Invasive Species Program

Health Assessment

Application of Chlorantraniliprole to Non-Commercial Turf for Japanese Beetle Treatment

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Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

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LIST OF KEY ABBREVIATIONS AND ACRONYMS

A	acre
a.i.	active ingredient
ACTH	adenocorticotropic hormone
atm m^3/mole	atmospheres cubic meter per mole
AUC	area under the curve
BMD	benchmark dose
BMDL	lower 95% confidence limit on the BMD
BMDS	benchmark dose software
BMR	benchmark response
BW	body weight
CalEPA	California Environmental Protection Agency
CDFA	California Department of Food and Agriculture (within CalEPA)
D	dose
DPR	California Department of Pesticide Regulation (within CalEPA)
ET	exposure time
F	female
FAO	Food and Agriculture Organization (of the United Nations)
g/mol	grams per mole
HDT	highest dose tested
JB	Japanese Beetle
K_{oc}	soil organic carbon-water partition coefficient
K_{ow}	octanol-water partition coefficient
M	male
µg/kg	micrograms per kilogram
mg/L	milligrams per liter
mg/kg	milligrams per kilogram of body weight
mg/kg-day	milligrams per kilogram of body weight per day
mm Hg	millimeter mercury
NOAEL	no-observed-adverse-effect level (mg/day or mg/kg-day)
OEHHA	Office of Environmental Health Hazard Assessment (within CalEPA)
ppb	parts per billion (e.g., µg/kg)
ppm	parts per million (e.g., mg/kg)
POD	point of departure
RfD	reference dose
RyR2	ryanodine receptor
$t_{½}$	half-life
TC	transfer coefficient
TDR	turf dislodgeable residue (µg/cm^2)
USDA	United States Department of Agriculture
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

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EXECUTIVE SUMMARY

This technical report of the Office of Environmental Health Hazard Assessment (OEHHA) describes a screening-level health risk assessment of potential residential exposures to the insecticide chlorantraniliprole from soil and turf treatment by the California Department of Food and Agriculture (CDFA) to control the Japanese Beetle (JB) (*Popillia japonica*).

JB is an invasive species in North America, and the larvae of this beetle are considered to be a serious pest in turf. The adult beetles also damage a wide variety of ornamental and agricultural plants. Under the invasive species treatment program, CDFA has used various insecticides in managing and controlling JB. Recently, CDFA conducted treatments using Acelepryn®, a liquid formulation of chlorantraniliprole, for soil and turf treatment targeting the young larvae feeding in the shallow root zone.

Chlorantraniliprole has a chemical structure similar to that of ryanodine, which is an alkaloid found in the South American plant *Ryania speciosa*, Salicaceae. It binds to the specific receptors on the muscle fibers of insects, and at a sufficiently high enough concentration causes lethargy and muscle paralysis and death in insects. It is classified by the US Environmental Protection Agency (US EPA) as a “reduced risk” pesticide when used on certain fruits and produce. Chlorantraniliprole was registered as the active ingredient in Acelepryn® with label use on turf and ornamentals on May 6, 2008.

As part of the toxicity review, OEHHA performed a thorough literature search in early 2019. Based on the toxicity studies reviewed and reports released by US EPA and other regulatory bodies, there is no information to indicate chlorantraniliprole is genotoxic, neurotoxic, immunotoxic, carcinogenic or teratogenic. For repeated exposures, the adrenal gland and liver are the main target organs. In subchronic and chronic oral rodent studies, the active ingredient caused microvesiculation in the adrenal cortex, increase in relative liver weight, and centrilobular hepatocellular hypertrophy. For the purpose of this screening-level risk assessment, the increase in relative liver weight in female rats reported in a 28-day dietary rat study by Donner (2006a) is determined to be the critical endpoint with an oral NOAEL (no-observed adverse effect level) of 24 milligrams per kilogram of bodyweight per day (mg/kg-day). This value is supported by an oral NOAEL of 26 mg/kg-day for liver effects in an 18-month dietary mouse study reported by Finlay (2006b). For dermal exposure, OEHHA selected a benchmark dose level of 166 mg/kg-day for decreased body weight gain in male rats exposed dermally to chlorantraniliprole for 28 days as the critical endpoint.

OEHHA conducted a screening-level exposure assessment of potential residential exposures resulting from CDFA’s soil and turf treatment with chlorantraniliprole for controlling JB. It is based on the approaches and methods described in the Standard Operating Procedure for Residential Pesticide Exposure Assessment (US EPA, 2012a),

and environmental monitoring data provided by the California Department of Pesticide Regulation (DPR) (DPR, 2020). OEHHA quantitatively evaluated relevant oral and dermal exposure pathways. The inhalation exposure pathway was not evaluated as all air samples collected during the applications were below detection limits.

JB detection is sporadic and the pest is only vulnerable to chlorantraniliprole at a specific time in its life cycle, as young larvae in the shallow root zone. A residential backyard is unlikely to be treated every year or more than 2-3 times a year. However, chlorantraniliprole is stable in soil and half-lives ranging from 52 days to over 200 days have been reported, depending on soil composition. Residents in treated areas can be exposed to residues on soil and turf following treatment. Exposure to children is of particular concern as they may play in a backyard and be exposed to the residues from dermal contact and incidental ingestion of the materials through hand-to-mouth contact. Due to their behavior and relatively high intake and dermal contact rates adjusted for body weight, children are considered an especially sensitive population. Maximum and mean monitoring levels and exposure parameters specific to 1 to 2 year olds (1<2) were used in evaluating these exposure pathways and calculating the high-end and mean exposure estimates.

For this screening-level risk assessment, OEHHA calculated reference doses (RfDs) for oral pathways at 80 micrograms per kilogram of bodyweight per day (µg/kg-day) and for dermal pathways at 533.3 µg/kg-day. RfDs were calculated from route-specific points of departure and a combined uncertainty factor (UF) of 300 to evaluate non-cancer hazards. The combined UF was composed of a factor of 10 for extrapolating from test animals to humans and a factor of 30 for variation in a diverse human population.

High-end and mean dose estimates were calculated for three exposure pathways:

- Dermal exposure to dislodgeable residue on turf
- Hand-to-mouth Ingestion of dislodgeable residue on turf
- Incidental ingestion of turf and soil

Comparing the dose estimates for each exposure pathway with the corresponding RfD, OEHHA determined that all hazard quotients are less than one, indicating that the use of chlorantraniliprole on turf for the treatment of JB by CDFA is not likely to pose a health hazard to residents.

I. INTRODUCTION

This technical report of the Office of Environmental Health Hazard Assessment (OEHHA) describes a screening-level health risk assessment of residential exposures to the insecticide chlorantraniliprole from soil and turf treatment by the California Department of Food and Agriculture (CFDA) to control the Japanese Beetle (JB) (*Popillia japonica*).

JB is an invasive species in North America, and the larvae of this beetle are considered a serious pest in turf. The adult beetles also damage a wide variety of ornamental and agricultural plants. CDFA is mandated to protect California's agriculture from invasive species such as JB. To prevent JB infestations, CDFA enforces the Japanese Beetle Exterior Quarantine, Title 3 of the California Code of Regulations, Section 301.48. CDFA also has an active eradication program in place for any incipient populations of JB per the requirements of the US Domestic Japanese Beetle Harmonization Plan. CDFA conducts statewide detection trapping to intercept JB, including in residential areas, and a single beetle find in a trap may trigger a delimitation survey to further identify the significance of the find. If further detection and trapping indicates that JB may be present (defined as two adult JB detections within three miles within the same year, or a single larva, pupa, or egg detected), an eradication project is initiated, which may include foliar and ground application of Acelepryn® (active ingredient (a.i.) chlorantraniliprole).

Chlorantraniliprole is an insecticide of the ryanoid class; it has a chemical structure similar to that of ryanodine, which is an alkaloid found in the South American plant *Ryania speciosa*, Salicaceae. It binds to the specific receptors on the muscle fibers of insects, and at sufficiently high concentration causes lethargy, muscle paralysis, and death. It controls the insect through unregulated activation of ryanodine receptor channels leading to internal calcium store depletion that impairs regulation of muscle contraction (Carver, 2007). Chlorantraniliprole was first registered by the US Environmental Protection Agency (US EPA) in 2008 (US EPA, 2016) as an insecticide called Rynaxypyr® Technical (352-728), and as a product called Acelepryn® with label use on turf and ornamentals (PestWeb, 2008). As of April 2007, chlorantraniliprole is classified as a "reduced risk" pesticide when used on apple, peach, pear, tomato, lettuce and turf by the Reduced Risk Committee of the US EPA (2008). Food tolerances are established for several crops (US EPA, 2009a).

OEHHA provides scientific support to the CDFA invasive species program by evaluating the toxicity, human exposure, and potential health risk of chemicals used by CDFA under the invasive species program. The California Department of Pesticide Regulation (DPR) is responsible for environmental monitoring of the pesticide treatments and preparation of monitoring reports. Upon request from CDFA, OEHHA uses DPR's monitoring data to assess human exposure and potential health risk.

In 2016, CDFA carried out treatments for JB in Sacramento and Santa Clara Counties; they consisted of spray applications of Acelepryn® to turf, ground cover, soil around rose plants, and bare soil under other ornamental host plants. DPR monitored the treatments of properties that occurred on April 29, 2016 in Sacramento County, and May 3, 2016 in Santa Clara County. In June 2020, DPR released a memo with the results of their environmental monitoring of these applications. Using the data provided in the memo, OEHHA conducted a screening-level health risk assessment of potential human exposures resulting from the use of chlorantraniliprole (a.i. in Acelepryn®) on soil and turf to control JB. This report describes the approach, method and data used, and findings of the assessment.

II. PHYSICAL AND CHEMICAL PROPERTIES, ENVIRONMENTAL FATE AND TRANSPORT

Chlorantraniliprole is the common name for 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. The chemical manufacturer, DuPont, refers to the a.i. as DPX-E2Y45. Chlorantraniliprole is sparingly soluble in water and is not volatile at ambient temperature. The chemical structure of chlorantraniliprole is shown in Figure 1 below, and some of its physical and chemical properties are listed in Table 1.

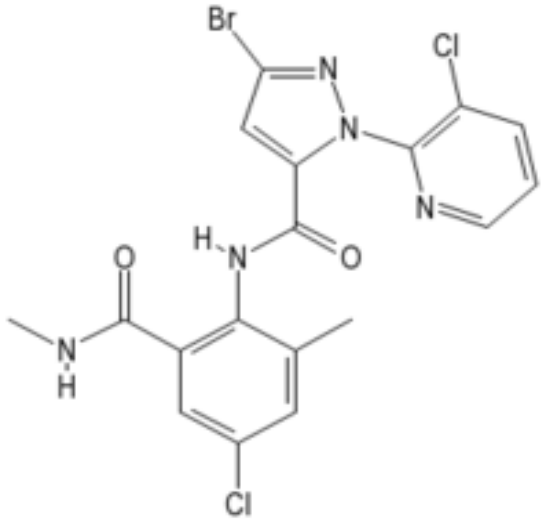

Figure 1: Chemical structure of chlorantraniliprole

Table 1. Chemical and physical properties of chlorantraniliprole.

Property	Value
Molecular weight	483.15 g/mole
Water solubility (20 °C)	1.023 mg/L (deionized water)[a] 0.880 mg/L (pH 7)[a]
Vapor pressure (25 °C[b])	2.1 x 10^{-13} mm Hg[b]; 1.57 x 10^{-13} Torr[a]
Hydrolysis half-life	Stable (pH 5 & 7); rapid hydrolysis (pH 9)[b]
Aqueous photolysis half-life	0.37 days pH 7[b]
Anaerobic aquatic metabolism half-life	208 days (loam soil, pH 7)[b]
Aerobic soil degradation half-life 25 °C	228-924 days at 25 °C[a]
Soil photolysis half-life (water/sediment system)	9.9 days (sandy loam) to 22 days (loamy sand)
Soil Dissipation (0.286 lb a.i./A) at 0 to 6 inches	181 to 222 days (bare ground)[c]
Soil Dissipation at 30 to 36 inches	379 days (2.7%)
Soil Dissipation of 20SC formulation (0.286 lb a.i./A)	52 days (California) 206 days (Texas) 697 days (New Jersey) 1130 days (Georgia)
Terrestrial field dissipation on turf (0 to 24 inches)	DT_{50} 150 to 258 days
Henry's Law constant	3.1 x 10^{-15} atm m^3/mole[a]
Octanol-water partitioning coefficient (K_{ow}, 20 °C)	589 (deionized)[a]; 721 (pH 7)[a]
Soil sorption coefficient (K_{oc})(mean values)	153 L/g (loam sand) – 526 L/g (loamy sand)[a]
Dissociation constant water (pKa)	ca. 10.88±0.71[a,c] at 20 °C
Soil organic carbon-water partitioning coefficient (K_{oc})	153 to 526 (loamy sand)[c]

[a] Data from US EPA 2008 and EFSA 2013, except as noted;
[b] Menrath 2012; [c] US EPA 2009b

In the environment, the principal routes of dissipation for chlorantraniliprole are expected to be alkaline-catalyzed hydrolysis, and photodegradation in water. In a water/sediment system, chlorantraniliprole has photodegradation half-lives ($t_{½}$) of 9.9 days in a sandy loam sediment, and 22 days in a loamy sand sediment (US EPA, 2009). It is stable in aerobic soils incubated at 25 °C with $t_{½}$ of 228 to 924 days. Dissipation studies in California and Texas bare ground fields showed $t_{½}$ of 181 to 222 days for a radiolabeled chlorantraniliprole at an application rate of 0.286 lb a.i./acre. Most of the radioactivity in the soil was detected in the surface 0 to 6-inches. When applied as a pesticide formulation, the $t_{½}$ of chlorantraniliprole on bare ground soils at an applicate rate of 0.286 lbs a.i./acre were: 52 days (California), 206 days (Texas), 697 days (New Jersey), and 1130 days (Georgia)(Sharma et al.,2005).

Based on two terrestrial field dissipation studies from New Jersey and Georgia, very little loss of chlorantraniliprole (1–4%) was from runoff and leaching (Huang, 2006a,b; APVMA, 2008). These studies showed that the residues were found primarily in the grass and thatch (0-2 inches) immediately after application. Chlorantraniliprole residues found below 6 inches were minimal, and only a small amount of migration of residues was found in the uppermost soil segment (2-24 inches) and at lower depths. The largest amount of residues was found in the thatch through the first 30 days and a significant portion remained there through 182 days.

Nine degradation products or metabolites have been identified in environmental fate studies (i.e., IN-EQW78, IN-LBA22, IN-LBA24, IN-LBA23, IN-ECD73, IN-F6L99, IN-EVK64, IN-F9N04, and IN-GAZ70). Chemical structures of the above metabolites, and other information such as the chemical names, results from the acute toxicity studies and bacterial reverse mutation assays are provided when available in Appendix A. The degradation product found in the highest concentration was IN-LBA22 (90%) in the aqueous photolysis study. The following degradation products from the bare field dissipation studies from California and Texas using radiolabeled chlorantraniliprole (0.286 lb/acre) have been identified as follows: IN-EQW78 ($\leq$ 42%); IN-GAZ70 ($\leq$ 7%); IN-ECD73 ($\leq$ 9.5%); and IN-F6L99 ($\leq$ 5%). Most of the radioactive metabolites were detected in the surface soil (0 to 6 inches). The available data from these degradation products showed no indication that they are more toxic than the parent compound (US EPA, 2009).

III. TOXICITY PROFILE

This section describes pharmacokinetics and metabolism, human and animal toxicity, determinations of toxicity endpoints, and points of departure (PODs) of chlorantraniliprole.

A. Pharmacokinetics and Metabolism

Chlorantraniliprole metabolism and pharmacokinetics have been studied extensively in laboratory animals such as rats, mice and dogs. In rats, the absorption was rapid after low (10 milligrams per kilogram [mg/kg]) and high (200 mg/kg) single oral dose administration with peak concentration occurring at 5 to 12 hours after dose. The plasma elimination half-lives ranged from 38 to 82 hours. The tissue distribution of the absorbed dose was extensive and indicated low potential for accumulation of residues (US EPA, 2012). Female rats had a longer elimination half-life and higher area under the curve (AUC) in plasma than males, which was consistent with the higher tissue residues found in females. Excretion was substantially completed by 42 to 72 hours after dosing, with fecal excretion being the primary route of elimination, followed by urine. No significant excretion occurred by exhalation. Metabolism of the absorbed dose was extensive showing sex difference in metabolite formation, with greater

hydroxylation metabolites found in males. Additional details for the two metabolism studies in rats are provided below.

In a rat metabolism study using ^{14}C-radiolabeled chlorantraniliprole at a dose of 10 mg/kg-day by oral gavage with 3 rats/group (Male (M): 2 groups; Female (F): 7 groups), males were dosed for 14-days and females were treated for 4, 8, 11 and 14 days. In this study the highest concentrations of residue were found in plasma, and demonstrated that females had higher ^{14}C residues in plasma and tissues than males. After cessation of dosing, ^{14}C residues were readily eliminated in both sexes. The potential of accumulation of chlorantraniliprole was considered to be minimal since the tissue to plasma ratios were less than one in both sexes at all time-points. The majority of radiolabel was excreted unchanged in feces (M:73%; F: 82%) through 7days post treatment after the 14 day dosing period. ^{14}C- radiolabeled chlorantraniliprole excreted in urine was 17% for males (M) and 12% for females (F), respectively (Himmelstein, 2006a in DPR, 2008).

In another rat metabolism study, 1, 4 or 8 rats/sex/group received a single oral gavage dose of ^{14}C chlorantraniliprole at 10 mg/kg and/or 200 mg/kg (Himmelstein, 2006b in DPR, 2008). The absorption was rapid with peak concentrations occurring at 5 to 12 hours after low or high (10 or 200 mg/kg) oral dose administration. The plasma elimination half-lives were in the 38 to 82 hour range. The tissue residues were higher in females than in male rats, which is consistent with the females having a longer elimination half-life (78 to 82 hours) versus males (38 to 43 hours), and higher AUC in plasma. The majority of administered ^{14}C was excreted by 48 to 72 hours after dosing in both high- and low-dose group. Fecal excretion was the primary route of elimination (M: 62%; F: 64%) followed by urine (M:29%; F:24%) at 10 mg/kg dose. No significant elimination occurred via exhalation. Metabolism of the absorbed dose was extensive and greater hydroxylation of metabolites was found in males. The metabolites found in this rat metabolism study were as follows: IN-K9T00, IN-HXH44, IN-KAA24, IN-H2H20, and IN-GAZ70 (US EPA, 2013). The structures and chemical names of these metabolites are provided in Appendix A.

The metabolites identified on the plants and in the environment were of low acute toxicity and tested negative in the Ames test. The acute toxicity of chlorantraniliprole metabolites (i.e., IN-EQW78-005, IN-LBA24-002, IN-ECD73-003, and IN-F6L99-004) in rats was low, with all $LD_{50} > 2000$ mg/kg. The in vitro bacterial mutagenicity assay of the metabolites (IN-EQW78-004, IN-LBA24-002 and IN-F6L99-004) with *S. typhimurium* and *E. coli* +/- S9 with concentrations up to 3333 or 5000 µg/plate were all negative (NFSA, 2010). IN-ECD73-003 up to 5000 µg/plate showed increased mutation frequencies in TA100 with S9; however, this increase was not ≥ 2-fold and showed no dose-response, and therefore was considered to be negative. The available chemical names and structures of these metabolites are provided in Appendix A.

There is also an impurity (IN-G2S78) found in low concentration (0.3%) with high acute toxicity (325.5 mg/kg-day), which does not affect the acute toxicity of the technical material due to its low concentration. However, it has not been demonstrated that this impurity will not affect the chronic toxicity of the technical material. This impurity also tested negative in the Ames test (VKM, 2010). The acute toxicity profile of IN-G2S78 is as follows: acute oral LD_{50}: 323.5 mg/kg; acute dermal LD_{50}: >5000 mg/kg-day; acute inhalation: LC_{50}: >2.1 mg/kg; eye irritation: slight, clearing in 42 hours; and skin sensitization: not sensitizing.

B. Reviews of Toxicity

The toxicity of chlorantraniliprole has been extensively reviewed by US EPA and other regulatory agencies: (1) Memorandum, Chlorantraniliprole: Human Health Risk Assessment for Proposed Use on Oilseeds and Soybeans (US EPA, 2012b); (2) Memorandum, Chlorantraniliprole chronic dietary (food and drinking water) exposure and risk assessment (US EPA, 2013); (3) Conclusion on the peer review of the pesticide risk assessment of the active substance chlorantraniliprole (EFSA, 2013); (4) Draft Human Health and Ecological Risk Assessment for Chlorantraniliprole Rangeland Grasshopper and Mormon Cricket Suppression Application (USDA, 2018); (5) Public Release Summary on Evaluation of the new active chlorantraniliprole in the products (APVM, 2008); (6) Evaluation of the plant protection product, Coragen 20 SC-chlorantraniliprole (NFSA, 2010); (7) Risk assessment of the pesticide Coragen 20 SC with the active substance chlorantraniliprole, (VKM, 2010) and (8) DPR's Toxicology Summary (DPR, 2008).

In addition to using the information in these reviews, OEHHA conducted a literature search on the toxicity of chlorantraniliprole in PubMed, Scopus, and Toxnet for studies published from 2008 to 2019. In addition to studies evaluated in the above reviews, one additional animal toxicity study was identified which evaluated the health effects of chlorantraniliprole using a Coragen® 20% SC formulation (Magdy et al., 2016). This study was limited by a lack of control groups, use of a formulated product rather than the technical grade a.i., and a lack of clarity in dosing method and intervals. For these reasons, details of the study and its results are not presented here.

Toxicity information considered relevant to this assessment is summarized in the following sections, followed by the determination of critical health endpoints and PODs.

C. Human Studies

There are no human health effects reported from the use of chlorantraniliprole (NSFA, 2010). However, there are incidents of an unusual insecticide poisoning in humans. A 26-year old female who was reported with deliberate self-harming use of chlorantraniliprole, developed symptomatic atrioventricular block after ingesting 10

milliliters (mL) of the pesticide formulation Coragen®, a.i.18.4% chlorantraniliprole (Mishra et al., 2016). This patient had bradycardia with atrioventricular blockage, and received temporary transvenous pacemaker placement. She was discharged after 48-hours when her electrocardiogram (ECG) returned to normal sinus rhythm and achieved baseline heart rate. According to Mishra et al., interference of chlorantraniliprole on the regulation of the calcium release from the sarcoplasmic reticulum of the RyR2 in the cardiac muscle may have been the cause of brachycardia in this patient.

In another intentional self-intoxication incident in India (Bhattacharya et al., 2015), 175 mL of an undescribed formulation of chlorantraniliprole was ingested by a 26-year old male in an attempted suicide. This patient exhibited decreasing sensorium and fever, and was intubated in emergency care and transferred to an intensive care unit with mechanical ventilation. The patient regained consciousness within 24 hours, within 72 hours was afebrile, and was discharged after a week. The author notes that if this patient was not intubated and ventilated in time, he may have succumbed to respiratory failure. However, the author notes that inactive ingredients such as solvents can also be the cause of toxicity in humans.

D. Animal Studies

Animal studies of various exposure durations, including acute, subchronic, and chronic, are discussed in this section.

1. Acute toxicity

A summary of the acute toxicity profile of chlorantraniliprole is provided in Table 2. Acute toxicity studies are short-term with high doses, and the toxicity is characterized by the lethal concentration (LC_{50}) or lethal dose (LD_{50}) that caused death in 50 percent of the tested animals. In general, chlorantraniliprole has low acute oral, dermal and inhalation toxicity. According to US EPA (2008), the acute toxicity category of chlorantraniliprole is very low (Toxicity Category IV) for all routes of exposure, and it has not been shown to be a skin sensitizer. However, it is mildly irritating to the eye (US EPA, 2012b).

Table 2. Acute toxicity profile of chlorantraniliprole (US EPA, 2012b).

Study Type	Results	Toxicity Category
Acute oral – rat	LD_{50} > 5000 mg/kg	IV
Acute dermal – rat	LD_{50} > 5000 mg/kg	IV
Acute inhalation – rat	LC50 > 5.1 mg/L	IV
Acute eye irritation - rabbit	Iritis score of 1 in 1/3 rabbits, conjunctival redness score of 1 in 2/3 rabbits. All eyes return to normal after 72 hours	IV
Acute dermal irritation - rabbit	No dermal irritation, clinical signs or body weight loss	IV
Skin sensitization - mouse	Not a dermal sensitizer	Negative

2. Subchronic Toxicity

There are 28- and 90-day dietary and 28-day repeated dose dermal animal bioassays of sufficient quality for evaluating the subchronic toxicity of chlorantraniliprole (Donner, 2006a; MacKenzie, 2004; and Finlay, 2006a). These studies are summarized in this section. Also, there is a multigeneration reproductive study in rats (Malley, 2006a) and a 1-year study in beagle dogs (Luckett, 2006) that can be used to evaluate the toxicity of subchronic exposure durations. Summaries of other available subchronic toxicity studies for chlorantraniliprole are presented in Appendix B.

28-Day Dietary Rat Study

Five Crl:CD(SD)IGS BR rats/sex/group received 0, 300, 1500 or 8000 parts per million (ppm) of chlorantraniliprole Technical (98.6% purity) in the diet for 28 days (i.e., M: 0, 20.7, 106, 584 mg/kg-day; F: 0, 24.0, 128, 675 mg/kg-day) (Donner, 2006a). In the 8000 ppm (675 mg/kg-day) females, mean serum total protein and globulin levels were greater than control ($p<0.05$), and centrilobular hypertrophy of the liver (0: 0/5 vs. 8000: 3/5) in the histopathological evaluation were observed. In the 1500 ppm (128 mg/kg-day) and above, females had increased relative liver weights and increased UDP-glucuronyl transferase activity compared to the control ($p<0.05$). Based on this data, a LOAEL (lowest-observed adverse effect level) of 128 mg/kg-day and a NOAEL of 24 mg/kg-day were determined for the increase in relative liver weight in female rats. Minimal centrilobular hypertrophy of the liver was also observed in female rats in the 675 mg/kg-day group, although there was no histomorphologic evidence of hepatocellular damage according to the study author. The treatment did not cause any effect in the liver of male rats.

It is OEHHA's policy to derive a POD from a toxicity study by fitting a dose-response model to the data using the US EPA Benchmark Dose Software[1] (BMDS version 2.7) when possible. BMDS uses mathematical models to fit data and determines the dose (benchmark dose or BMD) that corresponds to a pre-determined level of response (benchmark response or BMR). Typically OEHHA uses a BMR of 5% relative deviation (RD) or one standard deviation (1SD) from the control mean as the level of change that is considered biologically significant for continuous data. To account for uncertainty in the data, the model also calculates the 95% lower confidence limit of the BMD, known as the BMDL (L stands for lower confidence limit). OEHHA modeled the relative liver weight data from the study in BMDS and found that while the data returned models with acceptable fit statistics (p values); the visual fit to the dose-response data was poor. Models with acceptable visual fit had questionable fit statistics (high BMD/BMDL ratio, non-significant p value for test #1), and for these reasons we did not use any of the modeling results for this study.

An increased incidence of microvesiculation and lesion of the adrenal cortex was found in male rats at 8000 ppm (584 mg/kg-day) compared to controls (i.e., control: 0/5 vs. 584 mg/kg-day: 2/5). Also three of the five female rats in the 8000 ppm (675 mg/kg-day) group exhibited this lesion. Microvesiculation was also found in two of the five control females; therefore, the lesions in females were not considered to be treatment-related. The microvesiculation of the adrenal cortex in this study was only examined microscopically for the control and at the high dose groups, and the mid-doses were not examined. OEHHA did not determine a LOAEL or NOAEL for this effect. The biological relevance of microvesiculation of the adrenal gland has been reviewed and a summary is provided under Assessment of Adrenal Cortical Cell Structure and Function, in Section III.D.3 of this report.

90-Day Dietary Rat Study

In a subchronic 90-day study, ten Crl:CD(SD)IGS BR rats/sex/group received 0, 600, 2000, 6000 or 20,000 ppm of chlorantraniliprole (95.9% purity) in their diet for 13 weeks (i.e., M: 0, 36.9, 119.7, 358.9, 1188 mg/kg-day; F: 0, 47, 156.7, 459.8, 1526 mg/kg-day). In the 20,000 ppm group slight but statistically significant increases in mean absolute (17.8%) and relative liver weights (11%) were observed in female rats (Table 3). There were no lesions in the livers of these animals (MacKenzie, 2004). Also, there was no gross or microscopic finding that correlated with the increased female liver weights, and no increase in serum liver enzymes. Decreases in mean bilirubin values in females at $\geq$ 2000 ppm suggested hepatic enzyme induction. A LOAEL of 1526 mg/kg-day and a NOAEL of 459.8 mg/kg-day can be determined for the increase in relative liver weight in female rats. It is noted that the NOAEL of this study is higher than that from the 28-day dietary rat study, for the same endpoint. OEHHA modeled relative liver weights of

[1] Available at: https://www.epa.gov/bmds

female rats in BMDS and calculated a $BMDL_{1SD}$ of 22 mg/kg-day. While the model was viable, the BMD/BMDL ratio was greater than 5, and the BMDL derived was 20-times lower than the study NOAEL, thus there was a high-level of uncertainty in the modeling results.

Increased microvesiculation was noted in the zona fasciculata of the adrenal gland of 20000 ppm (1188 mg/kg-day) males (i.e., control: 0/10 vs. 1188 mg/kg-day: 4/10); however, the mid-dose ranges were not examined initially (MacKenzie, 2004). The mid-dose ranges were subsequently reexamined microscopically and the results are presented in Table 3 (Sykes, 2006).

Table 3. Microvesiculation in adrenal glands and relative liver weights of male and female rats exposed to chlorantraniliprole in the diet for 90-days (MacKenzie, 2004).

Concentration in the diet (ppm)	0	600	2000	6000	20,000
Dose in Males (mg/kg-day)	0	36.9	119.7	358.9	1188
Incidence of cortical microvesiculation in males	0/10	1/10	2/10	2/10	4/10*
Liver weight/% body weight in males Mean (SD)	2.573 (0.122)	2.729 (0.197)	2.739 (0.138)	2.738 (0.183)	2.777 (0.245)
Dose in Females (mg/kg-day)	0	47	156.7	459.8	1526
Incidence of cortical microvesiculation in females	1/10	0/10	0/10	0/10	2/10
Liver weight/% body weight in females Mean (SD)	2.736 (0.133)	2.854 (0.182) n=9	2.938 (0.274)	2.980 (0.243)	3.038** (0.264)

Number of animals (n) per group is 10, except where indicated.
***** Fisher's Exact test, significant at $p<0.05$; ** Dunn's test, significant at $p<0.05$

Histological grading of the adrenal cortex microvesiculation was based on a scale of 0 to 4, to indicate increasing severity. All incidences of microvesiculation in the study were graded minimal (grade 1), other than two males in the high dose group where the effect was graded as mild (grade 2). This increase was considered to be test substance related based on the increase in incidence and grade of the findings at high dose. In the females, the incidence and severity were minimal (2/10 at high dose, grade 1) and the incidence was not statistically significant compared to control (1/10).

According to Sykes (2006), the microvesiculation of the adrenal cortex was within the range of normal adrenal morphology, and there was no evidence of adrenal cellular

degeneration or toxicity. OEHHA did not determine a LOAEL or NOAEL for this effect. As previously stated, the biological relevance of microvesiculation of the adrenal gland has been reviewed and a summary is provided under Assessment of Adrenal Cortical Cell Structure and Function, in Section III.D.3 of this report.

One-Year Oral Dog Feeding Study

Beagles (5/sex/dose) were fed a diet containing chlorantraniliprole (96.45% purity) at 0, 1000, 4000, 10,000 or 40,000 ppm (male: 0, 32.0, 111.5, 316.6, 1164 mg/kg-day; female: 0, 34.0, 113.2, 277.8, 1233 mg/kg-day) for 1 year (Luckett, 2006). There were no significant treatment-related toxicological effects on mortality or clinical signs noted in physical or neurobehavioral examination. No treatment-related lesions were evident in the histopathological examinations. The only notable significant effects were elevated mean alkaline phosphatase activities and mean relative liver weight that were greater than control in both sexes at the high dose. The NOEL was M: 316 mg/kg-day and F: 277.8 mg/kg-day based on increased serum alkaline phosphatase activity and increased relative liver weights in both sexes at 40,000 ppm.

28-Day Repeated Dosing Dermal Rat Study

In a 28-day repeated dosing dermal rat study, the skin of 10 Crl:CD(SD)IGS BR rats/sex/group was exposed to 0, 100, 300 or 1000 mg/kg-day of chlorantraniliprole technical (96.45% purity) for 6-hours per day, for 29 consecutive days (Finlay, 2006a). The test material was moistened with deionized water into a paste for application. In the 1000 mg/kg males, the mean body weight gains, and mean food efficiency over the course of the study were less than the control group ($p<0.05$). Increased microvesiculation of the adrenal cortex was observed at 100 mg/kg-day and above; however, no electron microscopic evidence of adrenal cellular degeneration or in the capacity of adrenal to produce corticosterone under either basal or adrenal corticotropic hormone (ACTH) stimulation were observed. The increase appeared to be dose-dependent; however, was statistically significant only at the high dose (1000 mg/kg-day).

DPR (2008) identified a dermal NOAEL of <100 mg/kg-day for male rats due to incidence of microvesiculation at 100 mg/kg-day, and a dermal NOAEL of 300 mg/kg-day for female rats based on reduced body weight gain and food efficiency at 1000 mg/kg-day. A dermal NOAEL was not established by the US EPA due the lack of histopathological evidence of adrenal cellular degeneration, and lack of effects on the capacity of adrenal to produce corticosterone under either basal or adrenal corticotropic hormone (ACTH) stimulation (see the discussion in Assessment of Adrenal Cortical Cell Structure and Function in Section III.D.3). All incidence of microvesiculation were graded as minimal, and the study author considered this increase to be within the range of normal adrenal morphology (Finlay, 2006a).

Table 4. Mean body weight gain (in grams) from day 0 to 28 of male and female rats exposed to chlorantraniliprole via dermal exposure (Finley, 2006a).

Dose (mg/kg-day)	0	100	300	1000
Males, number of animals	10	10	10	10
Body weight gain (g)	129.9	131.5	115.1	101.2*#
Standard deviation	25.7	21.2	17.5	21.9
Females, number of animals	10	10	10	10
Body weight gain (g)	65.4	69.9	59.9	53.2
Standard deviation	17.6	22.0	18.5	17.1

* Statistically significant compared to control at p<0.05 Dunnett/Tamhane-Dunnett Test, calculated by study author

Statistically significant, unpaired t-test, two-tailed p value = 0.015 (see: http://www.graphpad.com/quickcalcs/ttest1/)

Using the data presented in Table 4, OEHHA determined a dermal NOAEL of 300 mg/kg-day based on the decrease in body weight gain in male rats. OEHHA also conducted a BMD modeling of this endpoint and calculated a $BMDL_{1SD}$ of 166 mg/kg-day.

3. Chronic Toxicity

There are four chronic/lifetime animal bioassays of sufficient quality for evaluating the chronic toxicity and carcinogenic potential of chlorantraniliprole (Technical grade) in both sexes in rats and mice (MacKenzie, 2006 and Finlay, 2006b). These studies are described below.

a. Chronic dietary rat study

Crl:CD(SD)IGS BR rats (60/sex/group, and satellite cohort of 10/sex/group) were fed technical chlorantraniliprole (96.45% purity) in diet for 23 months at concentrations of 0, 200, 1000, 4000 or 20,000 ppm, which corresponds to M: 0, 7.71, 39.0, 156.2, 805.3 mg/kg-day, and F: 0, 10.9, 51.0, 211.5, 1076 mg/kg-day as calculated by study authors (MacKenzie, 2006). The study was terminated early (around 23 months) before the 24-month duration due to excess mortality unrelated to the treatment. Effects from treatment with chlorantraniliprole were in liver in females and adrenal glands in males. A minimal to mild reduction in bilirubin was also observed in females exposed to $\geq$ 51

mg/kg-day (1000 ppm) at the interim sacrifice (385 days,Table 5). This decrease in bilirubin was considered to be attributed to enzyme induction, and subsequent increase in bilirubin metabolism according to study authors. Authors also stated that the effect was test-substance-related but has no clinical significance and was considered as non-adverse (MacKenzie, 2006). There were no other adverse test substance-related effects in rats exposed up to 20,000 ppm of chlorantraniliprole in diet.

Table 5. Summary of serum bilirubin values (mg/dL) and relative liver weights for female rats exposed to chlorantraniliprole in the diet at the interim sacrifice (MacKenzie, 2006).

Dose (mg/kg-day) / concentration in diet (ppm)	0 / 0	10.9 / 200	51 / 1000	211.5 / 4000	1076 / 20,000
Mean value bilirubin	0.16 (0.02)	0.14 (0.02)	0.11*,[a] (0.02)	0.12*,[a] (0.03)	0.11*,[a] (0.01)
Liver weight/% body weight	2.486 (0.273)	2.784 (0.307)	2.733 (0.239)	2.832*,[b] (0.253)	3.073*,[b] (0.266)

N=10 for all dose groups; Parenthetical numbers are standard deviation.
* Statistically significant from control at $p<0.05$ by [a] Dunn's Test or [b] by Dunnett/Tamhane-Dunnette test, as reported by study authors.

The NOAELs were 805 and 1076 mg/kg-day in male and female rats, respectively, according to the study author due to the lack of test substance related adverse effect at the highest dose tested (HDT) (MacKenzie, 2006). However, DPR (2008) determined a NOAEL of 51.0 mg/kg-day based on increases in relative liver weights in female rats at 211.5 mg/kg-day at the interim sacrifice (after approximately 12 months of treatment). The effect in mean relative liver weight in females at 211.5 and 1076 mg/kg-day was not apparent at the termination of this study. OEHHA agrees with DPR's determination and identified a NOAEL of 51 mg/kg-day. The interim relative liver weight data of female rats was not amenable to BMD modeling.

DPR also determined a NOAEL of 7.71 mg/kg-day based on incidence of increased microvesiculation of adrenal cortex at 39.0 mg/kg-day in male rats. Histopathology examination of adrenal cortex in males exhibited an increased incidence of microvesiculation in the adrenal gland after approximately 23 months of treatment (Table 6). Increased microvesiculation of the zona fasciculate of the adrenal cortex at the interim sacrifice after 12 months of treatment was also observed at a frequency of 0/10, 2/10, 5/10, 5/10, and 5/10 males given 0, 7.71, 39.0, 156.2, 805.3 mg/kg-day of the test substance, respectively. This finding was graded as minimal (grade 1) in all rats for the 12-month interim sacrifice with the exception of 4 males in the 4000 ppm dose group (156.2 mg/kg-day) and 2 males in the 20,000 ppm dose group (805.3 mg/kg-day) that were graded as mild (grade 2). Grading was conducted on a scale of 0

to 4 for increasing severity of the effect, as was done for other studies with this finding. There were no significant findings in females (Table 7).

Table 6. Incidence of microscopic findings in male rats exposed to chlorantraniliprole for 23 months in the diet (MacKenzie, 2006).

Dose (mg/kg-day) / concentration in diet (ppm)	0 / 0	7.7 / 200	39.0 / 1000	156.2 / 4000	805.3 / 20,000
Number of animals	60	59	60	60	58
Microvesiculation, minimal (grade 1)	10	11	17	14	13
Microvesiculation, mild (grade 2)	1	5	6	5	8
Microvesiculation, moderate (grade 3)					1
Adrenal gland- total incidence of microvesiculation	11	16	23*	19	22*

* Statistically significant from control ($p<0.05$) Fischer exact test, as reported by study authors.

Table 7. Incidence of microscopic findings in female rats exposed to chlorantraniliprole for 23 months in the diet (MacKenzie, 2006).

Dose (mg/kg-day) / concentration in diet (ppm)	0 / 0	10.9 / 200	51 / 1000	211.5 / 4000	1076 / 20,000
Number of animals	60	59	60	60	58
Adrenal gland- incidence of microvesiculation	6	6	4	7	8

* Statistically significant from control ($p<0.05$) Fischer exact test, as reported by study authors.

Histopathological examination of male and female rats after approximately two years revealed no treatment-related effect on basal corticosterone or incidence of adrenal functional impairment. The microvesiculation was similar in number and size for the controls and the treated groups; however, the density of the vacuoles varied among individual rats. The electron microscopic analysis of these lesions did not reveal any effect on organelle morphology. OEHHA did not determine a LOAEL or NOAEL for this effect. The biological relevance of microvesiculation of the adrenal gland has been reviewed and a summary is provided under Assessment of Adrenal Cortical Cell Structure and Function, presented in the discussion below.

Assessment of Adrenal Cortical Cell Structure and Function

The minimal to moderate microvesiculation of the adrenal cortex found in the rat studies are considered to be a non-critical effect based on the findings of US EPA (2014) and APVMA (2008), and are not used by these agencies as a basis for establishment of NOAELs in the studies conducted with chlorantraniliprole. This conclusion is also

shared by other agencies such as ESFA (2013) and USDA (2019). In the oral and dermal toxicity studies in rats, the slight increase in degree of microvesiculation due to the increase in lipid is considered to have no toxicological significance based on the investigation of the structure and functional basis for this change in adrenal cortical cells. Electron microscopy indicated that other cellular structures were unaffected from this increase in microvesiculation, and no other abnormality in other cellular structures were observed in the control or treated rats. Studies designed to assess the functional impact indicated that increased microvesiculation did not affect the adrenal corticosterone level or the functional capacity of the adrenal to produce corticosterone under both non-stressed (i.e., basal) and under simulated physiological stress (i.e., adrenal corticotropic hormone (ACTH)-induced). This slight increase in microvesiculation caused by accumulation of lipid is considered to be a morphological variation of what is normally observed in the control animals. Also, there were no correlative effects such as changes in clinical signs, hematology, clinical chemistry or urinalysis that are associated with altered adrenal corticosterone production.

The OECD's (Organisation for Economic Co-operation and Development).Guidelines Notes for Analysis and Evaluation of Repeat-Dose Toxicity Studies (OECD, 2001) define an adverse response as: "any treatment-related response that results in change in the morphology, physiology, growth, development, or life-span of an organism, which results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other environmental influences." As stated above, histological changes with administration of chlorantraniliprole are not associated with functional changes in the adrenal cortex or its capacity to respond to additional stress. Study authors considered the effect non-adverse and did not use the effect as the basis for establishing NOAELs in studies conducted with chlorantraniliprole (Sykes, 2006; MacKenzie, 2006 and Finlay, 2006a). Due to the question of the biological relevance of microvesiculation of the adrenal gland in rats, OEHHA decided not to use this effect for quantitative dose-response characterization of chlorantraniliprole.

Additionally, the adrenal cortex of rodent accumulates lipid inclusions (or lipofuscin) with age. In 24-month-old male rats, an independent study found that 4.4 and 22.6% of the intracellular volume of adrenal inner zonae fasiculata and reticularis, respectively, are occupied by lipid-containing residues or lipofuscin granules (Cheng et. al., 2006). In the current study, increases in microvesiculation were also observed in the control test animals after 23-months (11/60, 18%) versus at the 12-month interim sacrifice (0/10, 0%). Therefore, some of the changes at the study termination could be considered to be age related and unrelated to consumption of test substance.

i. Carcinogenicity Assessment in Rats

Carcinogenicity studies of chlorantraniliprole in male and female rats (MacKenzie, 2006) showed an increased incidence of follicular cell tumors in the thyroid gland after 23 months of treatment (controls: 0/60 vs 1076 mg/kg-day: 4/60) in females at the high dose (20,000 ppm) (Table 8). The tumors were all adenomas except for one carcinoma reported in the mid dose group (1000 ppm). The incidence of thyroid follicular cell tumors in females was statistically significant by trend, but not by pair-wise comparison at the high dose group. There was no accompanying increase in follicular cell hyperplasia or hypertrophy. The incidences in the high dose (4/60, 6.7%) was within the historical control range for the laboratory (2-12%). Study authors did not attribute the tumors to treatment. There was also no increase in treatment related tumors in male rats exposed to chlorantraniliprole in the diet for 23 months (MacKenzie, 2006). Due to the low incidence of tumors, lack of statistical significance by pairwise comparison, and absence of concordant tumors in male rats (who are typically more sensitive to thyroid follicular cell hypertrophy and neoplasm), OEHHA determined that thyroid follicular tumors in female rats were not treatment related.

Table 8. Incidence of thyroid follicular cell tumors in female rats exposed to chlorantraniliprole in the diet for 23 months (MacKenzie, 2006).

Dose (mg/kg-day) / Concentration in diet (ppm)	0 / 0	10.9 / 200	51 / 1000	211.5 / 4000	1076 / 20,000
Adenoma, thyroid follicular cell, unilateral	0/60*	0/60	1/60	2/60	4/60
Carcinoma, thyroid follicular cell, unilateral	0/60	0/60	1/60	0/60	0/60
Thyroid follicular tumors, combined	0/60*	0/60	2/60	2/60	4/60
%	0	0	3.3%	3.3%	6.7%

* Statistically significant by trend ($p<0.05$) by Cochran-Armitage trend test as calculated by OEHHA, indicated on the control group.

b. Chronic Dietary Mouse Study

In the mouse studies (Finlay, 2006b), 70 Crl:CD-1®(ICR)BR mice/sex/group received 0, 20, 70, 200, 1200, or 7000 ppm of chlorantraniliprole (purity: 96.45%) in the diet for 18 months. The estimated equivalent doses were 0, 2.6, 9.2, 26.1, 157.6, or 935.1 mg/kg-day for males and 0, 3.34, 11.6, 32.9, 195.6, or 1155 mg/kg-day for females, respectively. The mean absolute and relative liver weights of both sexes in the 1200 and 7000 ppm groups were greater than those of the controls ($p<0.05$) (Tables 9 and 10). The increased liver weighs correlated with the microscopic finding of hepatocellular hypertrophy in males at ≥1200 ppm; however, microscopic changes in females were not observed. The mean absolute and relative kidney weights of the females in the 7000 ppm group were less than the control values ($p<0.05$). Increased incidences of

hepatocellular hypertrophy in the 1200 and 7000 ppm males were also statistically significant.

Table 9. Mean absolute and relative (as % body weight) liver weights in male mice after exposed to chlorantraniliprole in diet for 18 months (Finlay, 2006b).

Dose (mg/kg-day) / Concentration in diet (ppm)	0 / 0	2.6 / 20	9.2 / 70	26.1 / 200	157.6 / 1200	935.1 / 7000
Number of animals examined	47	45	54	51	48	45
Body weight (grams)	41.5 (4.9)	42.1 (5.7)	43.7 (4.7)	43.2 (5.7)	42.3 (3.9)	41.6 (5.7)
Liver weight (grams)	2.087 (0.562)	2.102 (0.497)	2.241 (0.604)	2.211 (0.482)	2.260* (0.344)	2.475* (0.551)
Liver weight as % body weight	5.085 (1.581)	5.072 (1.444)	5.187 (1.591)	5.166 (1.246)	5.372* (0.996)	6.026* (1.506)
LW/BW % change from control	0	-1%	2%	1%	6%	19%

Parenthetical numbers are standard deviation; LW=liver weight; BW=body weight

* Statistically significant ($p<0.05$) Dunn's test for nonparametric data

Table 10. Mean absolute and relative (as % body weight) liver weights and kidney weights in female mice exposed to chlorantraniliprole in diet for 18 months (Finlay, 2006b).

Dose (mg/kg-day) / Concentration in diet (ppm)	0 / 0	3.34 / 20	11.6 / 70	32.9 / 200	195.6 / 1200	1155 / 7000
Number of animals	52	53	44	48	44	48
Body weight (grams)	35.6 (5.3)	35.8 (5.3)	34.5 (3.7)	35.9 (4.3)	36.3 (4.5)	36.1 (3.8)
Liver weight (grams)	1.752 (0.346)	1.701 (0.326)	1.807 (0.493)	1.837 (0.371)	1.949* (0.404)	2.065* (0.381)
Liver weight as % body weight	4.971 (0.968)	4.767 (0.748)	5.235 (1.291)	5.128 (0.939)	5.386* (0.875)	5.716* (0.840)
Liver weight/body weight (% change from control)	0	-4%	5%	3%	8%	15%
Kidney weight (grams)	0.544 (0.061)	0.559 (0.092)	0.534 (0.071)	0.543 (0.077)	0.535 (0.075)	0.502* (0.067)
Kidney weight as % body weight	1.555 (0.243)	1.572 (0.242)	1.555 (0.213)	1.523 (0.221)	1.485 (0.210)	1.397* (0.178)
KW/BW % change from control	0	0%	0%	-2%	-5%	-10%

Parenthetical numbers are standard deviation; KW=kidney weight; BW=body weight; * Statistically significant ($p<0.05$) Dunn's test for nonparametric data

Based on the data in Tables 9 and 10, OEHHA determined a NOAEL of 26.1 mg/kg-day for male mice and a NOAEL of 32.9 mg/kg-day for female mice. The dose-response modeling of the relative liver weights in male and female mice after 18-months did not provide any usable POD due to the lack of model fit (see Appendix D).

In the histopathological examinations, an increase in the incidence of eosinophilic foci of cellular alteration was noted in the livers of the 7000 ppm males (controls: 0/69 vs 7000 ppm: 5/70, $p<0.05$). All were graded as mild (grade 2), except for one in 20 ppm and one in 1200 ppm, which were graded as moderate (grade 3). Centrilobular hepatocellular hypertrophy was noted in the livers of the 1200 and 7000 ppm males (Table 11). All were graded minimal (grade 1) except for one in 7000 ppm, which was graded as mild (grade 2). Grading was conducted on a scale of 0 to 4 for increasing severity of the effect. Microscopic hepatocellular hypertrophy was not observed in females despite a slight increase in mean liver weights at $\geq$1200 ppm. US EPA (2013) established a chronic oral reference dose (RfD = 1.58 mg/kg-day) for chlorantraniliprole from the NOAEL value of 158 mg/kg-day with LOAEL of 935 mg/kg-day based on the increase in eosinophilic foci at high dose.

Table 11. Incidence of microscopic effects in the liver of male mice exposed to chlorantraniliprole in diet for 18 months (Finlay, 2006b).

Dose (mg/kg-day) / Concentration in diet (ppm)	0 / 0	2.6 / 20	9.2 / 70	26.1 / 200	157.6 / 1200	935.1 / 7000
Number of animals	69	70	70	70	70	70
Liver hepatocellular hypertrophy	0[a]	0	0	1	7*	9*
Liver eosinophilic foci	0[a]	1	1	0	1	5*

* Statistically significant from control ($p<0.05$) Fischer exact test.

[a] Statistically significant trend ($p<0.05$) Cochran-Armitage trend test, indicated on the control group

OEHHA determined a NOAEL of 26.1 mg/kg-day based on the increase of hepatocellular hypertrophy in male mice at 157.6 and 935.1 mg/kg-day. OEHHA also modelled this endpoint and determined a $BMDL_{05}$ of 52.9 mg/kg-day, and $BMDL_{10}$ of 200.6 mg/kg-day. The models selected were not the lowest BMDLs calculated. The model recommended by the BMDS Wizard was the dichotomous-hill model returning a $BMDL_{05}$ 0f 26.3 or a $BMDL_{10}$ of 28.6 mg/kg-day. However, it included an output file warning stating "*BMDL computation is at best imprecise for these data*," which is supported by the similar BMDLs calculated for either BMR of 5 or 10%. Thus, OEHHA chose the alternative model (log-probit) that didn't include the warning. However, because of the uncertainties with the BMD modeling results, OEHHA selected the NOAEL over the BMD approach for this endpoint.

i. Carcinogenicity Assessment in Mice

Carcinogenicity studies in male and female mice (Finlay, 2006b) found no test substance-related effects on the incidence of tumors, and incidences of primary neoplasm were not statistically significant in either sex by trend or pairwise comparison with controls. OEHHA does note that the sensitivity of the mice studies may have been limited by the duration of the study (18 months versus the recommended 2-year bioassay), and some tissues examined in the 20-1200 ppm dose groups had limited animals numbers. Other microscopic observations were consistent with normal background lesions in mice of this age and strain.

OEHHA finds the overall data to be an inadequate test of the carcinogenicity of chlorantraniliprole in mice. The 18-month exposure in mice reported by Finlay (2006b) is a less than “lifetime exposure” and several pathological findings had reduced statistical power due to the smaller number of tissues examined in doses ≤ 1200 ppm.

4. Genotoxicity

OEHHA reviewed the genotoxicity studies of chlorantraniliprole (Table 12) and determined that none of the studies reported positive results or evidence of genotoxicity of chlorantraniliprole. Also, US EPA (2013) noted that no mutagenic concern was reported in the genotoxicity studies.

Table 12. Genotoxicity profile of chlorantraniliprole.

Assay Type and endpoint	Test systems	Results (-S9)	Results (+S9)	Reference
In Vitro Gene Mutation				
Bacterial mutagenicity (Ames)	*S. typhimurium* TA98, TA100, TA1535, TA1537, , uvrA: 0–5000 µg/plate w/DPX-E2Y45 (92.05%)	negative	negative	Wagner & Atta-Safoh 2004[a,b]
Bacterial mutagenicity (Ames)	*E. coli* WP2P, uvrA: 0–5000 µg/plate w/DPX-E2Y45 (92.05%)	negative	negative	Wagner & Atta-Safoh 2004[a,b]
Bacterial mutagenicity (Ames)	*S. typhimurium* TA98, TA100, TA1535, TA1537, uvrA: 0–5000 µg/plate w/DPX-E2Y45 (96.45%)	negative	negative	Myhre 2006[a,b]
Bacterial mutagenicity (Ames)	*E. coli* WP2P, uvrA: 0–5000 µg/plate w/DPX-E2Y45 (96.45%)	negative	negative	Myhre 2006[a,b]
Chromosome aberration (clastogenecity)	Human lymphocytes w/DPX-E2Y45 (96.45%), 0–500 µg/mL	negative	negative	Gudi & Rao 2004[a,b]
Chromosome aberration (clastogenecity)	Human lymphocytes w/DPX-E2Y45 (92.05%), 0–500 µg/mL w/o S9, 0–25 µg/mL w/S9	negative	negative	Glatt 2006[a,b]
Mammalian cell mutagenicity (CHO/HGRP)	CHO cells w/DPX-E2Y45 (96.45%), 0–250 µg/mL	negative	negative	San & Clarke 2004[a,b]
In vivo Chromosomal Damage				
Micronucleus	Mouse bone marrow w/DPX-E2Y45 (92.05%); M and F: 0, 500, 1000 or 2000 mg/kg bw			Donner, 2006[a,b]

[a] NFSA (2010)

[b] DPR (2008) Abbreviations:S9: rat liver fraction of metabolic activation for in vitro assasys; DPX-E2Y45: DuPont technical grade chloranthraniliprole; CHO: Chinese hamster ovary; bw: body weight. All studies determined to be acceptable under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines by DPR.

5. Reproductive and Developmental Toxicity

There were no treatment-related critical effects on any parameters of reproductive performance, pup survival or sexual development noted in the two-generation dietary reproductive study in rats (Malley, 2006a). Reproductive toxicity tests in Beagle dogs raised concerns about effects on the developing testis of young male dogs, but limitations in study design and animal numbers made a determination for this effect difficult (Serota, 2003). There was no teratogenicity reported from the developmental toxicity tests performed with rats and rabbits (Malley, 2004a; Mylchreest, 2005). Based on these data, chlorantraniliprole is not determined to be a reproductive or developmental toxicant in rodents, and PODs derived in this assessment would be protective of any potential reproductive toxicity noted in male dogs.

Reproductive toxicity study in rats

Crl:CD (SD) rats (30/sex/dose) were administered chlorantraniliprole (96.45% purity) in diet at 0, 200, 1000, 4000 and 20,000 ppm prior to breeding, and continuing through breeding, gestation and lactation for two generations. The mean achieved dose levels for F0 and F1 generation parental animals of both sexes were within the range of 12.0–20.4, 60.4–104, 238–406, and 1199–2178 mg/kg-day (Malley, 2006a). Test substance intake for the premating F0 and F1 males, and F0 and F1 premating females, during gestation and lactation are provided in Appendix C (Table C-1). Under the conditions of this study, there were no adverse effects on indicators of reproduction and fertility or indications of systemic toxicity for the F0 and F1 adult rats and F1 and F2 offspring up to 20,000 ppm.

Test substance related effects on organ weight were observed for the adrenal glands in both sexes, and in liver for female F0 and F1 adults. Weanling organ weights were not affected. The mean relative and absolute liver weights in F0 and F1 females were significantly increased by 10-19% at 4000 and 20,000 ppm ($p<0.05$). The mean relative and absolute adrenal weights were increased in some dose groups of F0 and F1 males and females, but there was no dose-response relationship. The mean absolute and relative liver and adrenal weights of F_0 and F_1 males and females are provided in Appendix C. Based on the increased relative liver weight, OEHHA determined the NOAEL was 1000 ppm of chlorantraniliprole in diet for the female rats. This was equivalent to 77.8 mg/kg-day and 104 mg/kg-day for the F0 and F1 generations, respectively.

Test substance related increase in the number of adrenal cortical microvesiculation was observed in F0 and F1 adult males and females. The study author considered the microvesiculation of adrenal cortex as test substance related but not as adverse, because the adrenal morphology was generally within range of what was observed in the control animals, and the finding was not associated with any indication of cytotoxicity or evidence of structural or functional impairment of adrenal gland.

The study author and US EPA (2013) set the NOAEL as the highest dose (M: 1199 and F: 1594 mg/kg-day). The increased liver weights were considered as non-adverse pharmacological responses to induction of metabolism. DPR set the parental NOAEL as (M) <200 ppm due to the increased incidence of microvesiculation in adrenals for the adult males, and (F) 1000 ppm due to increased absolute and relative liver weights in F0 and F1 females at 4000 ppm (see Appendix C).

Reproductive toxicity study in dog

There is limited data to indicate that chlorantraniliprole may cause reproductive toxicity in dogs. In a 28-day dog oral range-finding toxicity study (Serota, 2003), two beagle

dogs/sex/group were dosed with 0, 300 or 1000 mg/kg-day of chlorantraniliprole (97.6% purity) in capsules for 4-weeks. The dogs were approximately 5-1/2 months old at the beginning of treatment. In a second study, four males/group received 0 or 1000 mg/kg-day of the test material in capsules for four weeks. In the first study, hypospermatogenesis was noted in the histopathological examination in the testes of one of two males in the 300 mg/kg group, and in both males in the 1000 mg/kg group. In the second study, one in four males in the control and two in four males in the 1000 mg/kg group demonstrated this lesion. Combining the two studies, a total of 1/6 males in the control, 1/2 males in the 300 mg/kg-day, and 4/6 males in the 1000 mg/kg dose group showed this lesion, demonstrating a dose-related trend. However, due to the design of this test and with the small number of animals used, there was a high uncertainty in making a determination for this effect. Study authors concluded that these incidences in male dogs were age-related, and due to the sexual immaturity and high incidence of spontaneous hypospermatogenesis in young test animals. Minimum hypospermatogenesis was found in one of 16 male dogs used in the 90-day study by Luckett (2004) and was not detected in the one-year dietary study in Beagle dogs with HDT at 1164 mg/kg-day (Luckett, 2006). Upon reviewing the available data, OEHHA determined that the high incidence of spontaneous testicular lesions in young dogs *may* indicate high vulnerability of the developing testis to chemical-induced damages; however, based on limitations in the study design and the small number of animals, definitive determination of the effect of chloranthraniliprole on the developing testes remains to be clarified.

No other treatment-related lesions were evident in any organs in the histopathological examination from the other subchronic and one-year dietary toxicity dog studies.

Developmental toxicity study in rats

In a developmental toxicity study in rats (Malley, 2004a); 22 mated female Crl:CD®(SD)IGS BR rats per group received chlorantraniliprole (purity: 96.45%) by oral gavage at 0, 20, 100, 300, or 1000 mg/kg-day on gestation days 6 through 20. The fetal incidence of ribs with extra ossification (variation) was slightly increased at 20, 100, and 300 mg/kg-day compared to controls; however, there was no effect at the high dose (1000 mg/kg-day). As shown in Table 13, the increase was not statistically significant with no dose-related response on a litter basis, thus the effect was not considered treatment-related. No other teratogenicity effects were reported, and the maternal and developmental NOAELs were 1000 mg/kg-day.

Table 13. Incidence of fetal variations (skeletal) in developmental toxicity study (teratology) in rat (Malley, 2004a).

Exposure (mg/kg-day)	0	20	100	300	1000
# examined fetus [litter]	271 [22]	292 [22]	275 [21]	256 [20]	231 [20]
Rib - Extra ossification	10 [7]	29 [10]	18 [8]	19 [8]	8 [4]
Vertebra – displaced ventrally	0	0	0	1 [1]	0
Total # affected (rib and vertebra)	10 [7]	29 [10]	18 [8]	20 [9]	8 [4]
Total % affected (rib and vertebra)	3.6% [32%]	9.9% [45%]	6.5% [38%]	7.8% [45%]	3.4% [20%]

Developmental toxicity study in rabbits

In a rabbit study (Mylchreest, 2005), 22 mated female rabbits per group received chlorantraniliprole (purity: 96.45%) by oral gavage at 0, 20, 100, 300, or 1000 mg/kg-day on gestation days 7 through 28. Fetuses were screened for external, soft tissue, and skeletal anomalies and variations; no treatment related adverse effects were identified. There were also no effects identified on reproductive endpoints in dams. Maternal and developmental NOAELs were 1000 mg/kg-day.

6. Neurotoxicity/Endocrine Disruption/Immunotoxicity

There was no evidence of neurotoxicity observed in the acute or subchronic neurotoxicity studies in rats, or in other feeding studies using rats, mice and dogs. According to US EPA (2008), a developmental neurotoxicity study was not required. Chlorantraniliprole is not listed as one of the 52 chemicals in the Tier 1 list of the US EPA Endocrine Disruptor Screening Program (US EPA, 2015). US EPA concluded that the toxicology database for chlorantraniliprole is adequate for the Food Quality Protection Act (FQPA), and that there are no concerns or residual uncertainties for pre- and post-natal toxicity. FQPA factor of 1 X was selected based on the completeness of toxicology database, no residual uncertainty to pre- and post-natal exposure, and lack of treatment-related neurotoxicity in acute and subchronic oral studies in rats.

There are two submitted studies addressing neurotoxicity (i.e., acute and subchronic 90-day neurotoxicity studies). In the acute neurotoxicity study with Crl:CD(SD)IGS BR rats (12/sex/group) were given by oral gavage chlorantraniliprole (purity 95.9%) at 0, 200, 700 or 2000 mg/kg (Malley, 2004b). There were no treatment-related clinical signs and no effects on body weight changes. Functional observational battery tests revealed no indication of treatment-related effects.

In a 90-days subchronic neurotoxicity study, Crl:CD(SD)IGS BR rats (12/sex/group) were given 0, 200, 1000, 4000 or 20,000 ppm (M: 0, 12.7, 64.2, 255, 1313 mg/kg-day; F: 0, 15.1, 77.3, 304, 1586 mg/k-day) chlorantraniliprole (purity 96.45%) in the diet for 13-weeks (Malley, 2006b). No treatment-related effects on the mean body weight or food consumption were reported. The FOB and motor activity assessments at 4, 8, and 13-weeks of treatment did not reveal any effects. There were no lesions evident in the histopathological examination. The rat subchronic neurotoxicity NOAEL was 20,000 ppm, the highest dose tested, for the lack of treatment-related effect in both sexes. Neurological assessments conducted in conjunction with the 18-month oncogenicity study in mice following 45, 60 and 90 days of dietary administration confirm the lack of potential neurotoxicity (Finlay, 2006b). Furthermore, no treatment-related clinical signs indicative of potential neurotoxicity were evident in other short-term and long-term exposure studies in rats, mice and dogs.

Chlorantraniliprole showed no evidence of immunotoxicity in rats (Munley, 2006a) and mice (Munley 2006b). In both studies, there was no evidence of treatment-related effects on the sheep red blood cells specific antibody (IgM) responses in either males or females at any dietary concentration tested. In the 28-day immunotoxicity feeding study in rats, the test animals received 0, 1000, 5000, and 20,000 ppm (M: 0, 74, 363, 1494 mg/kg-day; F: 0, 82, 397, 1601 mg/kg-day) of chlorantraniliprole (purity: 99.2%) in diet. There was no evidence of test substance-related toxicity or immunosupression in the male or female rats at dietary concentrations up to the highest dose, 20,000 ppm. The NOAEL was the highest dose tested.

In the 28-day immunotoxicity study in mice, the test animals received 0, 300, 1700 and 7000 ppm (M: 0, 48, 264, 1144 mg/kg-day; and F: 0, 64, 362, 1566 mg/kg-day) of chlorantraniliprole (purity: 99.2%) in diet. There was no evidence of test substance-related toxicity or immunosuppression in male or female mice at dietary concentrations up to the highest dose, 7000 ppm.

Chlorantraniliprole's potential as an endocrine disruptor has not been studied.

VI. HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENT

A. Non-cancer effects

The determination of critical animal studies, critical toxicity endpoints, PODs, and reference doses (RfDs) are discussed in this section. The POD is the critical dose level of a chemical that is used as a starting point for estimating non-cancer hazard. The POD is typically determined by fitting a dose-response model to the toxicity data using

US EPA's BMDS (US EPA, 2019). Generally, a BMD can be derived by setting the response level at 5% for quantal data and one standard deviation (1SD) for continuous data. The 95% lower confidence limit of the BMD is defined as the BMDL. OEHHA uses BMDL as POD for quantitative toxicity evaluation. When toxicity data are not amenable to BMD modeling, OEHHA uses the NOAEL/LOAEL approach in identifying a POD.

The RfD is typically determined by applying an uncertainty factor (UF) to the determined POD. OEHHA generally uses a UF of 10 for extrapolating from test animals to humans and a factor of 30 for variation in a diverse human population. Additional UF may be applied when there are limitations or gaps in the toxicity database or there are subgroups in the population that are known to be more sensitive to the toxic effects of the chemical.

In subchronic and chronic oral studies, the two main target organs were the adrenal gland and the liver. The minimal to moderate microvesiculation of the adrenal cortex found in the rat studies was considered a non-critical effect based on the findings of US EPA (2014), APVMA (2008), ESFA (2013), and USDA (2019). The details of this determination are discussed in the "Assessment of Adrenal Cortical Cell Structure and Function" section of this report. In some studies, there are also data to indicate increased absolute and relative weight of the adrenal gland; however, they did not show a clear dose-response relationship.

Due to the question of the biological relevance of microvesiculation of the adrenal cortex in the rat, OEHHA relied on effects in the liver for quantitative dose-response characterization of oral exposure to chlorantraniliprole. Liver effects were reported in many oral studies and in three species: rat, mouse, and dog (Table 14). The NOAEL of 24 mg/kg-day from the 28-day dietary rat study reported by Donner (2006a) was selected as the oral POD for non-cancer effects as it was the lowest NOAEL in the database for the critical endpoint. This value is supported by the NOAELs of 26.1 mg/kg-day in the chronic dietary mouse study reported by Finlay (2006b). By applying a combined UF of 300, an oral RfD of 0.08 mg/kg-day or 80 µg/kg-day was calculated.

MacKenzie (2004) reported a 90-day dietary rat study that showed a LOAEL and NOAEL of 1526 mg/kg-day and 459.8 mg/kg-day in females, respectively. Modeling of the female rat data indicated a $BMDL_{1SD}$ of 22 mg/kg-day. However, this value was not selected as the POD because it is lower than the two low doses (47 mg/kg-day and 156.7 mg/kg-day) of the study and no statistically significant effects were observed at these two doses.

Table 14. Oral toxicity studies showing liver effects in treated animals.

Study	Details of the study	Endpoint	LOAEL/NOAEL (mg/kg-day)	BMDL (mg/kg-day)
28-Day rat study (Donner, 2006a)	5 rats/sex/dose; 0, 300, 1500 or 8000 ppm in diet; 0, 24.0, 128, 675 mg/kg-day for female rats	Increased relative liver weight in females rats	128/24	Not amenable to modeling
90-Day rat study (MacKenzie, 2004)	10 rats/sex/dose; 0, 600, 2000, 6000 or 20,000 ppm in diet; 0, 47, 156.7, 459.8, 1526 mg/kg-day for female rats	Increased relative liver weight in females rats	1526/459.8	22 (BMR=1SD)
Chronic rat study (MacKenzie, 2006)	Satellite cohort of 10/sex/dose; 0, 200, 1000, 4000 or 20,000 ppm in diet; 0, 10.9, 51.0, 211.5, 1076 mg/kg-day for female rats	Increased relative liver weight in females rats at 12 month	211.5/51.0	Not amenable to modeling
Chronic mouse study (Finlay, 2006b)	70 mice/sex/dose; 0, 20, 70, 200, 1200, or 7000 ppm in diet; 0, 2.6, 9.2, 26.1, 157.6, or 935.1 mg/kg-day for male mice	Increased relative liver weight in male mice	157.6/26.1	Not amenable to modeling
Chronic mouse study (Finlay, 2006b)	70 mice/sex/dose; 0, 20, 70, 200, 1200, or 7000 ppm in diet; 0, 3.34, 11.6, 32.9, 195.6, or 1155 mg/kg-day for female mice	Increased relative liver weight in female mice	195.6/32.9	Not amenable to modeling
Chronic mouse study (Finlay, 2006b)	70 mice/sex/dose; 0, 20, 70, 200, 1200, or 7000 ppm in diet; 0, 2.6, 9.2, 26.1, 157.6, or 935.1 mg/kg-day for male mice	Increased hepatocellular hypertrophy in male mice	157.6/26.1	200.6 (BMR=10%)
One-year dog study (Luckett, 2006)	5/sex/dose; 0, 1000, 4000, 10,000 or 40,000 ppm in diet; 0, 32.0, 111.5, 316.6, 1164 mg/kg-day for males; 0, 34.0, 113.2, 277.8, 1233 mg/kg-day for females	Increased relative liver weight in both sexes	Male: 1164/316.6 Female: 1233/277.8	Not amenable to modeling

Table 14 (Continued)				
Study	Details of the study	Endpoint	LOAEL/NOAEL (mg/kg-day)	BMDL (mg/kg-day)
Rat reproductive study (Malley, 2006a); from prior to breeding, and continuing through breeding, gestation and lactation for two generations	30/sex/dose; 0, 200, 1000, 4000 and 20,000 ppm in diet; dose ranges for F0 and F1 generation parental animals of both sexes were: 0, 12.0–20.4, 60.4–104, 238–406, and 1199–2178 mg/kg-day	Increased relative liver weight in F0 and F1 female rats	NOAEL=1000 ppm F0 females: 77.8 F1 females: 104	Not modelled

There was only one dermal study; it is the 28-day dermal rat study reported by Finlay (2006a). In this study, decreased in body weight gain was reported for both male and female rats. However, the decreases in females were not statistically significant. Using the decreased body weight gain in males, OEHHA determined a dermal NOAEL of 300 mg/kg-day. OEHHA also conducted a BMD modeling of the data and calculated a $BMDL_{1SD}$ of 166 mg/kg-day.

Assuming a dermal absorption of 3% (Appendix E), OEHHA estimated an equivalent systemic dose of the dermal $BMDL_{1SD}$ determined in the rat study by multiplying 166 mg/kg-day by 0.03. This gave an estimated systemic dose of 5 mg/kg-day, which is lower than the oral POD of 24 mg/kg-day. For this reason, OEHHA used a dermal POD of 166 mg/kg-day for evaluating dermal exposures in this assessment. By applying a combined UF of 300, a dermal RfD of 0.5533 mg/kg-day or 553.3 µg/kg-day was calculated.

B. Cancer Effects

US EPA classifies chlorantraniliprole as “not likely to be carcinogenic to humans”, and does not expect the chemical to pose a cancer risk to humans (US EPA, 2008). This classification was based on lack of evidence of carcinogenicity and adverse findings in the two-year oral feeding studies in rats, 18-month oral feeding studies in mice, and no adverse finding in the one-year oral feeding study in dogs. Chlorantraniliprole has not been evaluated for listing on California’s Proposition 65 list of known carcinogens, nor has it been classified by the International Agency for Research on Cancer (IARC). OEHHA found that there were no significant treatment-related tumors reported in the submitted chronic/oncogenicity studies, but notes that chlorantraniliprole has not been adequately tested in mice, based on the less than 2-year study duration, and that the

one-year dog study was also not of sufficient duration for assessing lifetime carcinogenicity in the species. OEHHA also determined that there was no mutagenic concern reported in the genotoxicity studies. Based on the above weight of evidences, OEHHA did not quantitatively evaluate cancer risk in this assessment.

V. EXPOSURE ASSESSMENT

CDFA applies chlorantraniliprole for the control of JB in California. In this screening-level exposure assessment, OEHHA assessed potential residential exposure to chlorantraniliprole from applications to turf and soil. The assessment is based on the US EPA post-application exposure methodology, as described in the US EPA Standard Operating Procedure (SOP) for Residential Pesticide Exposure (US EPA, 2012a), and environmental monitoring data provided by DPR (2020).

DPR conducted a monitoring study for Acelepryn® which was used to treat JB in Sacramento County on April 29 2016 and Santa Clara County on May 3, 2016 (DPR 2020). In the treatments, the pesticide was sprayed to turf, ground cover, soil around rose plants, and bare soil under other ornamental host plants. Prior to the applications, Acelepryn® (18.4% chlorantraniliprole) was diluted with water to 0.017% chlorantraniliprole. The mixed product was then sprayed through a chemical applicator spray gun with a maximum application rate of 7.5 gallons per 1,000 ft^2 (0.5 lb chlorantraniliprole /acre), followed by an application of water.

In the monitoring study, DPR collected air samples, turf dislodgeable residue (TDR) samples, foliage total residue samples, and turf and soil core samples (Table 15). Potential pathways for residents exposed to chlorantraniliprole in treated areas are inhalation of droplets in the air, oral and dermal exposure to residues on soil, and grass and dermal exposure to residues on groundcover. Air samples were collected before, during and after the treatments. All the other types of samples were collected pre- and post-treatment. Details of the environmental monitoring methods, procedures, and results are provided in “Summary of Japanese Beetle Eradication Program Monitoring for Chlorantraniliprole in Sacramento and Santa Clara Counties, 2016” (DPR, 2020).

DPR collected two samples before application, four samples during and shortly after application, and four samples after application. Chlorantraniliprole was not detected in any of the 10 air samples collected by DPR. This is expected since chlorantraniliprole has very low vapor pressure at 2.1×10^{-13} mm Hg at 25 °C and the deposited residue is not likely to volatilize into the air. The detection limits of the eight air samples during and after applications ranged from 0.014 to 0.038 $\mu g/m^3$. As chlorantraniliprole was not detected in air samples collected during or after application, the inhalation exposure pathway was not evaluated quantitatively in this assessment.

Table 15. Environmental sample types collected by DPR (2020) and the exposure pathways considered in this screening-level risk assessment.

Environmental monitoring sample type	Exposure pathway for residents
Air samples	Inhalation exposure, not evaluated quantitatively
Turf dislodgeable residue samples	Dermal exposure
Turf dislodgeable residue samples	Hand to Mouth exposure
Turf and soil core samples	Incidental ingestion
Groundcover foliage samples	Dermal exposure, not evaluated quantitatively

DPR collected four ground cover foliage samples prior to treatment and once residues had dried following treatment. Chlorantraniliprole residues in these samples ranged from 1.44 to 5.83 ppm. Two ground cover foliar samples collected before treatment were below the detection limit. The only plausible exposure pathway to the dried chlorantraniliprole residue on ground cover foliage is dermal exposure. Foliage total residue samples (collected from ground cover plants) were not evaluated quantitatively because plants were determined to be a minor pathway (children are likely to spend more time on turf than on or near ground cover plants, and turf is being quantitatively evaluated), and foliage samples were measured as an amount per unit mass of ground cover, not an amount per unit surface area. Due to the units of measurement, dermal exposure to ground cover could not be quantitatively evaluated in this assessment.

The three exposure pathways evaluated quantitatively in this assessment are discussed in detail below and include dermal exposure to dislodgeable residue on turf, hand-to-mouth ingestion of dislodgeable residue on turf, and incidental ingestion of turf and soil.

Children are of particular concern in this health risk assessment as they may play on treated turf and be exposed to the residues through dermal contact and incidental oral ingestion of turf and soil. Moreover, children are considered an especially sensitive population. Therefore, exposure parameters that are specific to 1<2 years old are used for this assessment.

JB detection is sporadic and the pest is only vulnerable to chlorantraniliprole at a specific time in its life cycle, young larvae in the shallow root zone of turf. Therefore, a residential backyard is unlikely to be treated every year for an extended period of time or treated for more than two to three times in a given year. However, chlorantraniliprole is quite stable in soil, with estimates of half-lives ranging from 52 days to over 200 days have been reported (Sharma et al., 2005). For the purpose of this assessment, we assumed children could be exposed to the residues on a subchronic basis, i.e., repeated exposure over a few years.

A. Dermal exposure to dislodgeable residue on turf

For residents exposed to chlorantraniliprole through dermal contact of residue on turf, the dermal daily dose, DD_{dermal} (µg/kg-day), can be calculated using Eq. 1.

$$DD_{dermal} = (TDR \times TC \times ET)/BW \quad \textbf{Eq. 1}$$

Where:

TDR = turf dislodgeable residue (µg/cm^2) reported by the monitoring study (DPR, 2020);
TC = transfer coefficient, for children 1<2 years old, assumed to be 49,000 cm^2/hour;
ET = exposure time, for children 1<2 years old, assumed to be 1.5 hour/day;
BW = body weight, for children 1<2 years old, assumed to be 11.4 kg.

The input values selected for TC, ET, and BW followed the SOP of US EPA (2012a). DPR collected eight turf dislodgeable residue (TDR) post-treatment samples using the Modified California Roller method. The method uses a weighted cylinder rolling back and forth five times over a cotton fabric held in place on a turf surface, transferring the chemical residues to the fabric. The mean chlorantraniliprole residue in these TDR samples was 41.6 µg/sample with a maximum of 62.9 µg/sample, over a 5690 cm² sample area. The corresponding mean and maximum are 0.00731 and 0.0111 µg/ cm², respectively. All four background samples were non-detects. The estimated mean and high-end DD_{dermal} values are listed in Table 16.

Table 16. Estimated dermal exposure of a child to dislodgeable residue of chlorantraniliprole on turf.

Population	TDR µg/cm^2	TC cm^2/hr	ET hr/day	BW kg	DD_{dermal} µg/kg/day
Child (1<2 yr old)	0.00731 (mean)	49,000	1.5	11.4	47.1 (mean)
	0.0111 (maximum)	49,000	1.5	11.4	71.6 (high-end)

TDR=turf dislodgeable residue, TC=transfer coefficient, ET=exposure time, BW=body weight, DD=dermal dose

For comparative purpose, the dermal dose of pesticide for adults as a receptor can be estimated as TC /BW = 2,250 cm^2/hr-kg using the following point estimates: TC is 180,000 cm^2/hr and BW is 80 kg (US EPA, 2012a). For children 1<2 years old, this ratio is 4,298 cm^2/hr-kg. If we assume TDR and ET are not age dependent, the dose estimate for children 1<2 years old is almost twice as high as the corresponding dose estimate for adults.

B. Hand-to-mouth ingestion of dislodgeable residue on turf

Dose from hand-to-mouth ingestion of chlorantraniliprole residues from the treated turf was calculated for children 1<2 years based on the behavioral characteristics of this potentially exposed life-stage. The daily dose absorbed through the oral route is $DD_{oral-abs}$. The equation and input parameters used for the calculation followed the guideline of US EPA (2012a) as shown in Eq. 2:

$$DD_{oral-abs} = \frac{(HR \times F_M \times SA_H \times ET \times N\_Replen \times (1-(1-SE)^{Freq_{HtM}/N\_Replen})}{BW} \quad \textbf{Eq. 2}$$

Where:

HR = average residue available on the hands (μg/cm^2), estimated by Eq. 3

$$HR = \frac{Fai_{hands} \times DE}{2 \times SA_H} \quad \textbf{Eq. 3}$$

Fai_{hands} = fraction of the chemical on hands from dermal transfer coefficient study (unitless) for liquid formulation, assumed to be 0.06;
DE = dermal exposure (μg) for one day, calculated by Eq. 4
SA_H = typical surface area of one hand, for children 1<2 years old, assumed to be 150 cm^2;

$$DE = TDR \times TC \times ET \times 1\ day \quad \textbf{Eq. 4}$$

TDR = turf dislodgeable residue (μg/cm^2) reported by the monitoring study (DPR, 2020);
TC = transfer coefficient for child 1<2 years old, 49,000 cm^2/hour;
ET = exposure time, 1.5 hours/day;

Other terms:
F_M = fraction hand surface area mouthed, assumed to be 0.127 fraction/event;
N_Replen = replenishment intervals per hour, assumed to be 4 intervals/hour;
SE = saliva extraction factor, assumed to be 0.48 (unitless);
Freq_HtM = hand-to-mouth events per hour, assumed to be 13.9 events/hour;
BW = body weight for children 1<2 years old, assumed to be 11.4 kg.
Hand-to-mouth exposure used the same monitoring data with the dermal exposure due to TDR. With the mean TDR at 0.00731 and the maximum at 0.0111 μg/ cm², DE was estimated at 537 μg and 815 μg, respectively. The estimated mean and high-end DD_{abs} values are listed in Table 17.

Table 17. Estimated hand-to-mouth exposure of a child to dislodgeable residue of chlorantraniliprole on turf.

Population	TDR µg/cm^2	DE µg	HR_t µg/cm^2	$DD_{oral-abs}$ µg/kg/day
Child (1<2 yr old)	0.00731 (mean)	537	0.11	1.00 (mean)
	0.0111 (maximum)	816	0.16	1.52 (high-end)

C. Incidental ingestion of turf and soil

To estimate exposures through incidental soil ingestion, the absorbed daily dose through the oral route, $DD_{oral-abs}$ (µg/kg-day), can be calculated using Eq. 5.

$$DD_{oral-abs} = (C_{Soil} \times IR_{Soil} \times GA \times CF)/BW \quad \textbf{Eq. 5}$$

Where:

C_{Soil} = residues detected in turf plugs and soil cores (µg/g or ppm) reported by the monitoring study (DPR, 2020);
IR_{Soil} = ingestion rate of soil (mg/day), assumed to be 40mg/day;
GA = gastrointestinal absorption factor of chlorantraniliprole, assumed to be 100%;
CF = weight unit conversion factor (1×10^{-3} g/mg); and
BW = body weight, for children 1<2 years old, assumed to be 11.4 kg

DPR (2020) collected four turf samples and three soil samples from treated areas once the turf has dried. Each sample consisted of three randomly selected cores taken to a depth of 1 inch. As some turf cores had a substantial amount of soil, the two types of samples were combined in this evaluation. The combined dataset has a maximum and a mean of 1.97 µg/g and 0.961 µg/g, respectively. All six pre-treatment turf and soil samples were non-detects.

We followed US EPA guidelines for evaluating residential pesticide exposure (US EPA 2012a) and assumed that pesticide residues in soil could be ingested by children 1<2 years old when playing on treated areas with normal mouthing activities. US EPA updated the Exposure Factors Handbook chapter 5 for soil and dust ingestion in 2017 and recommended uses of 40 mg/day as the IR_{Soil} of children 1<2 years old (US EPA, 2017). Assuming 11.4 kg to be the BW for children 1<2 years old, we estimated DD_{abs} of 0.00691 µg/kg-day as the high-end exposure and 0.00337 µg/kg-day as the mean exposure (Table 18).

Table 18. Estimated incidental ingestion exposure of a child to chlorantraniliprole in turf and soil.

Population	C_{soil} µg/g	IR_{soil} cm mg/day	GA	BW kg	DD_{abs} µg/kg/day
Child (1<2 yr old)	0.961 (mean)	40	1	11.4	0.0034 (mean)
	1.97 (maximum)	40	1	11.4	0.0069 (high-end)

VI. RISK CHARACTERIZATION

One of the commonly used methods to evaluate non-cancer health risk is to use the hazard quotient approach. It compares the estimated dose with a level of exposure below which adverse health effects are not anticipated, also called a reference dose, or RfD. This approach can be represented by Eq 6:

$$\textbf{hazard quotient} = DD/RfD \qquad \textbf{Eq.6}$$

Where:

Hazard quotient = less than one indicates no health effects are anticipated, and greater than one indicates that there may be a health concern.

DD = Daily dose (µg/kg-day) associated with a specific route (i.e., oral or dermal).

RfD = Reference dose (in mg/kg bw-day or µg/kg bw-day). This is an estimate of a daily dose at or below which adverse health effects are not likely to occur.

Using the RfDs and dose estimates developed in this assessment, we calculated hazard quotients for high-end and mean exposure scenarios and the results are presented in Table 19. Since all the hazard quotients are less than one, indicating the use of chlorantraniliprole on turf for the treatment of JB by CDFA is not likely to pose a health hazard to the residents.

Table 19. Calculation of hazard quotients for various exposure pathways.

Exposure pathway	DD (µg/kg-day)	RfD (µg/kg-day)	Hazard Quotient
High-end estimate, dermal exposure to dislodgeable residue on turf Child (1<2 yr old)	71.6	533.3	0.13
Mean estimate, dermal exposure to dislodgeable residue on turf Child (1<2 yr old)	47.1	533.3	0.088
High-end estimate, hand-to-mouth Ingestion of dislodgeable residue on turf Child (1<2 yr old)	1.52	80	0.019
Mean estimate, hand-to-mouth ingestion of dislodgeable residue on turf Child (1<2 yr old)	1.0	80	0.013
High-end estimate, incidental ingestion of turf and soil Child (1<2 yr old)	0.0069	80	0.000086
Mean estimate, incidental ingestion of turf and soil Child (1<2 yr old)	0.0034	80	0.000043

It should be noted that several health-protective assumptions were used in the exposure assessment:

- We assumed the same level of exposure took place every day for an extended period of time. It is likely there are variations in behavior. For example, a child may not play in the treated lawn every day. It is unlikely that a child would be dermally exposed to dislodgeable residue on turf or ingest contaminated soil at the estimated rate every day.
- Exposures to residues on soil and turf were based on measurements taken shortly after treatment. We assumed there was no decrease in residue level over time (e.g., loss of dislodgeable residue due to human contact, photolysis), up to many weeks. The chemical has a relatively long half-life in soil, over 52 days.
- Intake rates, dermal contact rate, and body weight of a child were used in the estimation of dermal and oral exposures of chlorantraniliprole. Children are considered a sensitive population because of their behavior and relatively high exposure rates after adjustment for body weight.

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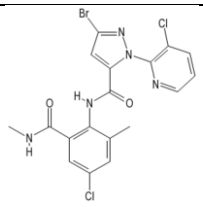
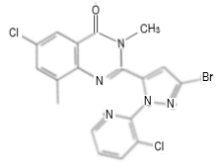
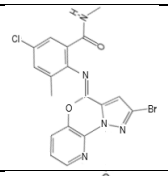
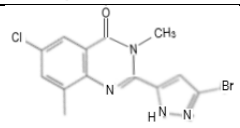
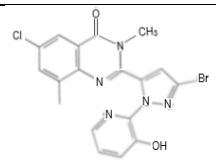
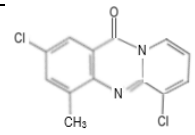
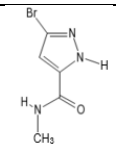
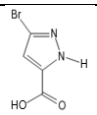
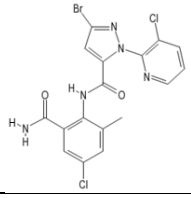
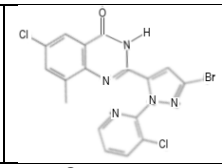
APPENDIX A. Environmental degradation products, metabolites and impurities of chlorantraniliprole

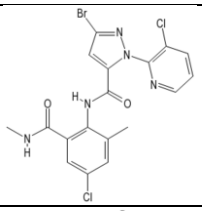
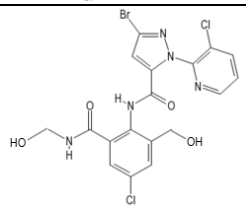
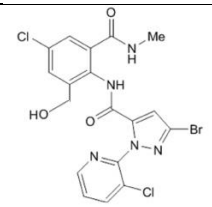
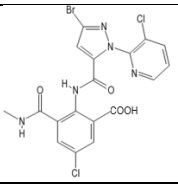
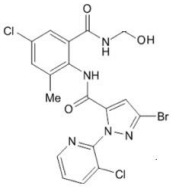
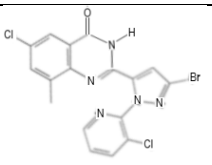
Environmental Degradation Products of Chlorantraniliprole

Chemical Name[A]	Structure[B, C]	Study[A]	LD_{50}[C]	Mutation Assay[C, D]
DPX-E2Y45 3-Bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide Chlorantraniliprole		Aqueous photolysis	>5000 mg/kg	Negative
IN-EQW78 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]- 6-chloro-3, 8-dimethyl-4(3*H*)-quinazolinone		Aerobic Soil Anaerobic Soil	>2000 mg/kg	Negative
IN-LBA22		Aqueous photolysis Anaerobic Soil		
IN-LBA24		Aqueous photolysis Anaerobic Soil	>2000 mg/kg	Negative
IN-LBA23		Aqueous photolysis		
IN-ECD73 2-[3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-yl]-6-chloro-3,8-dimethyl-4(3H)-quinazolinone		Aerobic Soil Anaerobic Soil	>2000 mg/kg	Negative
IN-F6L99 5-Bromo-*N*-methyl-1*H*-pyrazole-3-carboxamide		Aerobic Soil Anaerobic Soil	>2000 mg/kg	Negative
IN-EVK64[E] 5-Bromo-1H-pyrazole-3-carboxylic acid		Aerobic Soil		
IN-F9N04 *N*-[2-(Aminocarbonyl)-4-chloro-6-methylphenyl]-3-bromo-1-(3-chloro-2-pyridinyl)1*H*-pyrazole-5-carboxamide		Anaerobic Soil		

IN-GAZ70 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]- 6-chloro-8-methyl-4(3*H*)-quinazolinone		Aerobic Soil Anaerobic Soil		

[A] US EPA 2008, 2009, 2013; [B] APVMA 2008; [C] NFSA 2010; [D] DPR 2008; [E] Name & Structure for IN-EVK64: ChemSpider 2019

Metabolites of Chlorantraniliprole from Rat Studies

Chemical Name[A]	**Structure**[A]
DPX-E2Y45 3-Bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide Chlorantraniliprole	
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-HXH44 3-Bromo-*N*-[4-chloro-2-(hydroxymethyl)-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
IN-KAA24 2-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-chloro-3-[(methylamino)carbonyl]benzoic acid	
IN-H2H20 3-Bromo-*N*-[4-chloro-2-[[(hydroxymethyl)amino]carbonyl]-6-methylphenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
IN-GAZ70 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-chloro-8-methyl-4(3*H*)-quinazolinone	

[A] US EPA (2013 p. 19/21)

Impurities in Technical DPX-E2Y45[A]

Impurity		**IN-E8S90**	**IN-G2S78**
% in Technical DPX-E2Y45		2.05 g/kg (0.2%)	2.96 g/kg (0.3%)
Study Type	**Species**	**Result**	**Result**
Acute Oral LD_{50}	Rat	>5000 mg/kg	323.5 mg/kg
Acute Dermal LD_{50}	Rat	>5000 mg/kg	>5000 mg/kg
Acute Inhalation LC_{50}	Rat	-	>2.1 mg/kg
Skin Irritation	Rabbit	Not irritating	-
Eye Irritation	Rabbit	Mild irritation, clear w/in 72 h	Slightly irritating, clear w/in 42 h
Skin sensitization	Mouse	Not sensitizing	Not sensitizing
Bacterial Mutation	*S. typhimurium/E coli* +/-S9	Negative	Negative

[A] NFSA (2010) p. 5-15

Two impurities detected in the commercial products of chlorantraniliprole (Coragen® 20 SC) are IN-G2S78 and IN-E8S90. IN-G2S78, which has an acute lethal dose (LD50) of 323.5 mg/kg, occurred in higher amount in the technical material than in the material used for toxicity studies. However, this impurity did not affect the acute toxicity tests of chlorantraniliprole as demonstrated by the low acute toxicity of the technical material. This impurity was also negative in the Ames test; however, additional genotoxicity testing using mammalian cells was recommended by NFSA (2010). It is not demonstrated that this impurity will not affect the chronic toxicity of DPX-E2Y45 technical (NFSA, 2010). According to VKM (2010), a subchronic (90-day) study with DPX-E2Y45 (i.e., E2Y45-282) including a relevant concentration of this impurity (IN-G2S78) should be performed to provide additional information concerning its possible influence on the toxicological profile of chlorantraniliprole.

APPENDIX B. Other subchronic toxicity profiles of chlorantraniliprole

Other Subchronic Toxicity Profile of Chlorantraniliprole

Study	Dose mg/kg-day	EPA NOAEL (mg/kg-day)	EPA LOAEL (mg/kg-day)	Effects	References
2-week gavage/rats 5/sex/group	M/F: 0, 25, 100, 1000	DPR NOEL: (M): 1000 (F): 100	(M): not established (F): ↑cytochrome P450 in liver at 1000 mg/kg	No treatment related lesions noted in histopathology. ↑Cytochrome P-450 isozyme 3A in liver	Munley, 2006c, a
28 Day Dietary/mice Supplemental study; 5/sex/group	(M): 0, 52.1, 181.6, 538.3, 1443 (F): 0, 64.4, 206.1, 657.6, 1524	DPR NOEL: (M):538.3 (F): 206.1	(M): 1443: ↓BW gain & food efficiency, incidence of focal necrosis in liver (F): ↑absolute & relative liver wt	(F): ↑mean & absolute liver wt., ↑mean relative BW at 657.6 & 1524 mg/kg-d; (M): focal necrosis in liver in 2/5 at 1443 mg/kg-d	Finlay, 2006c, a
28 Day oral/dog (M/F) 2/sex/group Supplemental Study	(M): 26, 138, 266, 797, 1302; (F): 28, 138, 298, 888, 1240	N/A	N/A	No adverse effect indicated, no adverse effect or treatment related lesion	Luckett, 2003, a
28 Day Oral/dog Study 1: (M/F): 2/sex/group Study 2: (M): 4/group Supplemental Study	(M/F) study 1: 0, 300, 1000 (M): study 2: 0, 1000	DPR NOEL: (M/F): 300	(M): hypospermato-genesis at 1000 & (M/F): ↑cytochrome P450 (Hypospermatogenesis considered to be unrelated to test a.i,. administration; related to young age of test animals)	(M): Study 1: hypospermatogenesis in testes in 1 of 2 in 300 mg/kg; 2 of 2 in 1000 mg/kg, (M): Study 2: hypospermatogenesis in testes in 1 of 4 in control, 2 of 4 in 1000 mg/kg (M/F): ↑cytochrome P450 at 1000 mg/kg Hypospermatogenisis not observed in other 28-day or 90-day dog study	Serota, 2003, a, c
90-day oral feed/mice (M/F): 15/sex/group	(M): 0, 32.6, 115, 345, 1135; (F): 0, 40.7, 158, 422, 1529	US EPA: 1135 (M); 1529 (F) DPR NOEL: (M): 345 (F): 422	US EPA: Not established DPR: (M/F): ↓mean BW gain or BW loss at HDT; (M): ↑relative liver wt. at HDT	No adverse effect. A slight increase in liver wt at the HDT (M & F) w/no corresponding histopathology evidence of liver toxicity.	Finlay, Gannon (Suppl. No. 1), 2006, a, b
90-day oral feed/dog 4/sex/group	(M): 0, 32.2, 119, 303, 1163; (F): 0, 36.5, 133, 318, 1220	US EPA/DPR: 1163 (M); 1220 (F)	Not established	No adverse effects. A mild increase in liver wt. in (M) at 1163 mg/kg-d, w/no histopathology in liver	Luckett, 2004, a, b
28-day dermal mechanistic supplemental study; 10M/group	0, 1000	DPR NOEL: not determined		Mean BW gain less than control; ↑incidence of microvesiculation	Finlay, 2006d, a

[a] DPR, 2008; [b] US EPA 2012b; [c] NFSA, 2010

APPENDIX C. Reproductive toxicity study in rat (Malley, 2006): Test substance intake and mean absolute and relative liver and adrenal weights in F0 and F1 male and female rats.

Table C-1: Test Substance Intake (mg/kg-day)

	0 ppm	200 ppm	1000 ppm	4000 ppm	20,000 ppm
F0 male, premating (105-days)[A]	0	12.0	60.4	238	1199
F0 female, premating (70-days)[A]	0	15.5	77.8	318	1594
F0 female, gestation (21-days)[A]	0	13.7	68.4	278	1373
F0 female lactation (21-days)[A]	0	31.9	162	654	3118
F1 male, premating (105-days)[A]	0	18.1	89.4	370	1926
F1 female, premating (70-days)[A]	0	20.4	104	406	2178
F1 female gestation (21-days)[A]	0	13.9	70.5	272	1465
F1 female lactation (21-days)[A]	0	34.5	183	696	3641

[A] # days of treatment based on mean body weights Tables 17–32, pp. 97

Table C-2: Mean Absolute and Relative Liver Weights in F0 Male and Female Rats

ppm	0	200	1000	4000	20,000
Male mg/kg-day	0	12.0	60.4	238	1199
Male body wt. (g)	612	604	624	621	609
Male # Liver	30	30	30	30	30
Male Liver absolute wt. (g)	20.720	20.828	22.374	22.176	21.804
Male Liver/BW%	3.385	3.432	3.584*	3.564*	3.562
Female mg/kg-day	0	15.5	77.8	318	1594
Female body wt. (g)	324	323	324	326	334
Female # Liver	30	29	29	27	30
Female Liver absolute wt. (g)	13.828	14.401	14.663	15.329**[11%]	16.049**[16%]
Female Liver/BW%	4.270	4.464	4.528	4.686**[10%]	4.802**[12%]

wt. = weight; BW = body weight;
* statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test compared to control as report (p. 44)
** statistically significant (Dunn's non-parametric pairwise test compared to control as reported

Table C-3: Mean Absolute and Relative Adrenal Weights for F0 Male and Female Rats

ppm	0	200	1000	4000	20,000
Male mg/kg-day	0	12.0	60.4	238	1199
Male body wt. (g)	612	604	624	621	609
Male # Adrenal	30	29	30	30	30
Male Adrenal absolute wt. (g)	0.056	0.057	0.061	0.065*	0.063
Male Adrenal/BW%	0.009	0.009	0.010	0.010*[11%]	0.010*[11%]
Female mg/kg-day	0	15.5	77.8	318	1594
Female body wt. (g)	324	323	324	326	334
Female # Adrenal	29	28	29	27	30
Female Adrenal absolute wt. (g)	0.076	0.080	0.080	0.085*	0.083
Female Adrenal/BW%	0.024	0.025	0.025	0.026**	0.025

wt. = weight; BW = body weight;
* statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test compared to control as report (p. 45)
** statistically significant (Dunn's non-parametric pairwise test compared to control as reported

Table C-4: Mean Absolute and Relative Liver Weights in F1 Male and Female Rats

ppm	0	200	1000	4000	20,000
Male mg/kg-day	0	18.1	89.4	370	1926
Male body wt. (g)	599	608	607	600	585
Male # Liver	29	30	30	30	29
Male Liver absolute wt. (g)	20.901	21.729	21.982	21.735	21.226
Male Liver/BW%	3.486	3.567	3.609	3.614	3.622
Female mg/kg-day	0	20.4	104	406	2178
Female body wt. (g)	334	341	340	337	340
Female # Liver	30	30	30	30	29
Female Liver absolute wt. (g)	14.842	15.257	15.461	16.437*[11%]	17.706*[19%]
Female Liver/BW%	4.436	4.473	4.555	4.871*[10%]	5.201*[17%]

wt. = weight; BW = body weight;
* statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test compared to control as report (p. 44)
** statistically significant (Dunn's non-parametric pairwise test compared to control as reported

Table C-5: Mean Absolute and Relative Adrenal Weights for F1 Male and Female Rats

ppm	0	200	1000	4000	20,000
Male mg/kg-day	0	18.1	89.4	370	1926
Male body wt. (g)	599	608	607	600	585
Male # Adrenal	29	30	30	29	29
Male Adrenal absolute wt. (g)	0.057	0.058	0.059	0.059	0.061
Male Adrenal/BW%	0.009	0.010	0.010	0.010	0.011*[22%]
Female mg/kg-day	0	20.4	104	406	2178
Female body wt. (g)	334	341	340	337	340
Female # Adrenal	30	30	30	30	29
Female Adrenal absolute wt. (g)	0.080	0.084	0.085	0.089*	0.088
Female Adrenal/BW%	0.024	0.025	0.025	0.026	0.026

wt. = weight; BW = body weight;
* statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test compared to control as report (p. 45)
** statistically significant (Dunn's non-parametric pairwise test compared to control as reported

APPENDIX D. BMDS dose-response modeling results

Table 4. Mean Body Weight Gain from Day 0 to 28 in male rats exposed to chlorantraniliprole via dermal route: $BMDL_{STD1}$= 166 mg/kg-day and $BMDL_{0.5SD}$ = 66.8 mg/kg-day (Exp. M4, lowest BMDL); $BMDL_{Rel10}$= 93.9 mg/kg-day and $BMDL_{Rel5}$= 41.1 mg/kg-day (Exp. M4, lowest BMDL).

Table 9. Mean absolute and relative liver weights in male mice after an 18-month feeding study: All continuous standard deviation (1STD) and relative deviation (10%) models were unusable and did not model adequately.

Table 10. Mean absolute and relative liver weights in female mice after an 18-month feeding study: All continuous standard deviation (1STD) and relative deviation (10%) models were unusable and did not model adequately.

Table 11. Incidence of microscopic effects in male mice in an 18-month feeding study: Male mice hepatocellular hypertrophy yield $BMDL_5$ = 52.9 mg/kg-day (LogProbit model, w/no model warning) using dichotomous-added risk model, all other model w/warning or questionable w/goodness of fit p-value <0.1 or scale residual > 2.

APPENDIX E. Dermal absorption of chlorantraniliprole in male rats

NFSA (2010) described a dermal study in male rat by DuPont (Fasano, 2006). There were three groups of four adult male rats per dose level. Two doses were tested: (1) concentrated Coragen 20 SC (high dose, 2000 µg/cm^2); and (2) aqueous dilution of 20 SC formulation with 7.5 µg/cm^2. The chlorantraniliprole compound was (^{14}C) radiolabeled. The rats were exposed for 6 hours before the skin was washed with soap and water. One group was sacrificed after 6 hours, and the other groups were sacrificed after 24 or 504 hours after the beginning of administration. The stratum corneum was removed by tape stripping. Fasano (2006) noted that three weeks after dosing there were higher absorption than after 6 and 24 hours, both for the concentrated formulation and the diluted solution. Therefore, the test substance present in the stratum corneum will eventually become systemically available. Dermal absorption in rats in vivo was estimated to be 1% for the concentrated and 7.5 % (7.34% + 0.188%) for the diluted formulation after 24 hr. NFSA (2010) agreed with Fasano's assessment.

Table E-1. Dermal absorption of chlorantraniliprole in male rats (Kraggerud, 2010)

Dose	Low dose, 7.5 µg/cm^2			High dose, 2000 µg/cm^2		
Time of sacrifice (hours)	6	24	504 (3 weeks)	6	24	504 (3 weeks)
Total absorption* %	0.169	**0.188**	2.745	0.134	**0.287**	0.324
Tape strips** %	6.359	**7.340**	0.809	0.521	**0.656**	0.002
Not absorbed** %	95.109	95.434	91.849	98.042	99.192	97.199

* Amounts in urine, faces, in carcass, and in the skin (not stratum corneum), and from the washing of the cage. ** Amount remaining in stratum corneum

However, DPR did not consider the 7.34% in the stratum corneum (i.e., recovered chlorantraniliprole in the tape strip after 24 hr) as part of the absorbed dose. DPR's interpretation was that 2.745% is the absorbed dose after 504 weeks (DPR, 2008). OEHHA agrees with this determination and for the purpose of this assessment, the dermal absorption of chlorantraniliprole is assumed to be 3%.

This estimate is also supported by other in vivo and in vitro dermal studies described in Summary of Toxicology Data, Chlorantraniliprole (DPR, 2008). These study results are summarized below.

In Vivo Dermal Kinetics in the Rat: 12 male Crl:CD7(SD)IGS BR rats per group received a single non-occluded (mesh covered) dermal application of [^{14}C] DPX-E2Y45 35WG for 6 h. Group 1 received undiluted, 1750 µg/cm^2, and group 2 received aqueous diluted 7.5 µg/cm^2 samples. Four rats/group sacrificed 6, 24 and at 504 h after application. The mean absorbed of applied radioactivity of the undiluted samples were as follows: 6 h (0.529%); 24 h (0.47%); and 504 h (1.087%). The mean absorbed doses of the diluted samples were as follows: 6h (1.24%); 24 h (0.192%) and 504 h (2.103%).

In Vivo Dermal Absorption in the Rat: 2 groups, 12 male Crl:CD7(SD) rats received non-occluded (mesh covered) dermal application of [^{14}C] DPX-E2Y45 20SC at 2000 µg/cm^2 undiluted, and 7.5 µg/cm^2 aqueously diluted samples. The absorbed mean dose of undiluted sample was as follows: 6 h (0.112%); 24 h (0.261%); 504 h (0.322%). The absorbed mean dose of the diluted sample was as follows: 6 h (0.064%); 24 h (0.11%); 504 h (2.74%).

In Vitro Absorption in Rat and Human: 12 human and rat skin samples per group exposed (unoccluded) to [Pyrazole carbonyl-^{14}C] DPX-E2Y45 35WG (water dispersable granule); undiluted 1750 µg/cm^2, and aqueous diluted 7.5 µg/cm^2 samples. Radiolabel was not detected in the receptor fluid for skin of either species. The mean ^{14}C absorbed (in receptor fluid) in the aqueous dilution after 6 h was: rat skin, 0.37%; human skin, 1.43%; and after 24h: rat skin: 0.41%; human skin: 0%.

In Vitro Absorption in Rat and Human Skin: 12 human and rat skin samples per group received a single unoccluded treatment of [Pyrazole carbonyl-^{14}C] DPX-E2Y45 20SC for 6 and 24 h at application rate of 2000 µg/cm^2 undiluted, and 7.5 µg/cm^2 aqueously diluted samples. [^{14}C] of undiluted DPX-E2Y45 20SC was not detected in the receptor fluid of skin of either species after 6 and 24 h. [^{14}C] was not detected in receptor fluid of skin treated with aqueous dilution of DPX-E2Y45 20SC for either species after 6h, and after 24 h 0.62% (rat skin) and 0% (human skin) was measured in the receptor fluid.