Decision No.: 398689	**Registration No.:** 352-730
Petition No.: 8F7409	**Regulatory Action:** Section 3 Registration
Risk Assessment Type: Single Chemical Aggregate	**Case No.:** NA
TXR No.: NA	**CAS No.:** 500008-45-7
MRID No.: NA	**40 CFR:** 180.628

FROM: Nancy J. Tsaur, Risk Assessor/Chemist 03/04/09
Whang Phang, Toxicologist
Risk Assessment Branch 3 (RAB3)
Health Effects Division (7509P)

THROUGH: Paula Deschamp, Branch Chief
Risk Assessment Branch 3 (RAB3)
Health Effects Division (7509P)

TO: Venus Eagle/Kable Davis, Risk Management Team 01
Insecticide Rodenticide Branch (IRB)
Registration Division (7505P)

Rec'd in PCC 3/6/2009

Introduction

This document addresses two different actions submitted to the Agency regarding chlorantraniliprole (DPX-E2Y45): the registration of one agricultural end-use product (DuPont's Altacor® WG Insecticide) for use on the tree nut crop group and pistachio as well as a proposal for the removal of adjuvant restrictions on the label for pome fruits, stone fruits, and grapes, and corresponding increases in the established tolerances on pome fruits, stone fruits, grapes, and raisins.

E.I. du Pont de Nemours and Company (DuPont) has submitted a petition (PP#8F7409) to register the end use product Altacor® WG, a 35% active ingredient (ai) water dispersible granule (WG) of chlorantraniliprole (3-bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxamide) for use in/on tree nuts (crop group 14) and pistachios and proposed the following tolerances:

Commodity	Proposed Tolerance (ppm)
Almond Hulls	5
Nut, Tree, Crop Group 14	0.07
Pistachios	0.07

In addition to the proposed use on the tree nut crop group and pistachios, DuPont is proposing increases in the established tolerances for pome fruits, stone fruits, grapes, and raisins due to the removal of adjuvant restrictions from the label for pome fruits, stone fruits, and grapes. Thus, DuPont has also proposed the following increases to existing tolerances:

Commodity	Proposed Tolerance (ppm)
Fruit, pome, group 11	0.60
Fruit, stone, group 12	2.0
Grape	2.4
Grape, raisin	5.0

HED recommends that a revised Section F be submitted for the tree nut crop group and pistachios at a lower value of 0.04 ppm. The doubling of tolerances in response to the removal of adjuvant restrictions is not applicable to tree nuts as indicated by the Chemistry Science Advisory Council (ChemSAC minutes, 10/01/2009).

The most recent human-health risk assessment was conducted in conjunction with a request for use of chlorantraniliprole on pome fruits, stone fruits, leafy vegetables, *Brassica* leafy vegetables, cucurbit vegetables, fruiting vegetables, cotton, grapes, potatoes, turf and ornamentals (S. Winfield, 03/07/08; DP#336983). The following information from the 03/07/08 risk assessment can be applied directly to this action:

- Sections 2.2-2.3: Structure and Nomenclature, Physical and Chemical Properties,
- Section 3.0: Hazard Characterization/Assessment, and
- Sections 5.1.1-5.1.8: Pesticide Metabolism and Environmental Degradation.

This document contains only those aspects of the risk assessment which are affected by the proposed Section 3 request for use of chlorantraniliprole on the tree nut crop group and pistachios, and increases in the established tolerances for pome fruits, stone fruits, grapes, and raisins due to the removal of adjuvant restrictions from the label for pome fruits, stone fruits, and grapes.

This 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 were conducted by Whang Phang (RAB3) and the occupational exposure data review, residue chemistry data review, dietary exposure assessment, and human health risk assessment were conducted by Nancy J. Tsaur (RAB3); additionally, the drinking water assessment was conducted by Stephen P. Wente of the Office of Pesticide Programs' (OPP's) Environmental Fate and Effects Division (EFED).

Table of Contents

1.0 Executive Summary 5
2.0 Proposed Use Pattern 8
3.0 Hazard Characterization/FQPA Considerations 9
4.0 Public Health and Pesticide Epidemiology Data 11
5.0 Dietary Exposure/Risk Characterization 11
5.1 Food Residue Profile 11
5.2 International Residue Limits 14
5.3 Drinking Water Residue Profile 14
5.4 Chronic Dietary Exposure and Risk 15
6.0 Residential (Non-Occupational) Exposure/Risk Characterization 16
7.0 Aggregate Risk Assessments and Risk Characterization 17
8.0 Occupational Exposure/Risk Pathway 18
8.1 Occupational Pesticide Handler Exposure and Risk 18
8.2 Occupational Post-Application Worker Exposure and Risk 18
9.0 Data Needs and Label Recommendations 19
9.1 Toxicology 19
9.2 Residue Chemistry 19
9.3 Occupational and Residential Exposure 19
Appendix A: Toxicology Assessment 20
A.1 Toxicology Data Requirements 20
A.2 Toxicity Profiles 21
Appendix B: Environmental Fate and Effects Assessment 24

1.0 EXECUTIVE SUMMARY

Chlorantraniliprole (DPX-E2Y45) is a novel anthranilic diamide insecticide that belongs to a class of compounds that acts on the ryanodine receptor (Group 28 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 one agricultural end-use product (Altacor® WG Insecticide) and HED has been asked to conduct a human health risk assessment to address the proposed tolerances and new use. This action proposes 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 the tree nut crop group, almond hulls, and pistachios. Additionally, DuPont submitted a proposal for the removal of adjuvant restrictions on the label for pome fruits, stone fruits, and grapes, and corresponding increases in the established tolerances for pome fruits, stone fruits, grapes, and raisins.

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

Use Profile
For tree nuts (crop group 14) and pistachios, application rates range from 0.04 to 0.10 lb ai/A with a re-treatment interval (RTI) of 7 days and a pre-harvest interval (PHI) of 10 days. Crops can be treated up to 4 times per season not to exceed the maximum seasonal application rate of 0.2 lb ai/A. Application is expected via aerial and ground equipment. The label associated with this Section 3 action proposes a restricted entry interval (REI) of 4 hours.

For pome fruits, stone fruits, and grapes, the use directions are the same as previously discussed in the last risk assessment except for the removal of adjuvant restrictions.

Toxicity/Hazard Assessment
Chlorantraniliprole is not genotoxic, neurotoxic, immunotoxic, carcinogenic, or teratogenic. Chlorantraniliprole is classified in Acute Toxicity Category IV for oral toxicity, dermal toxicity, inhalation toxicity, eye irritation, and primary skin irritation. Also, chlorantraniliprole is not a dermal sensitizer. There was only one toxicity study in the toxicology database that indicated chlorantraniliprole yielded an adverse effect (18-month oral/mouse). This study was used to establish a point of departure (POD) based on hepatocellular effects for the chronic dietary exposure scenario.

Food Quality Protection Act (FQPA) Considerations
Based on the hazard and exposure data, the HED chlorantraniliprole risk assessment team recommends that the FQPA SF be reduced to 1x. The recommendation was 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.

Dietary Risk Estimates (Food + Water)

A conservative chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03). DEEM™ 7.81 default processing factors and 100% crop treated (CT), and tolerance-level residues were assumed for all commodities. Drinking water was incorporated directly into the dietary exposure assessment using the chronic estimated drinking water concentration (EDWC) of 36.5 µg/L for surface water (the non-cancer, 1 in 10 year annual average). The chronic dietary risk assessment shows that the **chronic dietary risk estimates do not exceed HED's level of concern [i.e., <100% of the chronic population-adjusted dose (cPAD)].** For the general U.S. population the exposure for food and water utilized <1% of the cPAD. The chronic dietary risk estimate for the highest exposed population subgroup, children 1-2 years old, is 2% of the cPAD.

Residential Exposure

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

Aggregate-Risk Estimates

Although there is potential residential exposure, there is no residential hazard/risk associated with the route/duration of the already existing uses; therefore, aggregate exposure is comprised of food and water only, and is considered in the dietary section of this document. A chronic aggregate exposure risk assessment was assessed by incorporating the drinking water directly into the dietary exposure assessment. **As the chronic dietary exposure estimates are not of concern to HED for the general U.S. population or any population subgroup, the chronic aggregate risk is not of concern for these populations**. Due to the lack of toxicity over the acute, short- and intermediate-term via the oral and dermal routes, no risk is expected from residential exposures. Acute and cancer aggregate-risk assessments were not performed because no appropriate endpoint was available to determine the acute reference dose (aRfD) for the general population or any population subgroup and chlorantraniliprole is not carcinogenic, respectively.

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

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in the 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/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.pdf). OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Review of Human Research
No studies involving human research were relied on in this human health risk assessment.

Recommendations for Tolerances
- Tree Nut Crop Group 14, Pistachios, and Almond Hulls (PP#8F7409)

Provided a revised Section F is submitted, there are no residue chemistry, toxicology, or occupational exposure issues that would preclude granting an unconditional registration and permanent tolerances for residues of chlorantraniliprole in/on: nut, tree, group 14 at 0.04 ppm; pistachio at 0.04 ppm; and almond, hulls at 5.0 ppm.

- Pome Fruit, Stone Fruit, Grapes, and Raisins (MRID#47525301)

Provided a revised Section F is submitted, there are no residue chemistry, toxicology, or occupational exposure issues that would preclude granting a 2x increase in established tolerances for residues of chlorantraniliprole in/on: fruit, pome, group 11 at 0.6 ppm; fruit, stone, group 12 at 2.0 ppm; grape at 2.4 ppm; and grape, raisin at 5.0 ppm.

2.0 PROPOSED USE PATTERN

Tree Nuts and Pistachios (PP# 8F7409)
DuPont submitted a proposed label for Altacor® WG (EPA Reg. No. 352-730) for use on the tree nut crop group and pistachios.

Pome Fruits, Stone Fruits, and Grapes (MRID#47525301)
DuPont submitted a request for the removal of adjuvant restrictions from the Altacor® WG (EPA Reg. No. 352-730) label for pome fruits, stone fruits, and grapes. Consequently, DuPont is proposing an increase in the established tolerances for pome fruits, stone fruits, grapes, and raisins.

A summary of the proposed use patterns for the tree nut crop group and pistachios along with established use patterns of pome fruits, stone fruits, and grapes is provided in Table 2.1.

Table 2.1. Summary of Directions for Use of Chlorantraniliprole.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Tree Nuts, Crop Group 14, and Pistachio [Almonds, Beech Nut, Brazil Nut, Butternut, Cashew, Chestnut, Chinquapin, Filbert (Hazelnut), Hickory Nut, Macadamia (Bush) Nut, Pecan, and Walnut (Black and English; Persian)]						
Postemergence Broadcast by ground or air	Altacor® 35WG [352-730]	0.044-0.099	4	0.197 [221]	10	Do not apply dilute applications of more than 200 gal water per acre. Minimum spray volumes are 100 gal/A (ground) or 10 gal/A (aerial); 7-day minimum RTI; 4-hour minimum REI.
Pome Fruits, Crop Group 11 [Apple, Crabapple, Loquat, Mayhaw, Pear, Pear (Oriental), and Quince]						
Postemergence Broadcast by ground or air	Altacor® 35WG	0.055-0.099	4	0.2 [221]	14	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 10-day minimum RTI; 4-hour minimum REI.
Stone Fruits, Crop Group 12 [Apricot, Cherry (Sweet), Cherry (Tart), Nectarine, Peach, Plum, Plum (Chicksaw, Damson, Japanese), Plumcot, and Prune]						
Postemergence Broadcast by ground or air	Altacor® 35WG	0.066-0.099	4	0.2 [221]	10	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 7-day minimum RTI; 4-hour minimum REI.
Grapes						
Postemergence Broadcast by ground or air	Altacor® 35WG	0.044-0.099	4	0.2 [221]	14	Minimum spray volumes are 50 gal/A (ground) or 10 gal/A (aerial); 7-day minimum RTI; 4-hour minimum REI.

For the proposed removal of adjuvant restrictions from pome fruits, stone fruits, and grapes on the Altacor® WG label (EPA Reg. No. 352-730), the existing use restrictions are summarized below in Table 2.2.

Table 2.2. Summary of Restrictions for Use of Adjuvants on Chlorantraniliprole.

Crop/ Crop Group	Label Language Regarding Specific Crop Instructions for Adjuvants
Crop Group 11 Pome Fruit	Do not use an adjuvant with applications of Chlorantraniliprole 35WG within 60 days of harvest.
Crop Group 12 Stone Fruit	For sweet cherry and tart cherry: Do not use an adjuvant with applications of Chlorantraniliprole 35WG.
Grapes	Do not use an adjuvant with applications of Chlorantraniliprole 35WG.

HED Conclusions: HED concludes that the use directions provided in the submitted label are sufficient and the label may be revised to remove the restrictions of adjuvants.

3.0 HAZARD CHARACTERIZATION/FQPA CONSIDERATIONS

References:

- *Chlorantraniliprole (DPX-E2Y45) Toxicology Assessment.* Mary Manibusan, TXR #0054555, DP#'s336940, 337737, 343520, and 345100, 11/17/2007.

- *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.* Sarah Winfield, DP#336983, 03/07/08.

The toxicology database for chlorantraniliprole is complete and considered adequate for this risk assessment (including 40 CFR 158.500 requirements for dermal toxicity, immunotoxicity, and acute/subchronic neurotoxicity effective December 26, 2007). The hazard characterization, dose response considerations, absorption, distribution, metabolism, excretion (ADME) determinations, FQPA safety factor determination, mode of action, and toxicological effects are detailed in the previous risk assessment (DP#336983, S. Winfield, 03/07/08). No new data are available at this time. Please refer to the listed references for further extensive details and refer to Appendix A for the toxicity profile tables. Since there are no new toxicity data associated with this action, the hazard characterization and endpoint selection from the previous risk assessment are applied directly to this section.

Based on the hazard and exposure data, the HED chlorantraniliprole risk assessment team recommends that the FQPA SF 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.

Tables 3.1 and 3.2 summarize the toxicological doses and endpoints for chlorantraniliprole for use in dietary and occupational human health risk assessments, respectively.

Table 3.1. 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 3.2. 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

4.0 PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

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

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

5.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

References:

- *Chlorantraniliprole (DPX-E2Y45). Summary of Analytical Chemistry and Residue Data. Section 3 Registration for Proposed Uses on Tree Nuts and Pistachios and for Increases in the Established Tolerances for Pome Fruit, Stone Fruit, Grape, and Raisin due to the Removal of Adjuvant Restrictions from the Label for Pome Fruit, Stone Fruit, and Grape.* DP#357727, Nancy J. Tsaur, 03/03/09.

- *Chlorantraniliprole (DPX-E2Y45). Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action for new use on tree nuts (and pistachios) and for a 2x modification of tolerances set on pome fruit, stone fruit, grapes, and raisins.* DP#357728, Nancy J. Tsaur, 02/09/09.

The exposure pathways resulting from use of this chemical are dietary (food and drinking water), residential, and occupational. The residue chemistry data submitted in support of the proposed use and increased existing tolerances were summarized in the HED memorandum by N. Tsaur DP#357727, (03/03/09). The chronic dietary exposure assessment was completed in a HED memorandum by N. Tsaur (02/09/09, DP#357728).

5.1 Food Residue Profile

References:

- *Chlorantraniliprole (DPX-E2Y45). Report of the Residues of Concern Knowledgebase Subcommittee.* DP#343519, Christine Olinger, 02/29/08.

- *Review of Proposed Tolerance Enforcement Methods for Chlorantraniliprole.* DP#340358, Charles J. Stafford, 02/06/08.

The nature of the residue in plants and livestock is adequately understood based on acceptable metabolism studies. Most residues are found on the surface of plants and HED has determined that the residue of concern is the parent chlorantraniliprole (C. Olinger, DP#343519, 02/29/09). 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. In the ruminant metabolism study, the parent was the major terminal residue identified in kidney, muscle, and fat, and it was also a residue in liver and milk. In the poultry study, the parent was also the major residue in eggs and skin with fat, and

was also detected in liver and muscle. The LC-MS/MS method, DuPont-11374, was used for data collection and as an enforcement method for plant commodities. The enforcement method for livestock commodities is an LC-MS/MS method described in MRID 46889003. Both plant and livestock methods have been reviewed and accepted by Agency chemists in the Analytical Chemistry Branch (ACB) of the Biological and Economic Analysis Division (BEAD) (DP#340358, C. Stafford, 02/06/08). 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 minimal RTIs and PHIs.

There are adequate storage stability data for plant and livestock matrices. Chlorantraniliprole was demonstrated to be stable for up to 24 months in/on various crop matrices and for 12 months in representative processed matrices.

Tree Nuts (PP#8F7409)

The crop field trial residue data on almonds and pecans (representatives of the tree nut crop group and pistachios) are classified as scientifically acceptable. The residue data reflect the use of two foliar air blast applications of the 35% ai WG formulation made to almond and pecan trees at 0.10 lb/ai/A/application, with a 6 to 8 day RTI, for a total seasonal rate of 0.20 lb/ai/A. Applications were made using ground equipment (airblast sprayer) in spray volumes of 93 to 106 gallons/A. An adjuvant was not added to the spray mixture for all applications. Almonds and pecans were harvested at the 10-day PHI.

The results from these trials show that maximum residues of chlorantraniliprole in/on treated representative commodities of tree nuts harvested at PHIs of 9 to 11 days are as follows: (i) for almond nutmeat – 0.003 to 0.009 mg/kg, (ii) for almond hull – 0.37 to 1.7 mg/kg, and (iii) for pecan nutmeat – not detected (<0.003 mg/kg) to 0.016 mg/kg. These data indicate that there is no significant difference in residues in/on tree nuts harvested at a 10 day PHI following applications. The results of the field trials are summarized below in Table 5.1.1.

Table 5.1.1. Summary of Residue Data from Crop Field Trials with Chlorantraniliprole. †

Commodity	Total Applic. Rate (lb a.i./A) (kg a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT‡	Median (STMdR)	Mean (STMR[a])	Std. Dev.
Almond Nutmeat	0.1993-0.2032	10-11	12	<0.01	<0.01	<0.01	<0.01	<0.01	---
Almond Hull			12	0.37	1.7	1.6	0.75	0.85	0.44
Pecan Nutmeat	0.201-0.2032	9-10	12	<0.01	0.016	0.015	0.01	0.012	0.0024

† For summary results, the LOQ (0.01 ppm) was used to calculate all values reported at or below the LOQ.
‡ HAFT = Highest Average Field Trial.
[a] STMR = Supervised Trial Mean Residue.

Except for almond hulls, the available data indicate that the appropriate tolerances for residues of chlorantraniliprole in/on the tree nut crop group and pistachios should be not be modified by the 2x factor in accordance with the impact of adjuvants supported by the Chemistry Science Advisory Council (ChemSAC minutes, 10/01/08). Since the nutmeat does not come in contact with adjuvants, only almond hulls should be modified with the 2x factor while tree nuts remain

unmodified at the 1x calculated tolerance. Thus, the available data for the representative crops (almond and pecan) support a tolerance of 0.04 ppm for residues of chlorantraniliprole per se in/on tree nuts (crop group 14) and pistachios, and a tolerance of 5.0 ppm for residues of chlorantraniliprole per se in/on almond hulls. **A revised Section F should be submitted to include the appropriate tolerance for tree nuts and pistachios, as well as the correct commodity definitions as listed in Table 5.1.2.**

Pome Fruit, Stone Fruit, and Grapes (MRID#47525301)
Currently, there are existing tolerances for residues of chlorantraniliprole in/on pome fruits (0.3 ppm), stone fruits (1.0 ppm), grapes (1.2 ppm), and raisins (2.5 ppm).

DuPont submitted a summary of residue data that was previously submitted in connection with an OECD Joint review (U.S. field trials described in Annex B.7.6 supervised trials.doc) and requested that the use of adjuvant restrictions be removed from the label for pome fruits, stone fruits, and grapes (MRID#47525301). Also, they proposed the tolerances for residues of chlorantraniliprole in/on these raw agricultural commodities and their processed commodities be doubled.

The ChemSAC initially examined these data and agreed that the average ratio of chlorantraniliprole residues in crops in the presence of adjuvant residues as compared to residues without adjuvant is about 2x (ChemSAC minutes, 04/16/08). ChemSAC then revisited this issue in October of 2008 to specify "for almond hulls, use 2x, for nuts, use 1x" in regards to crop group 14 (ChemSAC minutes, 10/01/08).

With the proposed removal of adjuvant restrictions from the WG label for pome fruits, stone fruits, and grapes, the proposed uses and the data submitted adequately support the 2x increases in the established tolerances for residues of chlorantraniliprole in/on stone fruits, pome fruits, grapes, and raisins. **A revised Section F should be submitted to include the appropriate tolerances for pome fruits, stone fruits, grapes, and raisins, as well as the correct commodity definitions as listed in Table 5.1.2.**

Table 5.1.2. Tolerance Summary for Chlorantraniliprole.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Almond Hulls	5	5.0	*Almond, hulls*
Nut, Tree, Crop Group 14	0.07	0.04	*Nut, tree, group 14*
Pistachios	0.07	0.04	*Pistachio*
Fruit, pome, group 11	0.60*	0.60	No Section F was submitted for any of the proposed increases on established tolerances.
Fruit, stone, group 12	2.0*	2.0	
Grape	2.4*	2.4	
Grape, raisin	5.0*	5.0	

* The petitioner has proposed 2x of the established tolerances. The established tolerances, as listed in the 40 CFR, are 0.30 ppm for pome fruits, 1.0 ppm for stone fruits, 1.2 ppm for grapes, and 2.5 ppm for raisins.

There are adequate storage stability data for plant and livestock matrices. Chlorantraniliprole was demonstrated to be stable for up to 24 months in/on various crop matrices and for 12 months in representative processed matrices. The maximum storage duration for tree nut commodity samples was 4.6 months. Chlorantraniliprole was also demonstrated to be stable for 6 months in

milk and for 3 months in bovine tissues. The maximum storage duration for milk and tissue samples, collected from the feeding study, was <3 months.

Livestock commodities associated with the new addition of use on tree nuts include almond hulls. The currently established tolerances for meat and milk (0.01 ppm in milk, meat, fat, and meat byproducts of cattle, goats, horses and sheep) are adequate. Tolerances for poultry and eggs are not required to support the proposed uses. **No change in tolerances on livestock commodities is required for this petition.**

5.2 International Residue Limits

No international harmonization issues are associated with this petition, as there are no established Canadian, Mexican, or Codex Maximum Residue Limits (MRLs) for residues of chlorantraniliprole on the proposed crops.

5.3 Drinking Water Residue Profile

References:

- *Chlorantraniliprole Drinking Water Assessment for Crop Group 14 - Tree Nuts, Almond Hulls, and Pistachios.* DP#357076, Stephen P. Wente, 01/29/09.

- *Drinking Water Assessment for Chlorantraniliprole.* DP#348133, James A. Hetrick, 01/10/08.

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 ground water.

EFED has completed a drinking water assessment for chlorantraniliprole (S. Wente, DP#357076, 01/29/09) and they have indicated that the previous assessment conducted by James Hetrick (DP#348133, 01/10/08) yields higher EDWCs. At this time, the Agency lacks sufficient monitoring exposure data for use in risk assessments, as this is a relatively 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 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 EDWC for chlorantraniliprole was 26.86 µg/L based on nursery applications in Tennessee. For the 1 in 10 year annual average, the highest PRZM/EXAMS EDWC was 3.65 µg/L, also based on nursery applications in Tennessee. For the 30 year annual average, the highest EDWC was 1.72 µg/L based on nursery applications in Florida.

Ground Water. In lieu of sufficient ground water monitoring data for chlorantraniliprole, the Tier 1 ground water screening model SCI-GROW was used to estimate concentration of chlorantraniliprole in shallow ground water sources. Ornamental plants, which represent the highest registered annual use rate (0.50 lbs ai/A) were used for the modeling, and resulted in a ground water EDWC of 1.06 µg/L.

Table 5.3 summarizes the EDWCs provided by EFED.

Table 5.3. Summary of Estimated Surface Water and Ground Water Concentrations for Chlorantraniliprole.		
	Surface Water Concentration (ppb [a])	Ground Water Concentration (ppb [b])
Acute	26.86	1.06
Chronic (non-cancer, 1 in 10 year annual average)	3.65	
Chronic (cancer, 30-year annual average)	1.72	

[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 0.50 lb ai/A, a K_{oc} of 272, and a half-life of 509 days from the aerobic soil metabolism study.

5.4 Chronic Dietary Exposure and Risk

Reference:

- *Chlorantraniliprole (DPX-E2Y45). Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action for new use on tree nuts (and pistachios) and for a 2x modification of tolerances set on pome fruit, stone fruit, grapes, and raisins.* DP#357728, Nancy J. Tsaur, 02/09/2009.

A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using the DEEM-FCID™ (Version 2.03), which uses food consumption data from the United States Department of Agriculture (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

No toxic effects attributable to a single (i.e., acute) exposure to chlorantraniliprole have been identified. Therefore, an aRfD has not been established for chlorantraniliprole and an acute dietary exposure assessment is not required. Also, there is no evidence that chlorantraniliprole is carcinogenic to humans; therefore, a dietary cancer assessment is not required.

The 1994-96, 98 CSFII data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessments, an estimate of the residue level in each food or food form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

A conservative chronic dietary assessment was conducted assuming tolerance-level residues for all commodities. DEEM™ 7.81 default processing factors and 100% CT were assumed for all commodities. Estimates of drinking water were incorporated directly into the dietary assessment using the EDWC of 3.65 µg/L for surface water concentrations (the maximum value relevant to chronic exposure). With the increased dietary exposure from the new use on tree nuts and the increased existing tolerances associated with the removal of adjuvant restrictions, the chronic dietary risk estimates have increased. Currently, for all included commodities for all registered and proposed uses, **the chronic dietary risk estimates do not exceed HED's level of concern (i.e., <100% cPAD).** For the general U.S. population the exposure for food and water utilized is still less than 1% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 1-2 years old, is 2% of the cPAD. Table 5.4 summarizes the results from the chronic dietary assessment.

Table 5.4. Results of Chronic Dietary Exposure and Risk Estimates for Chlorantraniliprole.*

Population Subgroup	cPAD (mg/kg/day)	Chronic Estimates (Food and Drinking Water)	
		Exposure (mg/kg/day)	Risk (%cPAD)
U.S. Population	1.58	0.011614	<1
All infants		0.015306	1
Children 1-2 yrs		**0.032600**	**2**
Children 3-5 yrs		0.024273	<2
Children 6-12 yrs		0.013979	<1
Youth 13-19 yrs		0.008616	<1
Adults 20-49 yrs		0.009591	<1
Adults 50+ yrs		0.010252	<1
Females 13-49 yrs		0.009798	<1

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

6.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

DuPont has previously registered 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

Aggregate exposure risk assessments were assessed by incorporating the drinking water directly into the dietary exposure assessment for the chronic exposure scenario. 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. Acute and cancer aggregate risk assessments were not performed because no appropriate endpoint was available to determine the aRfD for the general population or any population subgroup, as well as the fact that chlorantraniliprole is not carcinogenic.

The chronic dietary exposure estimates are not of concern to HED for the general U.S. population and all population subgroups (see Table 5.4). Therefore, the chronic aggregate risk for chlorantraniliprole does not exceed HED's level of concern for the general U.S. population or any population subgroups.

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).

8.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

8.1 Occupational Pesticide Handler Exposure and Risk

As mentioned in Section 2.1, DuPont is registering Altacor® WG for use on the tree nut crop group and pistachios. For tree nuts and pistachios, the maximum application rate is 0.10 lb ai/A with an RTI of 7 days and a PHI of 10 days. Application is expected via aerial and ground sprays (see Table 2.1 for a summary of the proposed use patterns). 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.

8.2 Occupational Post-Application Worker Exposure and Risk

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

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

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

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

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

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

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

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

9.0 DATA NEEDS AND LABEL RECOMMENDATIONS

9.1 Toxicology

- None.

9.2 Residue Chemistry

Tree Nuts and Pistachios (PP# 8F7409)

- **A revised Section F must be submitted to include the appropriate tolerance for the tree nut crop group and pistachios, as well as the correct commodity definitions as listed in Table 5.1.2.**

Pome Fruit, Stone Fruit, and Grapes (MRID#47525301)

- **A revised Section F should be submitted to include the appropriate tolerances for pome fruits, stone fruits, grapes, and raisins, as well as the correct commodity definitions as listed in Table 5.1.2.**

9.3 Occupational and Residential Exposure

- None.

Appendix A: Toxicology Assessment

Reference:

- *Chlorantraniliprole (DPX-E2Y45) Toxicology Assessment*, Mary Manibusan. TXR #0054555, DP#336940, DP#337737, DP#343520, DP#345100, 11/17/07.

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 Chlorantraniliprole (DPX-E2Y45)

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. Increased microvesiculation of adrenal cortex in males only, with no light or electronic microscopic

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**
				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: pre-mating: P1 m: 0, 12, 60, 238, 1199 F1 m: 0, 18, 89, 370, 1926	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 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.

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**
	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			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.

Appendix B: Environmental Fate and Effects Assessment

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^{0}C. It degrades faster at higher soil temperatures of 34-35^{0}C and 49^{0}C. 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).

cc: N. Tsaur
RDI: RAB3 Branch (02/24/09); N. Dodd (03/02/09); B. O'Keefe (03/02/09); P. Deschamp (03/03/09)
N. Tsaur: S-10322: Potomac Yard 1 (PY1): (703) 603-8905: 7509P: RAB3

13544

R167832

Chemical Name: Chlorantraniliprole

PC Code: 090100
HED File Code: 14000 Risk Reviews
Memo Date: 3/4/2009
File ID: 00000000
Accession #: 000-00-0127

HED Records Reference Center
3/10/2009