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Final Human Health and Ecological Risk Assessment for Diflubenzuron Rangeland Grasshopper and Mormon Cricket Suppression Applications

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EXECUTIVE SUMMARY

The United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Plant Protection and Quarantine (PPQ) is proposing the use of the insecticide diflubenzuron liquid ultra-low volume (ULV) spray in its cooperative rangeland grasshopper and Mormon cricket suppression program. Diflubenzuron is an insect growth inhibitor. The proposed formulation, Dimilin® 2L, is a liquid that can be applied by ground-based equipment or aerially at reduced rates compared to the current labelled rates for grasshopper control. The formulation is a restricted use pesticide due to its toxicity to aquatic invertebrates. It is used only by certified applicators, or persons under their direct supervision, and only for those uses covered by the certified applicator's certification.

USDA-APHIS evaluated the potential human health and ecological risks from the proposed use of the Dimilin® 2L formulation in this assessment and determined that the risks to human health and the environment are low. The proposed use of diflubenzuron as a ULV spray with a low volume application rate and adherence to label requirements substantially reduces the potential for exposure to humans and the environment. APHIS does not expect adverse health risks to workers based on the low potential for exposure to diflubenzuron when applied according to label directions, and use of personal protective equipment during applications. APHIS quantified the potential risks associated with accidental exposure of diflubenzuron for workers during mixing, loading, and application based on the proposed program use. The quantitative risk evaluation results indicate no concerns for adverse health risk for program workers from the program application. APHIS treatments are conducted in rural rangeland areas, where agriculture is a primary economic factor with widely scattered single rural dwellings with low population density. The risk to the general public from diflubenzuron exposure in the treatment areas from ground or aerial applications is also minimal due to label requirements and additional program measures designed to reduce exposure to the public.

Diflubenzuron's risk to most non-target terrestrial and aquatic wildlife is low based on the available effects data and proposed use pattern in the program. The Program makes applications below label rates and uses buffers around aquatic habitats to reduce the potential for exposure and risk to aquatic flora and fauna. Risk to terrestrial vertebrates is also low based on available toxicity data. Diflubenzuron has low toxicity and risk to some nontarget terrestrial invertebrates, including pollinators such as honey bees. The impacts of diflubenzuron to sensitive nontarget terrestrial invertebrates will be greatest for those insect groups that feed on treated vegetation. The risk to sensitive terrestrial invertebrates will be minimized due to program measures such as applying it only once per season, and the use of lower application rates and reduced agent area treatments (RAATs).

1.0 INTRODUCTION

The United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Plant Protection and Quarantine (PPQ) proposes the use of diflubenzuron in its rangeland grasshopper and Mormon cricket suppression program. This human health and ecological risk assessment (HHERA) provides a qualitative and quantitative evaluation of the potential risks and hazards to human health, nontarget fish, and wildlife as a result of exposure to diflubenzuron. The program would apply the insecticide using ULV and RAATs aerial or ground applications to suppress populations of rangeland grasshopper species, such as migratory grasshopper, valley grasshopper, bigheaded grasshopper, clearwinged grasshopper, and Mormon cricket. Diflubenzuron is an insect growth inhibitor.

The methods used in the human health risk assessment portion of this document follow standard regulatory guidance and methodologies (NRC, 1983; USEPA, 2016a), and generally conform to those methods used by other Federal agencies such as the U.S. Environmental Protection Agency, Office of Pesticide Programs (USEPA/OPP). The methods used in the ecological risk assessment portion of this document that assess potential ecological risk to nontarget fish and wildlife follow USEPA and other published methodologies regarding eco-risk assessment.

The risk assessment is divided into four sections beginning with the problem formulation (identifying hazard), a toxicity assessment (the dose-response assessment), and an exposure assessment (identifying potentially exposed populations and determining potential exposure pathways for these populations). In the fourth section (risk characterization), the information from the exposure and toxicity assessments is integrated to characterize the risk of diflubenzuron applications to human health and the environment.

2.0 PROBLEM FORMULATION

Grasshoppers and Mormon crickets are closely related insects that belong to the order Orthoptera. Nearly 400 grasshopper species inhabit the 17 western States involved in the USDA-APHIS grasshopper program, but only a small percentage are pest species. Anywhere from 15 to 45 species of grasshoppers can be found in a particular rangeland ecosystem, and economic damage can occur when grasshopper populations exceed population thresholds.

Mormon crickets (*Anabrus simplex*) are flightless, shield-backed katydids. Although they do not fly, Mormon crickets are highly mobile and capable of migrating great distances. They move by walking or jumping, and may devour much of the forage in their path.

Both insects damage grasses and other vegetation by consuming plant stems and leaves. Their feeding causes direct damage to plant growth and seed production, thus reducing valuable livestock forage. In addition, the damage they cause to plants may result in soil erosion and degradation, disruption of nutrient cycles, interference with water filtration, and potentially irreversible changes in the flora and fauna of the rangeland ecosystem. In addition, some populations that develop on rangelands can invade adjacent cropland where the value of crop plants is much higher than rangeland (USDA-APHIS, 2015a).

Diflubenzuron is an insect growth regulator that inhibits chitin synthesis (interference with the formation of the insect's exoskeleton). The likely mechanism is through blockage of chitin synthetase, an enzyme in the biosynthesis pathway of chitin (Cohen, 1993; USEPA, 1997). Exposure of insect life stages to diflubenzuron can result in larvicidal and ovicidal effects. The larvae are unable to molt properly due to a lack of chitin in the new cuticle. Exposure of larvae may occur through dermal contact, but the primary route of intoxication is ingestion. Ovicidal effects may occur through direct contact of eggs or through exposure of gravid females by ingestion or dermal routes. The larva develops fully in the egg, but is either unable to hatch or dies soon after hatching due to chitin deficiency in the cuticle. This inhibition of chitin synthesis affects primarily immature insects, but can also affect other arthropods and some fungi.

Diflubenzuron is used to control agricultural pests such as twig borer, stink bug, grasshopper, beet armyworm, soybean looper, rust mite, artichoke plume moth, and peanut root knot nematode (USEPA, 2012a). USDA-APHIS uses diflubenzuron to suppress pest species of grasshopper and Mormon crickets. Diflubenzuron is the most widely used insecticide in the USDA-APHIS grasshopper and Mormon cricket suppression program (USDA-APHIS, 2015b). The diflubenzuron ULV spray is effective only against immature grasshoppers and crickets and can only be used in the early-season. It is used typically at a RAAT rate with a skipped swath width of typically no more than 200 feet for aerial applications. Diflubenzuron treatments are used commonly in the program with slow acting results that can take a week or longer to notice.

The following sections discuss the Chemical Description and Product Use; Physical and Chemical Properties; Environmental Fate; and Hazard Identification for diflubenzuron.

2.1 Chemical Description and Product Use

Diflubenzuron (CAS No. 35367-38-5, $C_{14}H_9ClF_2N_2O_2$) is the common name of chemical N-[[(4-chlorophenyl)amino] carbonyl]-2,6-difluorobenzamide or 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea. The chemical structure is illustrated in figure 2-1.

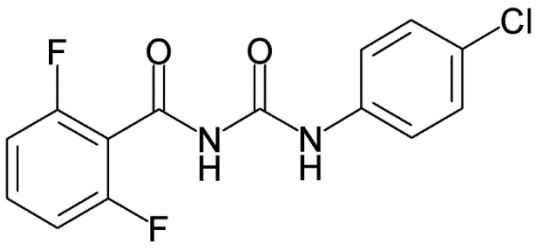

Figure 2-1 The chemical structure of diflubenzuron

First registered with USEPA in 1979, diflubenzuron is the active ingredient (a.i.) in several products named Dimilin®, Vigilante, Micromite, and Adept (USEPA, 1997). The Program uses the diflubenzuron ULV spray (Dimilin® 2L, EPA Reg. No. 400-461) (MacDermid Agricultural Solutions, Inc., 2017). A ULV application is defined as an application of 0.5 gallon or less per acre of insecticide in liquid form. Dimilin® 2L contains 2 pounds diflubenzuron per gallon (22% of active ingredient of diflubenzuron and 78% of other ingredients). The formulation is a restricted use pesticide because of its toxicity to aquatic invertebrates. It is used only by certified applicators, or persons under their direct supervision, and only for those uses covered by the certified applicator's certification. The product label (MacDermid Agricultural Solutions, Inc., 2017) also specifies it is not for use in and around residential areas. Applications are made in accordance with the label requirements for Dimilin® 2L and related formulations registered for grasshopper control.

2.2 Physical and Chemical Properties

Diflubenzuron is a white crystalline solid with a molecular weight of 310.7 g/mole and a melting point of 210–230 ºC. It has a vapor pressure of 9.0 $x10^{-10}$ mm Hg, a Henry's Law constant of 1.19 x 10^{-11} atm-m^3/mole at 25 ºC, and an octanol-water coefficient of 3.70. Diflubenzuron is insoluble in water with a water solubility of 0.08 mg/L at 25 ºC (USEPA, 2015, 2018). However, it is soluble in organic solvents such as acetonitrile (2 g/L), acetone (6.5 g/L), dimethylsulfoxide and dimethylformamide (120 g/L), and N-methylpyrolidone (200 g/L) (USEPA, 1997).

The Dimilin® 2L formulation is an off-white to tan liquid with a slight odor. Its pH ranges between 8 and 10. It has a boiling point of >100 °C and a flash point at 93 °C. Its density ranges between 1.071 and 1.111 g/cm^3 (25 °C). It is dispersible in water and partly soluble in organic solvents (MacDermid Agricultural Solutions, Inc., 2015).

2.3 Environmental Fate

The environmental fate describes the processes by which diflubenzuron moves and is transformed in the environment. The environmental fate processes include: 1) persistence and degradation, 2) mobility and migration potential to groundwater and surface water, and 3) plant uptake.

Diflubenzuron is non-persistent in soil when soil microbes are present. Biodegradation is the major route of dissipation for diflubenzuron with an aerobic soil half-life of 2.2 to 6.2 days and an anaerobic soil half-life of 2 to 14 days in sandy loam soil (USEPA, 2012a, 2018). The major bio-degradate is 4-chlorophenyl urea. Diflubenzuron is relatively stable to light with a half-life of 144 days in a soil photolysis study. Terrestrial field dissipation studies in orchards and on bare ground report half-lives of 5.8 to 13.2 days, respectively. However, diflubenzuron dissipated slower with half-live values of 68.2 to 78 days in California citrus and Oregon apple orchards under terrestrial field conditions. Forestry field dissipation studies reported half-lives of 30 to 35 days.

Diflubenzuron released in soil is slightly mobile in the environment, but it is unlikely to leach into groundwater because diflubenzuron has low water solubility, and has been shown to bind readily with organic matter in soils (USEPA, 1997, 2012a). Adsorption to organic carbon values vary depending on soil type (20, 25, 40, 40, 130, 110, 150, and 3,500 L/kg for a silt loam, loamy sand, sandy clay loam, silty clay loam, clay, sandy clay loam, clay hydrosoil, and peat hydrosoil, respectively) and indicate preferential adsorption to soil over remaining in solution due to low solubility (Sundaram, et al., 1997; USEPA, 2012a). Adsorption to fraction organic carbon values are 34.2 L/kg (sand) and 36.8 L/kg (sandy clay) (USEPA, 2012a). Soil adsorption coefficients ranging from 8,700 to 10,000 have also been reported in the literature (US FS, 2004). Spray drift and transport with eroded soil in runoff are the main mechanisms of transport for diflubenzuron (USEPA, 2012a).

Diflubenzuron is not persistent in water with a dissipation half-life of 2 to 6 days from aquatic field dissipation studies (USEPA, 2012a). Diflubenzuron degrades through aerobic aquatic metabolism with a half-life ranging from 3.7 to 26 days in two aerobic aquatic studies. Under anaerobic conditions, the metabolic half-life for diflubenzuron is reported as 34 days. The major degradates of aquatic biodegradation are 4-chlorophenyl urea and 2,6-difluorobenzoic acid. Degradation of diflubenzuron through hydrolysis is pH dependent (more stable under acidic and neutral conditions and less stable under basic conditions). Diflubenzuron was stable to hydrolysis in acidic and neutral conditions with half-life values ranging from 187 to 433 days at pH 5, 117 to 247 days at pH 7. Half-life values were shorter in more alkaline conditions with values ranging from 32.5 to 44 days at pH 9, and a 7.5 days at pH 12 (USEPA, 2012a). Diflubenzuron is stable to hydrolysis under dark aqueous photolysis control at pH 7. Diflubenzuron is less stable to direct aqueous photolysis with a half-life of 80 days assuming a 12-hour light/dark cycle. Degradation half-lives in the presence of oxygen are slightly shorter ($T_{½}$ = 0.42 days) compared to degradation in the absence of oxygen ($T_{½}$ = 0.97 days) (Anton et al., 1993). Due to its low solubility (0.08 mg/L) and preferential binding to organic matter, diflubenzuron seldom persists

more than a few days in water (Schaefer and Dupras, 1977; Schaefer et al., 1980). Half-life values in sediment were similar to those in water, with reported half-life values ranging from 6.2 to 10.4 days. Sundaram et al. (1991) reported maximum dissipation half-lives (DT_{50} and DT_{90}) values of 1.3 and 4.2 days, respectively in pond water and 0.2 and 1.0 days in streams.

Diflubenzuron has a low vapor pressure (9.0×10^{-10} mm Hg), which suggests it will not volatilize readily into the atmosphere from soil or plants. Volatilization from water is also not expected based on the reported low Henry's Law Constant value (1.8×10^{-9} atm-m^3/mol) that measures the tendency of chemicals to move from solution into the atmosphere (Wauchope et al., 1992; USEPA, 1997, 2018).

Diflubenzuron is not systemic in plants. Diflubenzuron applied to foliage remains adsorbed to leaf surfaces for several weeks with little or no absorption or translocation from plant surfaces (USDA-APHIS, 2015b).

Diflubenzuron is not expected to bioconcentrate in fish substantially based on the depuration results from a bioconcentration factor (BCF) study using the bluegill, *Lepomis macrochirus*. During a 28-day exposure, levels reached steady state in the tissue and viscera (bioconcentration factors of 34 to 200x for fillet, 78 to 360x for whole fish, and 100 to 550x for viscera) by day 3 to 7 of the uptake period, and greater than 99% of the test material was excreted during the 14-day depuration period. The main metabolite is 2,6-difluorobenzamide (USEPA, 1997, 2012a, 2018).

2.4 Hazard Identification

The adverse health effects of diflubenzuron to mammals and humans involve damage to hemoglobin in blood and the transport of oxygen. Diflubenzuron causes the formation of methemoglobin. Methemoglobin is a form of hemoglobin that is not able to transport oxygen (US FS, 2004).

2.4.1 Toxicological Effects

Following oral, dermal, and inhalation exposures, the primary toxic effects of diflubenzuron in mammals are associated with the hematopoietic system with an excessive formation of methemoglobin (methemoglobinemia) and/or sulfmethoglobin (sulfhemoglobinemia) in the blood. Methemoglobinemia and/or sulfhemoglobinemia lead to the impairment of the oxygen transportation capacity of the blood (USEPA, 2015).

2.4.2 Metabolism

Diflubenzuron is rapidly absorbed through the oral route and excreted in feces and urine (US FS, 2004, USEPA, 2015). The absorption of diflubenzuron from the gastrointestinal tract decreases with increasing dose. Approximately half of the administered diflubenzuron is absorbed at

relatively low doses in the range of 1 mg/kg/day; approximately 5% is absorbed at much higher doses in the range of 1,000 mg/kg/day (WHO, 1996; US FS, 2004).

A diflubenzuron metabolism study in rats indicates that diflubenzuron does not metabolize to 4-chlorophenylurea (CPU) or 4-chloroaniline (PCA) in either the feces or urine. Most of the administered radiolabeled diflubenzuron (about 83%) was recovered within 48 hours post-dosing. Most of the administered diflubenzuron (87.4%) was excreted in feces as unchanged with no other detectable fecal metabolites. Small amounts (2.22%) of the administered diflubenzuron (2.22%) were excreted in urine with two major metabolites (4-chloroaniline-2-sulfate (45% of total recovered radioactivity (TRR) in urine) and N-(4-chlorophenyl)oxamic acid (13% of the TRR)) and small amounts (0.1 to 1.3% of the TRR) of seven other metabolites. There was no detectable levels of non-metabolized CPU identified in the urine (USEPA, 2015).

A CPU metabolism study in rats indicates that CPU does not convert to PCA. Most of the administered radiolabeled CPU (approximately 70% to 93%) was recovered between 20–48 hours post-dosing. Ninety-one percent of the administered CPU was recovered in the urine, 7% in the feces, and 1% each in the carcass and cage wash. Five major metabolites (>5% of administered dose) of CPU include CPU-2-sulfate (25.60% of administered dose), phenylurea-4-hydroxide (20.82%), CPU-2-glucuronide (16.70%), CPU-3-sulfate (7.93%) and phenylurea-4-sulfate (6.65%). CPU was almost completely metabolized, with only 1.45% of the unchanged CPU compound recovered in the urine and feces. There was no 4-chloroaniline and N-hydroxy metabolites of 4-chloroaniline or CPU found in either the urine or feces of treated rats (USEPA, 2015).

2.4.3 Human Incidents

USEPA evaluated human poisoning incidents in the OPP incident data system (IDS) (USEPA, 2012b). The IDS from January 1, 2007 to February 22, 2012 reported two human incidents related to diflubenzuron. One incident was classified as moderate severity and the other as minor. The review indicates a low frequency and severity of incident cases reported for diflubenzuron. USEPA's incident review also examined the Agricultural Health Study Database, where there were no listings for diflubenzuron.

2.4.4 Acute Toxicity

Diflubenzuron has low acute dermal toxicity (Category III) with a dermal LD_{50} of >2,000 mg/kg in rabbits. Diflubenzuron has very low acute oral and inhalation toxicity (Category IV) with an oral LD_{50} of >5,000 mg/kg in rats, and an inhalation LC_{50} of >2.49 mg/L in rats. It is a mild eye irritant and not a skin irritant in rabbits. It is negative for skin sensitization in the guinea pig (USEPA, 1997, 2015). The Dimilin® 2L formulation safety data sheet (MacDermid Agricultural Solutions, Inc., 2015) reports an acute oral LD_{50} of >5,000 mg/kg (Category IV), and an acute dermal LD_{50} of >5,000 mg/kg in rats (Category IV). The Dimilin® 2L formulation has lower dermal toxicity compared to technical diflubenzuron.

2.4.5 Subchronic and Chronic Toxicity

Studies of subchronic exposure to diflubenzuron (table 2-1) indicate that the most sensitive endpoint from exposure to diflubenzuron is the occurrence of methemoglobinemia and/or sulfhemoglobinemia. This primary toxic effect was observed in both sexes of mice, rats, and dogs by oral route as well as dermal and inhalation routes in rats.

Table 2-1. Subchronic mammalian toxicity of diflubenzuron

Toxicity Study Type	No Observed Adverse Effect Level (NOAEL)	Lowest Observed Adverse Effect Level (LOAEL) (Toxic Effects)
14-day gavage study (mice)	40 mg/kg/day	200 mg/kg/day (increased sulfhemoglobin)
28-day feeding study (rats)	40 mg/kg/day	200 mg/kg/day (increased methemoglobin in males, increased sulfhemoglobin in males and females, increased spleen weights in males and females)
21-day dermal study (rabbits)	Not established	69 mg/kg/day (increased methemoglobin at 4.64% suspension applied at the rate of 1.5 mL/kg/day)
21-day inhalation study (rats)	Not established	0.121 mg/L (of 25% wettable powder) (methemoglobin and sulfhemoglobinemia)
13-week feeding study (rats)	Not established	8 mg/kg/day (increased methemoglobin and signs of hemolytic anemia, erythrocyte destruction in the spleen and liver and regeneration of erythrocytes in the bone marrow)
13-week feeding study (mice)	2.4 mg/kg/day	12 mg/kg/day (dose-related, statistically significant increases in methemoglobin and sulfhemoglobin)
13-week feeding study (dogs)	1.64 mg/kg/day	6.24 mg/kg/day (increased methemoglobinemia)

Source: USEPA, 2015

Studies of chronic exposure to diflubenzuron (table 2-2) also indicate hematological effects such as methemoglobinemia and increases in methemoglobin and sulfhemoglobin in mammals. USEPA established a chronic reference dose (RfD) based on the NOAEL of 2 mg/kg/day resulting from methemoglobinemia and sulfhemoglobinemia at 10 mg/kg/day (LOAEL) from a 52-week feeding study in dogs.

Table 2-2. Chronic mammalian toxicity of diflubenzuron

Toxicity Study Type	No Observed Adverse Effect Level (NOAEL)	Lowest Observed Adverse Effect Level (LOAEL) (Toxic Effects)
104-week feeding study (rats)	Not established	7.8 mg/kg/day (A dose-dependent, statistically significant increases in methemoglobin and sulfhemoglobin)
52-week feeding study (dogs)	2 mg/kg/day	10 mg/kg/day (statistically significant increases in methemoglobin and sulfhemoglobin).

Source: USEPA, 2015

2.4.6 Nervous System Effects

Diflubenzuron is not neurotoxic in subchronic or chronic studies testing multiple species with the primary toxic effect being the formation of methemoglobinemia and/or sulfhemoglobinemia in blood. USEPA waived the acute and subchronic neurotoxicity studies (USEPA, 2015).

2.4.7 Reproductive or Developmental Effects

A two-generation reproductive study in rats (administrated diflubenzuron at doses of 0, 25, 250 or 2,500 mg/kg/day in diet) reported a maternal LOAEL of 25 mg/kg/day based on methemoglobinemia, hemolytic anemia, destruction of erythrocytes, and pathological changes in the spleen and liver without identifying a NOAEL. The reproductive toxicity NOAEL was 2,500 mg/kg/day (the high dose tested), and LOAEL was not identified. The study also reported a NOAEL of 250 mg/kg/day for reproductive effects in the offspring, and a LOAEL of 2,500 mg/kg/day based on decreased body weights in F1 pups from birth to 21 days post-partum (USEPA, 2015).

A developmental toxicity study in pregnant rats and a developmental study in rabbits (administrated doses of 0 or 1,000 mg/kg/day by gavage) did not observe maternal toxicity or toxicity to the fetus. Both studies reported a NOAEL of 1,000 mg/kg/day for maternal and developmental toxicity (USEPA, 2015).

The developmental toxicity studies in rats and rabbits did not indicate increased susceptibility to fetuses exposed *in utero*, or abnormalities in fetal development at the maternal limit doses of 1,000 mg/kg/day. In addition, the two-generation reproduction study in rats did not show evidence of sensitivity following pre- and/or post-natal exposure. Based on the lack of sensitivity in these studies and USEPA's waiver of neurotoxicity studies, the USEPA reduced the Food Quality Protection Act (FQPA) safety factor to 1x (USEPA, 2015).

2.4.8 Carcinogenicity and Mutagenicity

USEPA has classified diflubenzuron as a "Group E – Evidence of Non-carcinogenicity for Humans" chemical based on the lack of evidence of carcinogenicity in rats (a 104-week carcinogenicity study) and mice (a 91-week carcinogenicity study) (USEPA, 1997, 2015). Treatment with diflubenzuron in both studies was not associated with an increased incidence of neoplastic lesions in either males or females. Although the highest tested dose level of 500 mg/kg/day in the rat study is lower than the limit dose of 1,000 mg/kg/day for carcinogenicity studies, significant toxicity (particularly methemoglobinemia, sulfhemoglobinemia, erythrocyte destruction, compensatory regeneration of erythrocytes, and hemolytic anemia) was observed at the highest dose. The highest tested dose level of 1,500 mg/kg/day in the mouse study exceeded the limit dose of 1,000 mg/kg/day for carcinogenicity studies. The rat study reported a LOAEL of 7.8 mg/kg/day based on non-cancer effects (histopathological signs of erythrocyte destruction and compensatory regeneration). The study observed increases in methemoglobin and sulfhemoglobin at all treatment levels and did not report a NOAEL. The mouse study reported a NOAEL of 2.4 mg/kg/day and a LOAEL of 12 mg/mg/day based on increases in methemoglobin and sulfhemoglobin.

Diflubenzuron is not mutagenic based on a *Salmonella*/mammalian microsome plate incorporation assay, an *in vitro* chromosome damage assay in Chinese hamsters, and an unscheduled DNA synthesis assay in rats. The microsome plate incorporation and the chromosome damage assays did not show evidence of diflubenzuron-induced mutant colonies or an increase in structural chromosome aberrations over background levels at any concentration. The unscheduled DNA synthesis assay did not indicate that diflubenzuron causes an appreciable increase in net nuclear grain counts compared to the solvent control at any concentration, or induces a genotoxic effect (USEPA, 2015).

Other studies report a lack of mutagenic activity including a dominant lethal study in mice (US FS, 2004), cell transformation assays (US FS, 2004), and transplacental hamster cell transformation assays (Quarles et al., 1980). Diflubenzuron induced cell transformations in the absence of metabolic activation, but the effect was not observed with metabolic activation (Perocco et al., 1993).

The degradation product PCA is classified as "Group B2 – probable human carcinogen" because it has tested positive for splenic tumors in male rats and hepatocellular adenomas/carcinomas in male mice in a National Toxicology Program study (USEPA, 2015).

2.4.9 Endocrine System Effects

Available information does not indicate that diflubenzuron causes endocrine disruption in mammals (US FS, 2004). USEPA performed an evaluation of estrogen receptor (ER) bioactivity of diflubenzuron under the Endocrine Disruptor Screening Program using the ToxCast (TM) "Endocrine Receptor Model". The evaluation results for diflubenzuron as a pesticide active ingredient indicated no activity for ER Agonist Area Under Curve (AUC), ER Antagonist AUC, and ER bioactivity (USEPA, 2017).

2.4.10 Immune System Effects

Diflubenzuron is not immunotoxic based on a USEPA guideline 28-day dietary immunotoxicity study in mice. This study reported an immunotoxicity NOAEL of 10,000 parts per million (ppm) (equivalent to 1,832 mg/kg/day), or the highest test concentration tested. However, the immunotoxicity LOAEL was not established (USEPA, 2015).

2.4.11 Toxicity of Other Ingredients

Limited mammalian toxicity information for the formulation is available from the safety data sheet (MacDermid Agricultural Solutions, Inc., 2015). The Dimilin® 2L formulation has approximately 78% inert or other ingredients (MacDermid Agricultural Solutions, Inc., 2017). Other ingredients listed in the safety data sheet include propane-1,2-diol (5–10%), silicon dioxide (1–5%), and kaolin (0.1–1%). Propane-1,2-diol has very low acute oral (LD_{50} of 20,000 mg/kg in rats and 18,500 mg/kg in rabbits) and low acute dermal (LD_{50} of 20,800 mg/kg in rabbits) toxicity. Silicon dioxide has low acute oral (LD_{50} >2,000 mg/kg in rats) and dermal (LD_{50} >2,000 mg/kg in rabbits) toxicity. Kaolin also has very low acute oral and dermal toxicity (both LD_{50s} of >5,000 mg/kg in rats). The formulation caused slight skin irritation and mild eye irritation to rabbits. However, silicon dioxide as a component does not cause skin or eye irritation, or skin sensitization. Animal testing in rats and mice did not show carcinogenic or mutagenic effects for silicon dioxide. Kaolin is carcinogenic to humans (IARC, 2016).

2.4.12 Fire Hazards

The safety data sheet (MacDermid Agricultural Solutions, Inc., 2015) indicates that the formulation is a Category 4 flammable liquid under the United Nations Globally Harmonized System of Classification and Labeling of Chemicals. A Category 4 flammable liquid is a combustible liquid, which presents a fire hazard above normal room temperature (OSHA, 2016). Combustion products of diflubenzuron formed under fire conditions include carbon oxides, nitrogen oxides, hydrogen chloride gas, and hydrogen fluoride (NIH, 2014). The safety data sheet identified specific health hazards from burning during fire-fighting as noxious and toxic fumes. The specific protective equipment for firefighters include body covering protective clothing, full “turn-out” gear, and a self-contained breathing apparatus (MacDermid Agricultural Solutions, Inc., 2015).

3.0 DOSE-RESPONSE ASSESSMENT

3.1 Human Health Dose-Response Assessment

A dose-response assessment evaluates the dose levels (toxicity criteria) for potential human health effects, including acute and chronic toxicity.

The USEPA/OPP did not establish an acute RfD for diflubenzuron because there was no appropriate toxicological endpoint from a single exposure identified in the toxicity studies. The marginal increases in methemoglobin resulting from a single oral dose of 1,000 mg/kg to mice and rats suggest that multiple doses are required to cause methemoglobinemia (USEPA, 2015).

The USEPA/OPP has derived a chronic RfD of 0.02 mg/kg/day for diflubenzuron (USEPA, 2015). The chronic RfD was developed by applying an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation and a FQPA safety factor of 1 to a NOAEL of 2 mg/kg/day from a chronic oral study in dogs. The NOAEL was based on methemoglobinemia and sulfhemoglobinemia observed at a LOAEL of 10 mg/kg/day. USEPA considers the toxicity of CPA and PCA equal to diflubenzuron for the non-cancer effects (USEPA, 2015).

The USEPA/OPP determined a dermal absorption factor of 0.5% based on a study in rats where systemic absorption was less than 0.5%, and approximately 4.7–6.2% diflubenzuron was bound to the skin (USEPA, 2015). They also classified diflubenzuron as "evidence of non-carcinogenic to humans" and did not derive a cancer potency factor. However, the degradates CUP and PCA are probable human carcinogens. The human cancer potency (Q1*) value for CPU is 1.52×10^{-2} and the Q1* value for PCA is 1.12×10^{-1}.

The USEPA has established tolerances for residues of diflubenzuron including its metabolites and degradates, and the insecticide diflubenzuron, in or on commodities (40 CFR §180.377 (1) and (2) https://www.law.cornell.edu/cfr/text/40/180.377). The tolerance level in or on grass, forage, fodder, and hay is 6 ppm. The tolerance levels are 0.05 ppm for meat and fat (cattle, goat, hog, horse, and sheep) and milk, and 0.15 ppm for meat by-products (cattle, goat, hog, horse, and sheep).

3.2 Ecological Dose-Response Assessment

3.2.1 Wild Mammal, Avian and Reptile Toxicity

The acute toxicity of diflubenzuron to mammals is summarized above in section 2.4, Hazard Identification. In general, diflubenzuron has low acute oral, inhalation, and dermal toxicity to mammals based on available data.

Acute toxicity studies show that diflubenzuron is practically non-toxic to birds, with acute oral LD_{50} values exceeding 2,000 mg/kg (Eisler, 2000). The acute oral median lethal dose of diflubenzuron to birds ranges from 3,762 mg/kg for red-winged blackbird to in excess of 5,000

mg/kg for bobwhite quail and mallard duck (Willcox and Coffey, 1978). A NOEL of 2,500 mg/kg body weight was noted in the red-winged blackbird study based on one individual that showed signs of piloerection, ataxia, and asthenia. A 5-day dietary study on the mallard duck and bobwhite quail dosed with levels of up to 4,640 ppm revealed no observable signs of toxicity with a resulting NOEC of 4,640 ppm.

Chronic reproductive studies using standard surrogate test species for pesticide registration revealed that the NOEC value for the mallard and bobwhite was 500 ppm. The LOEC values were determined to be 1,000 ppm for the mallard and bobwhite based on effects to eggshell thickness and egg production, respectively (USEPA, 2018). Reproductive studies using chickens and diflubenzuron have resulted in NOEC concentrations at the highest level used in the studies. These values ranged from 250 to 500 ppm (Kubena, 1981; Kubena, 1982; US FS, 2004). Only one study has noted a dose-related decrease in testosterone in chickens (Smalley, 1976), but this study is inconsistent with the full report for the same facility (Kubena, 1982) and with other studies (Cecil et al., 1981).

The primary concern for bird species is related to indirect effects to insectivorous species by decreases in insect populations from insecticide applications rather than direct toxicity from diflubenzuron exposure. Widespread use of diflubenzuron to suppress forest defoliators may lead to harmful effects on forest songbirds by reducing populations of insects upon which they feed (Eisler, 2000). These types of large scale applications over a large percentage of rangeland would not be anticipated based on recent use patterns of program insecticides.

Little information is available about the toxicity of diflubenzuron to reptiles, but it is likely that diflubenzuron is of low toxicity to these species based upon the mode of action. USEPA/OPP uses bird toxicity data to represent toxicity to reptiles. While there is a great deal of uncertainty in making this extrapolation, the effect data from avian surrogates would suggest low toxicity to reptiles.

Based on acute toxicity, amphibians appear to be tolerant to diflubenzuron with a *Rana brevipoda porosa* tadpole 48-hour LC_{50} of 100,000 µg/L (Nishiuchi, 1989). Amphibians are relatively tolerant of diflubenzuron (i.e., no observable adverse effects at ≤ 45 µg/L) (Eisler, 2000). This value is not based on an actual study in the review so there is uncertainty regarding its applicability to amphibians. A surrogate approach to evaluating potential effects to amphibians is the assessment of the toxicity data for fish. USEPA/OPP assumes that acute and chronic toxicity to fish is representative of the sensitivity to amphibians. As with the extrapolation of bird to reptile effects data, there is a great deal of uncertainty in the applicability of fish data to represent the sensitivity range to amphibians. Making this assumption, the above 48-hour LC_{50} falls within the range of sensitivities given for the fish toxicity section discussed below.

3.2.2 Terrestrial Invertebrate Toxicity

A large amount of data exists regarding the toxicity of diflubenzuron to terrestrial invertebrates. Comparing toxicity values between the different studies, however, is problematic because dosing

is not standardized relative to other non-target testing, and the doses can be presented in numerous units. Based on the available data, sensitivity of terrestrial invertebrates to diflubenzuron is highly variable depending on which group of insects and which life stages are being exposed. Due to its mode of action, diflubenzuron has greater activity on immature stages of terrestrial invertebrates. Based on standardized laboratory testing diflubenzuron is considered practically non-toxic to adult honeybees. The contact LD_{50} value for the honeybee, *Apis mellifera*, is reported at greater than 114.8 µg a.i./bee while the oral LD_{50} value was reported at greater than 30 µg a.i./bee. USEPA (2018) reports diflubenzuron toxicity values to adult honeybees are typically greater than the highest test concentration using the end-use product or technical active ingredient. The lack of toxicity to honeybees, as well as other bees, in laboratory studies has been confirmed in additional studies (Nation et al., 1986; Chandel and Gupta, 1992; Mommaerts et al., 2006). Mommaerts et al. (2006) and Thompson et al. (2005) documented sublethal effects on reproduction-related endpoints for the bumble bee, *Bombus terrestris* and *A. mellifera*, respectively, testing a formulation of diflubenzuron. However, these effects were observed at much higher use rates relative to those used in the program. Comparative toxicity using insecticides other than diflubenzuron have shown that sensitivity between *Bombus* spp. and *Apis* spp. are similar while the alfalfa leafcutting bee (*Megachile rotundata*) and alkali bee (*Nomia melanderi*) are more susceptible (Devillers et al., 2003). USEPA (2018) reported a chronic 21-day ED_{50} and NOAEL of 0.012 and <0.0064 µg a.i.larva, respectively. A ED_{50} and NOAEL of 0.0624 and 0.038 µg a.i.larva was reported in an 8-day exposure using technical grade diflubenzuron. USEPA reports a NOAEL of >5 pounds per acre in a pollinator field study (USEPA, 2018).

Immature grasshoppers, beetle larvae, lepidopteran larvae, and chewing herbivorous insects appear to be more susceptible to diflubenzuron than other invertebrates (Murphy et al., 1994; Eisler, 2000; US FS, 2004). Within this group, however, grasshoppers appear to be more sensitive based on the proposed use rates for Dimilin® 2L (table 3-1). Based on the highest use in the program, rates are one half to 48 times less than rates for other invertebrate taxa.

Table 3-1. Proposed labeled use rates for different invertebrate orders based on the formulation Dimilin® 2L.

Invertebrate Order	**Range of Dimilin® 2L Use Rates (fl oz/ac)**
Orthoptera	0.75 – 2.00*
Coleoptera	2.0 – 16.00
Lepidpoptera	2.0 – 16.00
Homoptera	12.00 – 48.00
Acari	40.00 – 48.00

*Rate range on the label for grasshoppers and Mormon cricket. Program rates are 0.75 fl oz/ac (RAATs) and 1.00 fl oz/ac (Full).

Honeybees, parasitic wasps, predatory insects, and sucking insects show greater tolerance to diflubenzuron exposure (Eisler, 2000; Murphy et al., 1994; US FS, 2004). In an analysis of

approximately 143 toxicity values for predators and parasites, Theiling and Croft (1988) found that diflubenzuron had comparatively low toxicity. Diflubenzuron is moderately toxic to spiders and mites.

Secondary toxicity of diflubenzuron to invertebrates that could feed on treated grasshoppers via cannabilism or necrophagy has been evaluated using the grasshopper (*Melanoplus sanguinipes*) and the darkling beetle (Tenebrionidae) (Smith and Lockwood, 2003). Significant mortality was observed in *M. sanguinipes* when fed cadavers dosed at 2,000 times the grasshopper application rate. No mortality was observed at 25 or 250 times the grasshopper rate for diflubenzuron. Although based on a small sample size, no acute effects were noted in darkling beetles fed field-collected grasshopper cadavers.

3.2.3 Terrestrial Plant Toxicity

Phytotoxicity is low for terrestrial plants when diflubenzuron is applied at the recommended rates of application. There is little to no absorption and translocation of diflubenzuron residues from plant surfaces (Eisler, 1992). Photosynthesis, respiration, and leaf ultrastructure of soybeans were unaffected by diflubenzuron at doses up to a level of 0.269 kg a.i./ha (Hatzios and Penner, 1978).

3.2.4 Aquatic Vertebrate Toxicity

Toxicity of diflubenzuron to aquatic organisms varies by taxa. On an acute basis, diflubenzuron is considered slightly to practically nontoxic to fish. The median lethal concentration of diflubenzuron in water ranges from 10 mg/L for smallmouth bass to 660 mg/L in bluegill sunfish (Willcox and Coffey, 1978; Julin and Sanders, 1978; USEPA, 2018; US FS, 2004). In several cases, LC_{50} values are above the highest test concentration used in the study. Toxicity values and references are summarized in appendix B-1. Sublethal acute effects have also been observed in exposures ranging from 6 to 96 hours. Maduenho and Martinez (2008) observed several sublethal impacts including reductions in erythrocytes and hemoglobin content as well as the induction of glutathione-s-transferase in *Prochilodus lineatus* after exposure to 25 mg/L of diflubenzuron. Granett et al. (1978) measured swimming behavior response in male Atlantic salmon parr in repeated 10-minute exposure trials to a granular formulation of diflubenzuron at a nominal concentration of 10 µg/L. The time spent in dosed plumes as well as the choice of plumes was found to be statistically significant when compared to controls. Available vertebrate toxicity data suggests that formulations of diflubenzuron are comparable in toxicity to the technical active ingredient (USEPA, 2018). Available data for metabolites of diflubenzuron demonstrate comparable toxicity to the parent material with the exception of PCA which appears to be more toxic to fish with median lethality values ranging from 2.4 to 23 mg/L (USEPA, 2018).

In a subacute 30-day study using steelhead trout, fathead minnow, and guppies (*Poecilia reticulata*), the NOEC was determined to be greater than the highest test concentration of 45 µg/L based on survival and growth endpoints in early life stages (Hansen and Garton, 1982a).

Julin and Sanders (1978) exposed rainbow trout eyed eggs and fingerlings continuously for 30 days to diflubenzuron and found no effects at concentrations ranging from 0.029 to 0.30 mg/L.

A life-cycle study with the fathead minnow was conducted to support registration of diflubenzuron. These multi-generation studies are required by USEPA/OPP when the pesticide meets certain criteria regarding toxicity and availability in aquatic ecosystems. In the 10-month continuous exposure life-cycle study, the LOEC and maximum acceptable toxicant concentration values were found to be greater than 100 µg/L, with a NOEC value of 100 µg/L (USEPA, 1997). The NOEC value does not indicate that concentrations above this level caused an adverse effect, but that it is an artifact of the study design where the highest test concentration was 100 µg/L. In another long-term exposure study using the mummichog (*Fundulus heteroclitus*), the reproductive NOEC was reported as approximately 50 µg/L (US FS, 2004). Diflubenzuron does not bioconcentrate to significant levels, based on bioconcentration studies that were conducted using the bluegill sunfish and white crappie (Pomoxis annularis) (Eisler, 2000).

3.2.5 Aquatic Invertebrate Toxicity

The acute and chronic toxicity of diflubenzuron to aquatic invertebrates is variable and dependent on the group of aquatic organism being tested (figure 3-1; appendix B-2). The acute median lethal concentration of diflubenzuron in water to crustaceans ranges from 0.75 µg/L in *Daphnia magna* (US FS, 2004) to 2.95 µg/L in the grass shrimp *Palaemonetes pugio* (Wilson and Costlow, 1986). The median lethal concentration of diflubenzuron in water to immature stages of aquatic insects ranges from 0.5 µg/L in the mosquito *Aedes nigromaculatum* (Miura and Takahashi, 1974) to 57 mg/L in the perlodid stonefly, *Skwala* sp. (Mayer and Ellersieck, 1986). The median lethal concentration of diflubenzuron in water to the snail (*Physa* sp.) is greater than 125 mg/L (Willcox and Coffey, 1978). Available diflubenzuron formulation and degradate aquatic invertebrate toxicity studies show comparable or decreased toxicity when compared to similar studies using the technical active (USEPA, 2018).

Based on the available sublethal data for diflubenzuron, cladocerans and copepods appear to be the more sensitive group with an acute NOEC range of 0.3 to 1.0 µg/L and a chronic NOEC range of 0.04 to 0.25 µg/L (USEPA, 2012c; US FS, 2004). Adverse effects on growth, survival, reproduction, and behavior occur between 0.062 and 2 µg/L (Tester and Costlow, 1981; Nebeker et al., 1983; Eisler, 2000). USEPA (2018) reported sublethal effects to the midge, *Chironomus tentans* with reported no observable concentrations of 14.03 µg/L and 13.67 µg/kg, in pore water and sediments, respectively (appendix B-3).

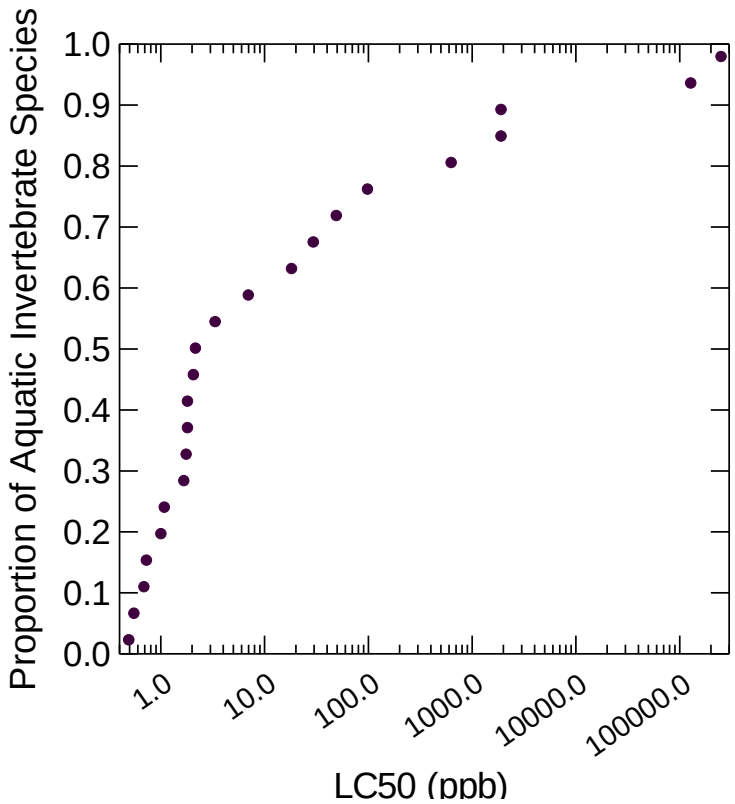

Figure 3–1. Distribution of aquatic invertebrate toxicity values for diflubenzuron

3.2.6 Aquatic Plant Toxicity

The lowest aquatic plant toxicity value is the NOEC for duckweed (*Lemna minor*) (190 µg/L) (Thompson and Swigert, 1993). The EC_{50} for the green algae *Selenastrum capricornutum* is >200 µg/L (USEPA, 2018). Chitinous algae (diatoms) are not adversely affected by diflubenzuron (Antia et al., 1985).

4.0 EXPOSURE ASSESSMENT

4.1 Human Health Exposure Assessment

The exposure assessment estimates the potential exposure of humans to diflubenzuron. The exposure assessment begins with the use and application method for diflubenzuron in the grasshopper program. A complete exposure pathway for diflubenzuron includes: (1) a release from a diflubenzuron source; (2) an exposure point where contact can occur; and (3) an exposure route such as ingestion, inhalation, or dermal contact by which contact can occur. In this way, the potentially exposed human populations and complete exposure pathways are identified. Finally, exposures for the identified human populations are qualitatively and quantitatively evaluated for each exposure pathway.

4.1.1 Identification of Potentially Exposed Human Populations and Complete Exposure Pathways

USDA-APHIS proposes to use the Dimilin® 2L formulation via aerial or ground spray applications to suppress rangeland grasshoppers. Dimilin® 2L is a suspension concentrate that is mixed with water and vegetable or petroleum based oil for application as a foliar spray. The program uses application rates of 0.016 lb a.i. per acre for conventional treatment, and 0.012 and 0.006 lb a.i. per acre (maximum and average, respectively) for RAATs. The application rate of 31 fl oz per acre for the conventional treatment is 1 part Dimilin®, 20 parts water, and 10 parts vegetable or petroleum based oil. The total volumes for ground equipment may vary.

Based on the use pattern, workers in the program are the most likely human population segment to be exposed to diflubenzuron. Short-term occupational exposure to diflubenzuron may occur through direct contact with this compound during application (mixing, loading, applying, and post-application activities). However, direct contact exposure is minimized by adherence to label required safety procedures and the use of personal protective equipment (PPE), as further discussed in the next section. Exposure to diflubenzuron through drift from aerial and ground spray applications is expected to be minimal because only protected handlers are in the area during application and workers are not allowed entry into treated areas during the 12-hour restricted-entry interval (REI).

Diflubenzuron exposure to the general public is not expected based on label requirements and program standard operating procedures that prevent potential exposure to the general public (USDA-APHIS, 2016a). Only protected handlers may be in the area during application, and entry of the general public into the treated area is not allowed during the REI period. Program treatments are conducted on rural rangelands, where agriculture is a primary economic factor with widely scattered single rural dwellings in ranching communities with low population density. The USDA-APHIS program application statement of work (2016a) requires avoiding flights over congested areas, water bodies, and other sensitive areas. The required buffer zones for water bodies are 500 feet for aerial ULV and 200 feet for ground ULV applications. Aerial applications are not allowed while school buses are operating in the treatment area; within 500

feet of schools or recreational facilities; or when wind velocity exceeds 10 miles per hour (mph) (unless a lower wind speed is required under State law); air turbulence could seriously affect the normal spray pattern and/or temperature inversions could lead to off-site movement of spray. The program also notifies residents within treatment areas, or their designated representatives, prior to proposed operations to reduce the potential for incidental exposure (USDA-APHIS, 2015c). Label restrictions and program standard operating procedures reduce the potential exposure to diflubenzuron through direct contact to the general public, suggesting a lack of a significant exposure pathway.

The primary use areas for diflubenzuron include rangeland that could be grazed by livestock. Farmers in areas near proposed suppression areas may grow crops such as alfalfa and corn that are used for livestock. They also grow potatoes, sugar beets, wheat, barley, sweet corn, beans, and a variety of other crops (USDA-APHIS, 2016b). Exposure to the general public from diflubenzuron through dietary food consumption (meat and dairy products) at levels higher than tolerance levels for diflubenzuron is not expected based on the proposed use pattern for the program which includes reduced application rates compared to those on the label.

Diflubenzuron has environmental fate properties that suggest a potential for transport (such as runoff or drift of spray in wind) to surface and groundwater (section 2.3) with a potential for runoff for several months or more after application, especially in areas where soils are poorly drained, and the water table is shallow (MacDermid Agricultural Solutions, Inc., 2017). However, the potential exposure to diflubenzuron for the general public from drinking water sources as a result of program use is not expected based on adherence to the label requirements, the proposed use rates, and USDA-APHIS program treatment guidelines (USDA-APHIS, 2015c; 2016a). The program restricts insecticide applications directly to water bodies (surface water or to intertidal areas below the mean high water mark), as stated on the label, and also requires a no treatment buffer from water bodies (500 foot buffer for aerial and 200 foot buffer for ground applications) to minimize the potential for migration. Other label recommended measures to reduce runoff include avoiding applications when rainfall is forecasted to occur within 48 hours, and implementing sound erosion control practices. In addition, only one application is made per season to a treatment block and at low use rates.

4.1.2 Exposure Evaluation

This section quantitatively evaluates worker exposure from dermal contact and inhalation exposure routes while mixing and loading Dimilin® 2L based on the program application rates. The quantified potential worker exposures are acute or short-term. Long-term worker exposure to diflubenzuron is not expected because only one application is proposed per season.

Direct contact to diflubenzuron to workers during application is not expected to occur under normal conditions with label-required PPE and proper worker hygiene. The Dimilin® 2L formulation (MacDermid Agricultural Solutions, Inc., 2017) PPE for pesticide applicators and other handlers when mixing and loading and using hand-held equipment includes: long-sleeved shirt and long pants, chemical resistant gloves greater than 14 mils (such as barrier laminate,

butyl rubber, nitrile rubber, neoprene rubber, natural rubber, polyethylene, PVC, or viton), and shoes plus socks. Mixers and loaders using fixed-wing aircraft must also wear a dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C or a NIOSH approved respirator with any R, P or HE filter). The PPE requirements for handlers may be modified if they meet the requirements listed in the Worker Protection Standard for agricultural pesticides [40 CFR 170.240(d)(4-6)] when handlers use closed systems (including water soluble bags), enclosed cabs, or aircraft. The safety data sheet (MacDermid Agricultural Solutions, Inc., 2015) includes occupational permissible concentrations as workplace control parameters for components such as propane-1,2-diolin, silicon dioxide, and kaolin in the formulation, as well as mechanical ventilation for general area control as engineering measures.

Accidental exposure may occur from splash or transfer from contaminated gloves or clothing to an unprotected skin area (face). To quantify the potential exposure from dermal and inhalation pathways during mixing, loading, and application for workers, USDA-APHIS estimated dermal and inhalation doses using the following equation:

> Dermal Dose = Application Rate (lb a.i./acre) × Area Treated (acre/day) x Dermal Unit Exposure (µg/lb a.i.) × Dermal Absorption Factor x Conversion Factor (0.001 mg/µg)) ÷ Body Weight (BW) (kg)
>
> Inhalation Dose = (Application Rate (lb a.i./acre) × Area Treated (acre/day) x Inhalation Unit Exposure (µg/lb a.i.) × Conversion Factor (0.001 mg/µg)) ÷ BW (kg)

The mixing/loading liquids exposure scenario in the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (USEPA, 2016b) is the closest to the program mixing, loading and application exposure scenario.

The dermal unit exposure of 220 µg/lb a.i. (single layer, no gloves PPE level), and inhalation unit exposure of 0.219 µg/lb a.i. (no respirator PPE level) of the mixing/loading liquids exposure scenarios were used for the exposure estimates. Average dermal and inhalation doses were quantified based on USDA-APHIS average RAATs application rate of 0.006 pounds a.i. per acre. Maximum dermal and inhalation doses were quantified based on the USDA-APHIS full application rate of 0.016 pounds a.i. per acre. Area treated for the program was assumed to be 20,000 acres per day. A body weight of 69 kg for women instead of the mean body weight of 80 kg for all adults (USEPA, 2011a) was used for the exposure estimation as a conservative approach because the lower body weight results in a higher dose. The exposure dose estimations for dermal and inhalation routes are included in appendix A.

4.2 Ecological Exposure Assessment

4.2.1 Terrestrial Exposure Assessment

Exposure levels on vegetation and other forage items for terrestrial non-target vertebrate organisms were calculated using the Terrestrial Residue Exposure Model (T-REX) (USEPA,

2005). T-REX provides an updated version of the Fletcher residue model that was based originally on the Kenaga nomogram used by USEPA/OPP in their risk assessment process for pesticide registration. T-REX allows the user to input variables such as use, application rate/type, percent active ingredient, soil or foliar dissipation half-life, application interval, and number of applications to calculate exposure concentrations on a variety of food items. For foliar sprays, the estimates of exposure are based on the original Kenaga nomogram using field collected residue data for several pesticide classes to calculate residue levels for a wide variety of food items. Minimum and maximum residue levels were calculated for each food item (Hoerger and Kenaga, 1972). The model was updated by Fletcher to account for any potential differences in new chemistry classes that had been developed after Kenaga (Fletcher et al., 1994). Based on over 200 residue studies the model was shown to provide an accurate representation of residues for certain food items, but in some cases such as long grass, it overestimated residues. The current T-REX model provides daily residue values as a mean and upper bound estimate. All exposure values in this risk assessment are based on the upper bound residue estimates. In addition to the calculated residue data, the T-REX model allows the user to input toxicity endpoints that can be compared to exposure values to determine if exposure levels exceed benchmark effect levels.

The T-REX model does not provide exposure estimates for residues based on any potential reduction that would be seen from the implementation of application buffer zones. The exposure values that T-REX calculates are those that would result from a direct application to the food item of interest. In cases where there is an exceedance of residues above a selected toxicological endpoint, there is a need to develop application buffer zones from any habitat that may contain a non-target terrestrial species. These measures can be used as a method of reducing exposure below levels that would cause adverse impacts to non-target species.

4.2.2 Aquatic Exposure Assessment

The method of calculating aquatic exposure concentrations for the program was through the use of two aerial drift deposition models. The models (AgDrift and AgDisp) allow for specific application information to be used as input into the model, and then determine the amount of drift that would occur at a user-defined distance from the spray block. The difference between deposition at the edge of a field and a selected buffer zone can be used as a means to reduce the total amount of insecticide that would be expected at a certain distance from the spray block. Buffer zones, in addition to the previously mentioned mitigation measures can be established, based on the reduction in exposure to levels that would not be expected to result in direct or indirect effects to individuals, populations, or species as a whole.

AgDrift and AgDisp are pesticide drift deposition models that provide the user with the ability to provide site- and application-specific information as input to determine application efficiency and off-site drift residues. AgDisp is a model that was developed by the U.S. Forest Service beginning in the early 1980's, and served as the platform for the development of the AgDrift model, which has become a regulatory tool for the USEPA/OPP in the registration of pesticides (Hewitt et al., 2002; Teske and Curbishley, 2003). Both models have a tiered approach that allows the user to choose default values or provide more specific data, based on the available

information. Both models have been validated under various application scenarios in the literature (Duan et al., 1992a; Duan et al., 1992b; Teske et al., 2000; Teske and Thistle, 2004). In general, aerial application predictions slightly underestimate drift within the first 80 m, but over predict at increasing distances by a factor of two to four at distances up to approximately 300 m (Duan et al., 1992a,b; Bird et al., 2002; Teske and Thistle, 2003; Thistle et al, 2008).

For this risk assessment, the AgDrift model was used to simulate all ground applications, while AgDisp was used to simulate all aerial ULV and bait applications. The AgDisp model was used for aerial applications to assess buffer distances and application heights that are beyond those that have been validated using AgDrift (Teske and Thistle, 2004). Input data for the AgDrift and AgDisp models were based on the product label and specific application information available in the USDA-APHIS workplan for the program (USDA-APHIS, 2016a). While several types of aircraft are available for application in the program, the quantitative differences in drift are minimal at the buffer zones being assessed. Therefore, the focus of the modeling work was to emphasize those parameters that have the greatest influence on drift. Multiple factors can influence pesticide drift; however, release height, wind speed and direction, and nozzle atomization/orientation are the primary factors (Bird et al., 1996; Teske et al., 2000).

Unless otherwise specified, release height for aerial applications was set at 75 ft with a maximum allowed sustained wind speed of 10 mph, and the American Society of Agricultural and Biological Engineers (ASABE) droplet size distribution of fine to very fine (median diameter = 137.5 µm). ASABE has developed standardized parameters for different droplet size spectra that can be selected in both drift models. The very fine-to-fine droplet size spectrum selected for all of the air and ground ULV simulations is consistent with an application recommended for use in the program. For aerial applications of bait the very coarse to extremely coarse bait size was selected with a median particle size of 521.34 µm. Application rates selected for modeling were based on the maximum RAATs rates assuming 100% coverage during application. Lower RAATs rates may be used in cases where reduced application and coverage can be implemented to effectively suppress grasshopper and Mormon cricket populations.

The intent of the program is to make applications as close to the ground as possible. However, in some cases where rapid elevation changes are likely to occur, applications must be made at a height that will ensure pilot safety and the appropriate swath width. All applications were simulated on an area where the buffer was on a zero grade and there was no upslope or downslope between the spray block and sensitive habitat. In addition, the maximum height of vegetation between the spray block and habitat was no greater than 0.1 meters high. This provides a conservative estimate regarding the ability of plants and terrain to intercept drift between the spray block and sensitive areas.

A sustained 10-mph wind speed was used as a representative maximum that is allowed in program applications in all simulations. The wind direction was assumed to be at -90^{o} directly towards the sensitive habitat for the entire length of all swaths with no reduced area of application occurring over the spray block.

Other parameters that influence drift are meteorological conditions. In addition to wind speed, both drift models allow the user to input temperature and humidity. Temperature and humidity values for this exercise were selected from all geographically representative areas where the program could potentially make applications. Meteorological data was obtained from the AgDisp model which allows the user to view a 30-year compendium of meteorological data from 239 sites in the United States (1961–1990 National Solar Radiation Data Base, Version 1.0, Solar and Meterological Surface Observational Network) (Teske and Curbishley, 2003).

The 25th percentile humidity value and the 75th percentile highest temperature were selected based on weather data from Lubbock, Texas, which reported a temperature value of (90 ^{o}F) with a humidity value of 36%. Bismarck, North Dakota, and Pocatello, Idaho, were also evaluated, and based on a combination of maximum temperature and minimum humidity values for those areas, all three had similar application efficiencies and drift fractions based on their respective worst-case temperature and humidity values. Therefore, the temperature and humidity value from Lubbock, Texas, was used because it would maximize the potential for insecticide drift.

AgDisp and AgDrift provide estimates of off-site residues related to drift in terrestrial and aquatic environments. However, they do not provide an estimate of the amount of runoff that could occur into aquatic habitats. Several aquatic fate models exist to estimate environmental loading into aquatic habitats. USEPA/OPP has developed a tiered approach for the use of aquatic fate models that allow the user to estimate aquatic concentrations based on default "reasonable worst-case conditions," or to calculate estimated aquatic concentrations based on crop-specific soil and weather conditions (USEPA, 2004). None of the available models allow the user to calculate the effects of application buffers in reducing pesticide runoff.

The runoff contribution from applications in the program is considered minimal due to the application buffers that are applied adjacent to aquatic environments. The effectiveness in the use of application buffers to reduce runoff can vary based on site conditions, the type of vegetation present in the buffer, and the fate of the insecticide. However, the products used in the program and the large buffers ensure that runoff will not be a significant contribution of off-site pesticide movement when products are applied according to label specifications and APHIS policy.

Aquatic residue estimates were made using the program 200-foot ground buffer and the 500-foot aerial no treatment buffer. Water body sizes were one acre in area and 6.56 feet deep to simulate a pond scenario, and one acre in area and 0.49 feet deep to simulate a wetland scenario. All residues were average acute values assuming no degradation of the insecticide over time in a static system. Residues from ground applications ranged from 5.41 to 72.14 parts per trillion (ppt) while aerial application residues ranged from 91.52 ppt to 1.2 parts per billion. These are considered highly conservative values based on assumptions in the model and when compared to monitoring data that has been collected to validate field applications (USDA-APHIS, 2015b).

5.0 RISK CHARACTERIZATION

This section qualitatively and quantitatively characterizes the risk associated with potential exposure to diflubenzuron.

5.1 Human Health

Diflubenzuron has low acute toxicity. Adverse effects associated with the hematopoietic system include an excessive formation of methemoglobin (methemoglobinemia) and/or sulfhemoglobin (sulfhemoglobinemia) in the blood in subchronic and chronic toxicity studies. Accidental risks are quantified for program workers using the chronic toxicity value even though the anticipated exposure from program applications would be either acute or short-term. Program applications are infrequent with only one application would be made per season in a spray block.

Adverse risk to workers exposed to diflubenzuron via oral, inhalation, and dermal routes during program ULV applications is not expected due to minimized exposure through the use of PPE and adherence to other label requirements such as restricted entry to treated areas.

Accidental exposure during mixing, loading, and application may occur. However, there is a low potential for accidental exposure due to measures such as working under or as a certified applicator. Dermal contact is the primary occupational exposure route and inhalation may also occur during mixing, loading, and applying diflubenzuron. Incidental ingestion is an unlikely exposure route for a well-trained worker. USDA-APHIS quantified the risks from potential dermal and inhalation exposure for workers and calculated a hazard quotient (HQ) using the following equation for non-carcinogens:

HQ = Exposure or Intake or Dose / Reference Dose

Only non-cancer risk was evaluated because USEPA classified diflubenzuron as “not likely to be carcinogenic to humans”. The calculated dermal HQs of 0.1/0.3, inhalation HQs of 0.02/0.05, and dermal and inhalation combined HQ values of 0.1/0.3 under the average and maximum exposure scenarios (table 5-1) are all below the USEPA’s level of concern (HQ=1) indicating no concerns for adverse health risk. The risk calculations are included in appendix A.

Table 5-1. Hazard quotients estimated for dermal and inhalation exposures of workers.

	Dermal Exposure Average/Maximum	**Inhalation Exposure Average/Maximum**
Exposure intake or dose (mg/kg-day)	1.9E-03/5.1E-03	3.8E-04/1.0E-03
Reference dose (mg/kg-day)	0.02	0.02
HQ	**0.1/0.3**	**0.02/0.05**
Combined dermal and inhalation HQ = **0.1/0.3**		

Risks to the general public in the treatment areas from the ground or aerial applications are not expected because USDA-APHIS treatments are conducted in rural rangeland areas, where

agriculture is a primary economic factor with widely scattered single rural dwellings in ranching communities with low population density. The program notifies residents and implements mitigation measures beyond label requirements to ensure that no treatments occur within the required buffer zones from structures, such as homes and schools (USDA-APHIS, 2016a).

5.2 Terrestrial and Aquatic Risk Characterization

5.2.1 Terrestrial Risk Characterization

5.2.1.1. Direct and Indirect Risk to Mammals

To assess the potential acute and sublethal risk to mammals, the lowest acute and chronic effect endpoints were used as benchmark toxicity values. In this case, the LD_{50} value of 4,640 mg/kg was used to approximate acute risk and the 2-year rat study NOEL of 1.43 mg/kg/day was used as the most sensitive chronic endpoint. This value is extremely conservative because it is based on continuous exposure over a 104-week period and the endpoint measured was a statistically significant increase in methemoglobin production. The toxicity endpoints were then adjusted for different sized mammals with various consumption rates (table 5-2). The values were then compared to upper bound estimates using the T-REX residue model. Because a wide variety of mammals exist within the potential area of application representative mammals of different sizes and consumption rates were selected to determine potential exposure and risk.

Table 5-2. Different mammal class parameters used to calculate adjusted LD_{50} and NOEL values.

Mammalian Class	Body Weight (g)	Ingestion (dry) (g bw/day)	Ingestion (wet) (g/day)	% body weight consumed	(kg-diet/day)	Adjusted LD_{50}	Adjusted NOEL
Herbivores/ insectivores	15	3	14	95	1.43E-02	10,197.93	3.14
	35	5	23	66	2.31E-02	8,251.22	2.54
	1,000	31	153	15	1.53E-01	3,568.91	1.10
Granivores	15	3	3	21	3.18E-03	10,197.93	3.14
	35	5	5	15	5.13E-03	8,251.22	2.54
	1,000	31	34	3	3.40E-02	3,568.91	1.10

These values were then compared to the dosed based estimated environmental concentrations that were calculated for diflubenzuron to determine if any of the exposures exceeded the toxicity endpoints with the assumption of no application buffer zone (table 5-3).

Table 5-3. Calculated mammalian risk quotient values for diflubenzuron assuming no application buffer zone.

Dose-based RQs (Dose-based EEC/LD_{50} or NOAEL)	15 g mammal		35 g mammal		1000 g mammal	
	Acute	Chronic	Acute	Chronic	Acute	Chronic
Short Grass	0.00*	1.16	0.00	1.00	0.00	0.53
Tall Grass	0.00	0.53	0.00	0.46	0.00	0.24
Broadleaf plants/small insects	0.00	0.66	0.00	0.56	0.00	0.30
Fruits/pods/large insects	0.00	0.07	0.00	0.06	0.00	0.03
Seeds (granivore)	0.00	0.02	0.00	0.01	0.00	0.01

EEC - estimated environmental concentration *Values are less than 0.001

Based on the lowest reported LD_{50} value for rats, and the expected residues, minimal direct acute risk is expected due to the low calculated risk quotient values (table 5-3). Because of the very conservative chronic endpoint there is a slight exceedance in mammals of 15 and 35 g who consume short grass only. Based on reductions in exposure to food items that would occur using 200 (ground) and 500 (aerial) foot application buffers the direct chronic risks to mammals would be minimal.

Possible indirect effects to small mammals could include a loss of habitat or food items. Habitat effects could include impacts to terrestrial and aquatic plants. Based on the lack of terrestrial phytotoxic effects for diflubenzuron, indirect risk to mammals from impacts to terrestrial plants is expected to be minimal for those species that depend on terrestrial plants as food or habitat. Aquatic plants may also serve as habitat or food items for select mammals. A detailed evaluation of the risk to aquatic plants from diflubenzuron applications is provided later in this section; however, in short, diflubenzuron poses minimal risk to aquatic plants. Another possible indirect risk to mammals that should be considered is the loss of food items for those mammals that are insectivorous. Risk of diflubenzuron applications to terrestrial invertebrates are discussed in more detail below. Diflubenzuron has a wide range of toxicity to different terrestrial invertebrate species and is more selective to immature stages. At the proposed application rates, grasshoppers have the highest risk of being impacted while other taxa have a much reduced risk based on the higher application rates that are needed for control of other taxa, and the lack of effects seen in multiple field studies on invertebrates at use rates much higher than those proposed for the program. The lower use rates and application buffer zones will minimize impacts to terrestrial invertebrates.

Available field data regarding the direct and indirect impacts to mammalian species supports the above risk characterization. In a review of mammalian field studies, Dimilin® applications at a rate of 60 to 280 g a.i./ha had no effects on the abundance and reproduction in voles, field mice, and shrews (US FS, 2004). These rates are approximately 3 to 16 times greater than the highest application rate proposed in the program. Seidel and Whitmore (1995) documented no effects on white-footed mice (*Peromyscus leucopus*) densities in untreated and treated areas with 140 g a.i./ha diflubenzuron. Mice on treated plots consumed less lepidopteran larvae compared to

controls; however, the total amount of food consumed did not differ between treated and untreated plots. Body measurements, weight, and fat content in mice collected from treated and non-treated areas did not differ. The lack of effects found in field studies where substantially higher rates of diflubenzuron were used than are used in the program, and the risk assessment that is based on laboratory effects, demonstrates minimal direct and indirect impacts to mammals that utilize plants and insects as food items.

5.2.1.2 Direct and Indirect Risk to Birds

Typically, the lowest acute toxicity value from the avian LD_{50} studies is used to calculate adjusted toxicity values. However, a NOEL of 2,500 mg/kg was used as a more sensitive endpoint with the adjusted NOEL value listed below for each avian class (table 5-4).

Table 5-4. Adjusted toxicity value (NOEL) for different avian class sizes.

Avian Class	Body Weight (g)	Ingestion (dry) (g bw/day)	Ingestion (wet) (g/day)	% body weight consumed	(kg-diet/day)	Adjusted NOEL (mg/kg-bw)
Small	20	5	23	114	2.28E-02	1,801.07
Mid	100	13	65	65	6.49E-02	2,292.86
Large	1,000	58	291	29	2.91E-01	3,238.75

Based on the adjusted NOEL value and the calculated residues for diflubenzuron estimated using T-REX, the risk quotient values were extremely low suggesting negligible direct acute impacts on birds that feed on contaminated plants and/or insects (table 5-5).

Table 5-5. Acute risk quotients for diflubenzuron based on the lowest acute NOEL value.

Dose-based RQs (Dose-based EEC/adjusted NOEL)	Avian Acute RQs 20g	100g	1,000g
Short Grass	0.00*	0.00	0.00
Tall Grass	0.00	0.00	0.00
Broadleaf plants/small insects	0.00	0.00	0.00
Fruits/pods/seeds/large insects	0.00	0.00	0.00

*Values are less than 0.001

Using upper bound dietary exposure estimates for diflubenzuron (3.84 ppm), and the lowest dietary toxicity value (NOEC = 4,640 ppm), the calculated risk quotient value is 0.0008 suggesting minimal acute dietary risk to surrogate avian species. Based on the lowest reported

avian reproduction NOEC (500 ppm), and the highest dietary residue on short grass (3.84 ppm), the calculated risk quotient is 0.008 suggesting minimal chronic risk to birds.
As previously discussed for mammals, there is a potential indirect effect on birds from loss of habitat and prey items. These potential effects are similar to those described for mammals. The available laboratory toxicity data and fate modeling indicate minimal indirect risk to avian species. The relatively low indirect risk has been documented in multiple field studies designed to assess the loss of invertebrate prey items to select avian species.

In field studies, small songbirds in a forest ecosystem were not affected after aerial application of diflubenzuron at 350 g a.i./ha (0.31 lb a.i./ac). No effects to the great tit, *Parus major*, or tree sparrow, *Passer montarus*, nestlings were noted based on growth and breeding endpoints as well as the calculated maximum daily intake of insects. Poisoning of insectivorous birds by diflubenzuron after spraying in orchards at labeled rates is unlikely (Muzzarelli, 1986).

A majority of the fieldwork involving impacts to avian species has focused on indirect effects from the loss of invertebrates. Sample et al. (1993) noted a shift in the diet of five out of nine songbird species after applications of a 25% formulation of diflubenzuron at a rate of 70.75 g/ha (0.063 lb a.i./ac) to control gypsy moth, which is well above full and RAATs diflubenzuron rates. Overall, insect biomass was the same between treated and untreated sites. Lepidopteran biomass declined in treated areas while Diptera, Coleoptera, Hemiptera, and other orders of insects increased. Shifting diets in insectivorous birds in response to prey densities is not uncommon in undisturbed areas (Rosenberg et al. 1982; Cooper et al., 1990; Sample et al., 1993).

5.2.1.3. Direct and Indirect Risk to Amphibians and Reptiles

Direct risk to amphibians and reptiles is expected to be minimal from applications of diflubenzuron. When compared to the 48-hour LC_{50} value of 100 mg/L that has been calculated for *Rana brevipoda porosa,* the highest estimated aquatic residue (1.2 µg/L) is approximately five orders of magnitude below the calculated LC_{50} value, suggesting low risk to amphibians. Based on assumptions by USEPA/OPP, the risk to reptiles and amphibians is assumed to be represented by birds and fish, respectively. While there is a great deal of uncertainty in these types of extrapolations, they can be of some use in cases where limited data is available, such as in this case. Based on this assumption and the results for assessing direct risk to avian and fish species, minimal risk to amphibians and reptiles is expected.

A potential indirect effect of diflubenzuron applications is loss of habitat or food items. Aquatic habitat would consist of aquatic plants while aquatic food items would consist of algae, aquatic invertebrates, and small fish. To understand better the potential indirect effects of these applications, diflubenzuron levels were compared to the available diflubenzuron effects data for aquatic plants, invertebrates, and fish. The details of this risk characterization are covered under the aquatic section below within the potential direct and indirect risk to fish section. The reader is referred to that section for details. However, to summarize, indirect risk to amphibians is expected to be minimal because residues do not exceed any effect endpoint for aquatic plants,

invertebrates, or fish. The potential terrestrial indirect risk to amphibians and reptiles is also expected to be minimal. Diflubenzuron is not phytotoxic; therefore, risk to terrestrial habitat is minimal. Diflubenzuron is expected to have an effect on terrestrial invertebrates that would serve as a food source; however, due to the selectivity of the insecticide and the range of sensitivities to different invertebrate species, widespread declines are not expected. In addition, the use of the proposed application buffer zones, and in some cases RAATs, will allow rapid recolonization of treated areas.

This conclusion is supported by a field study that assessed the impacts of diflubenzuron applications to aquatic and terrestrial salamanders (Pauley, 1995a, b). Applications occurred over two large watersheds at a rate of 0.03 lb/ac, which is approximately twice the maximum rate used in the program. In terrestrial and aquatic salamanders, a shift in prey items was noted; however, there was no effect on body size or population in the aquatic salamanders, and no effects on body size or body fat in the terrestrial salamanders (Pauley, 1995a, b).

5.2.1.4. Risk to Terrestrial Invertebrates

Multiple field studies in a variety of application settings, including grasshopper control, have been conducted regarding the impacts of diflubenzuron to terrestrial invertebrates.

A field study in apples where diflubenzuron was applied at 0.357 lb a.i./ac to trees in full bloom with honey bees foraging on the blossoms showed no reduction in adult or larval bee populations (Emmett and Archer, 1980). This rate is well above the 0.016 lb a.i./ac rate that is used for full coverage in the program. These results support the findings of other field studies where diflubenzuron has been shown to have no effect on honey bees in field studies applied at up to 0.5 lb a.i./ac (Atkins et al., 1976; Johansen, 1983). In a commercial citrus grove, diflubenzuron was applied eight times at 0.312 lb a.i./ac at approximately monthly intervals to evaluate the impact on honey bee brood. No effects were observed on bee brood development (Schroeder et al., 1980). A similar lack of effects to honey bee broods has been observed with repeated diflubenzuron applications in cotton fields at rates much higher than those used in the program (Robinson, 1979).

Several field studies have been conducted and summarized regarding the potential effects of diflubenzuron applications to other terrestrial invertebrates. Deakle and Bradley (1980) measured the effects of four diflubenzuron applications on predators of *Heliothis* spp. at a rate of 0.06 lb a.i./ac and found no effects on several predator groups. This supported earlier studies by Keever et al. (1977) that demonstrated no effects on the arthropod predator community after multiple applications of diflubenzuron in cotton fields. Sample et al. (1993) assessed the impacts of forestry applications of diflubenzuron on non-target invertebrates at a rate of 70.75 g a.i./ha (0.063 lb a.i./ac) applied once per year for a 2-year study. On the level of invertebrate order, there were no statistically significant effects between treated and untreated blocks when considering median abundance of the insect orders Lepidoptera, Coleoptera, Diptera, Trichoptera, Hymenoptera, Heteroptera, Homoptera, Neuroptera, and Plecoptera. Within each order, there were significant effects in both years of the study for the moth families Arctiidae and

Notodontidae, out of 26 families that were assessed. These results are somewhat confirmed in another forestry application of diflubenzuron. Butler et al. (1997) measured forestry invertebrate abundance three years post-application to determine potential impacts from gypsy moth applications to non-target invertebrates. Some effects in diversity were noted. Abundance was not statistically significant between treated and untreated sites using burlap band sampling but some differences were noted in microlepidoptera and Coleoptera abundance for the year of treatment for a foliage sampling method. These application rates occurred at levels above those used by the program.

Previously conducted research, as well as field studies carried out as part of the grasshopper integrated pest management (IPM) project, indicates that diflubenzuron has minimal impact on most terrestrial nontarget arthropods (Catangui et al., 1996). Weiland et al. (2002) in Wyoming monitored the effects of Dimilin 25W for 21 days post-application on terrestrial invertebrates after full treatment applications of 17.5 and 52.5 g a.i./ha. From high and low sweep net captures, no effect on invertebrates in the orders Homoptera, Hymenoptera, Coleoptera, Hemiptera, Lepidoptera, or Neuroptera were found. There was a statistically significant increase in Diptera and a statistically significant decrease in Araneae (spiders) but the authors question the spider analysis because untreated populations also dropped dramatically during the study. Tingle (1996) assessed the impacts of diflubenzuron applications in two field trials occurring in two separate years with applications of 93 g a.i./ha (0.08 lb a.i./ac). Based on an analysis of 28 taxonomic groupings, only two were affected and included non-target grasshoppers and lepidopteran larvae. This effect only occurred in the treated areas but did not occur in the untreated buffer areas that were sampled. Grasshopper IPM field studies have shown diflubenzuron to have a minimal impact on ants, spiders, predatory beetles, and scavenger beetles. There was no significant reduction in populations of these species from 7 to 76 days after treatment. Although ant populations exhibited declines of up to 50%, these reductions were temporary, and population recovery was described as immediate (Catangui et al., 1996). No significant reductions in flying non-target arthropods, including honey bees, were reported. Within one year of diflubenzuron applications in a rangeland environment, no significant reductions of bee predators, parasites, or pollinators were observed for any level of diflubenzuron treatment (Catangui et al., 1996). Graham et al. (2008) evaluated the impacts of diflubenzuron treatments on aquatic and terrestrial invertebrates for Mormon cricket suppression in Utah. A majority of terrestrial invertebrate taxa were not significantly different pre- and post-treatment among three sites that were evaluated. There was a noted decrease in some ant genera but results were not consistent between sites and not all genera were impacted. Non-ant Hymenoptera showed increased numbers at two of the three sites and a decrease at a third site when comparing numbers pre- and post-treatment.

5.2.1.5. Direct and Indirect Risk to Terrestrial Plants

The direct risk to terrestrial plants is expected to be minimal based on results from laboratory and field studies that demonstrate no effects using diflubenzuron over a range of application rates. The indirect risk to terrestrial plants is the potential loss of pollinators from program applications.

The majority of rangeland plants require insect-mediated pollination. Native, solitary bee species are the most important pollinators on western rangeland (Tepedino, 1979). Potential negative effects of insecticides on pollinators are of concern because a decrease in their numbers has been associated with a decline in fruit and seed production of plants. Rangeland species populations that depend on plants for food may be affected indirectly due to changes in vegetation patterns (Alston and Tepedino, 1996).

Although negative effects of diflubenzuron on honey bees have been demonstrated at high application levels and relatively long periods of exposure, these application rates exceed the rates used in the program. Diflubenzuron application rates as high as 0.125 to 0.25 lb a.i./ac resulted in no effect to adult mortality and brood production (Robinson and Johansen, 1978). Based on the review of laboratory and field toxicity data for terrestrial invertebrates, applications of diflubenzuron are expected to have minimal risk to pollinators of terrestrial plants. The use of RAATs provide additional benefits by creating reduced rates and/or untreated swaths within the spray block that will further reduce the potential risk to pollinators.

5.2.2 Aquatic Risk Characterization

Characterization of risk to aquatic species from diflubenzuron applications was made by comparing the residue values in the exposure analysis from ground and aerial applications to the distribution of available acute and chronic fish toxicity data (figure 5-1). Residue values were below the distribution of acute and chronic response data, suggesting that direct risk to aquatic species is not expected from diflubenzuron applications.

Indirect risk to fish species can be defined as a loss of habitat or prey base that provides food and shelter for fish populations. To determine the potential impacts of diflubenzuron applications on habitat loss through effects to aquatic plants, the most sensitive plant species (*Lemna minor*) was used as a benchmark endpoint for protection of aquatic habitat. The NOEC concentration in a 5-day exposure study was 190 µg/L. Residues from ground and aerial applications are greater than 2,000 times below the NOEC concentration for aquatic plants, suggesting that impacts to aquatic plants that serve as habitat or as a food source to prey items are not expected.

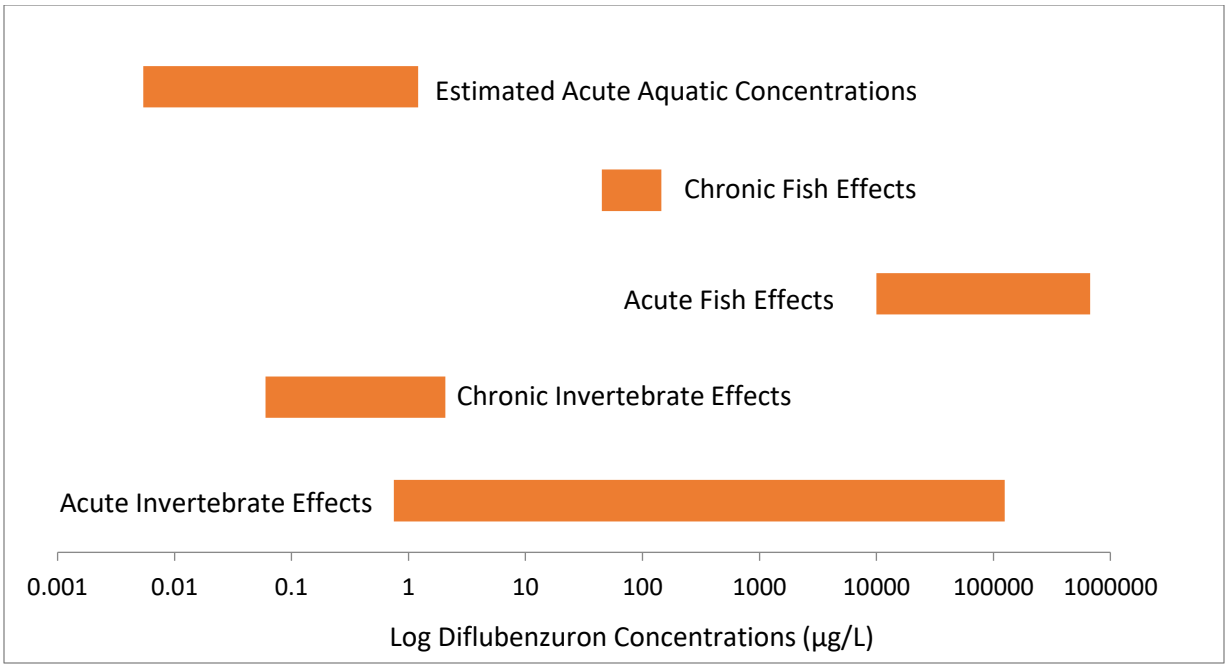

Figure 5-1. Diflubenzuron risk characterization for fish and aquatic invertebrates.

Indirect impacts to aquatic species through the loss of prey items are also not expected based on the available fish and invertebrate toxicity data. As previously mentioned, the fish toxicity data is well above the estimated residues from the drift analysis, and the distribution of aquatic invertebrate toxicity data is also above the residues estimated from ground and aerial applications of diflubenzuron. Risk from the consumption of contaminated prey is not expected based on the low BCF values that have been reported for diflubenzuron. These comparisons can also be used to characterize the risk to aquatic invertebrates that were considered in this HHERA. The estimated residues from aerial applications suggest chronic risk to some aquatic invertebrates. However, as previously mentioned, these residues are considered conservative estimates when compared to observed residues that have been measured in the field. Average residue values collected from drift cards collected at 500 feet from actual applications were greater than 20 times lower than values determined using the drift models (USDA-APHIS, 2015b). In addition, the lowest chronic effect endpoints are based on 21- to 28-day continuous exposure studies, which would not occur in this program because only one application is being made per year and available environmental fate data suggests diflubenzuron would not persist in water.

5.2.2.1. Aquatic Field Studies Regarding Fish and Aquatic Invertebrates

The laboratory variability in sensitivities to diflubenzuron is supported by several field studies that have assessed the impacts of diflubenzuron in different aquatic habitats. A review of several aquatic field studies demonstrated that when effects were observed it was at diflubenzuron levels not expected from program activities (Fischer and Hall, 1992; USEPA, 1997; Eisler, 2000; US

FS, 2004). While these studies may have limited use because of study design and relevance to the program, they can provide support to laboratory results and insight into ecosystem level impacts that would not be observed in standard laboratory toxicity studies.

Ali and Mulla (1978a) tested a formulation of diflubenzuron and found that crustaceans, such as cladocerans and copepods, were the most sensitive taxa after two applications to a lake at a rate of 156 g a.i./ha. In addition, mayfly nymphs were severely reduced, supporting other ecosystem-type exposure studies testing the effects of diflubenzuron. Mayfly nymphs were reduced after continuous applications of diflubenzuron in laboratory streams over a 5-month period (Hansen and Garton, 1982b). Mayfly nymphs within the genera *Baetis*, *Rithrogena*, *Paralepthophlebia*, and *Ephemerella* were the most sensitive. Coleoptera (family Elmidae), Oligochaeta, and Gastropoda numbers were not affected at the highest test concentration (10 µg/L). The same trend was also observed in other flowing water ecosystems where diflubenzuron application rates of 0.4 to 0.8 oz a.i./ac reduced numbers of dipterans, as well as cladocerans, copepods, mayfly nymphs, corixids, and springtails (Eisler, 1992). Cladocerans and certain aquatic hemipterans have also been shown to be the most sensitive organisms in dosing studies in ephemeral pools (Lahr, 1998). In freshwater lakes, ponds, and marshes, the types of invertebrates most susceptible to diflubenzuron are amphipods (scuds), cladocerans, some midges, caddisflies, and mayflies (Ali and Mulla, 1978a, b; Apperson et al., 1978; Hansen and Garton, 1982b; Sundaram et al., 1991; Fischer and Hall, 1992). In particular, cladocerans (*Daphnia* sp.) and caddisflies (*Clistoronia* sp.) are at high risk of adverse effects from full coverage applications of diflubenzuron. Mayflies (*Callibaetis* sp.), amphipods (*Gammarus* sp.), and some midges (*Tanytarsus* sp.) are at moderate risk. Dragonfly larvae, stonefly larvae, aquatic beetles, crayfish, bivalves, chironomid midges, and snails are at low risk. Recovery of invertebrate taxa affected by diflubenzuron at a dose of 10 µg/L has been observed in outdoor pond studies during the duration of the study while other taxa may take longer (Ali and Kok-Yokomi, 1989).

Several studies are available which assessed the direct effects of diflubenzuron to invertebrates, while comparatively few exist which assess effects to fish. Tanner and Moffett (1995) noted effects on fish growth at diflubenzuron levels as low as 2.5 µg/L, while ponds directly treated with diflubenzuron at a concentration of 5 or 13 µg/L did not show any effects on fish growth (Apperson et al., 1978; Colwell and Schaefer, 1980). A shift in diet was noted by Colwell and Schaefer (1980); however, this did not translate into an effect on growth in fish. Boyle et al. (1996) noted diflubenzuron-related impacts to some aquatic invertebrates indirectly resulting in increased algal biomass in an outdoor micorocosm dosed bi-weekly or monthly at 10 µg/L. These reductions did not result in indirect impacts to bluegill and largemouth bass.

6.0 UNCERTAINTIES AND CUMULATIVE IMPACTS

The uncertainties associated with this risk evaluation arise primarily from lack of information about the effects of diflubenzuron, the formulation, metabolites, and potential mixtures to non-target organisms that can occur in the environment. These uncertainties are not unique to this assessment but are consistent with uncertainties in human health and ecological risk assessments with any environmental stressor. In addition, there is uncertainty in where an infestation may occur in a specific state, and the rest of the United States, and the extent of diflubenzuron use in a given infestation because its use is based on site-specific factors.

Another area of uncertainty is the potential for cumulative impacts to human health and the environment from the proposed use of diflubenzuron in the grasshopper suppression program. Areas where cumulative impacts could occur are: 1) repeated worker and environmental exposures to diflubenzuron from program activities in conjunction with other crop use sources; 2) co-exposure to other chemicals with a similar mode of action; and 3) exposures to other chemicals in mixtures and how that may affect the toxicity of diflubenzuron.

Diflubenzuron is used as both an acaricide and insecticide on agricultural and non-agricultural sites. Based on pesticide use data from the USDA's National Agricultural Statistics Service and private pesticide market research (2003 to 2010), and the pesticide use reporting data from California Department of Pesticide Regulation (2003 to 2009), the average annual pounds of diflubenzuron applied for agriculture use was estimated to be <500 to 20,000 pounds of active ingredient (USEPA, 2011b). The highest estimated agricultural use was for almonds with 10% (average) and 20% (maximum) of the crop being treated. The USDA-APHIS grasshopper program use of diflubenzuron in rangelands is unlikely to be in conjunction with other insecticide uses. There may be herbicide use on rangeland but the level of treatment will depend on the value of the rangeland and whether treatments are warranted. Greater than 99% of the total number of applications for the grasshopper program between 2006 and 2012 used RAATs. The size of treatment blocks vary with areas as small as 30 acres to greater than 219,000 acres. Grasshopper treatment areas greater than 3,000 acres have been treated almost exclusively with diflubenzuron. The APHIS maximum RAATs rate for diflubenzuron is 0.016 lb a.i./ac which is lower than labeled application rates for rangeland and other crops (USDA-APHIS, 2015b).

Cumulative impacts from the potential for co-exposure of diflubenzuron and other chemicals used in the program that have a similar mode of action resulting in synergism, potentiation, additive, or antagonistic effects are not expected. Diflubenzuron is an insect growth inhibitor and affects the hematopoietic system in mammals, which is not the same toxic action as other insecticides used within the program. The other insecticides used in the grasshopper program include carbaryl, malathion, and chlorantraniliprole. Carbaryl targets the nervous system (carbamylation of acetylcholinesterase resulting in accumulation of the neurotransmitter, acetylcholine). Malathion inhibits the enzyme acetylcholinesterase in the central and or peripheral nervous system. Chlorantraniliprole acts on the ryanodine receptor. As previously stated, the program only makes one insecticide application in a given area per growing season so other program insecticides would not be applied in the same area.

7.0 REFERENCES

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Appendix A. Risk estimates of potential dermal and inhalation exposures during mixing and loading for workers

Equations:

Dermal Dose = (Application Rate x Area Treated x Dermal Unit Exposure (DUE) x Dermal Absorption Factor (DAF) x Conversion Factor (CF)) / Body Weight (BW)

Inhalation Dose = (Application Rate x Area Treated x Inhalation Unit Exposure (IUE) x Conversion Factor (CF)) / Body Weight (BW)

Dermal Hazard Quotient (DHQ) = Dermal Dose/Dermal RfD

Inhalation Hazard Quotient (IHQ) = Inhalation Dose/Inhalation RfD

Assumptions for risk estimation:

Input Parameters		Values	Sources
Application Rate (lb a.i./acre)	Average	0.006	USDA-APHIS, 2015b[1]
	Maximum	0.016	
Area treated (acre/day)		20,000	USDA-APHIS, 2015b[2]
DUE (µg/lb a.i.)		220	USEPA, 2016b[3]
IUE (µg/lb a.i.)		0.219	USEPA, 2016b[4]
DAF (unitless)		0.005	USEPA, 2015[5]
CF (mg/µg)		0.001	
BW (kg)		69	USEPA, 2016b[6]
Dermal Dose (mg/kg-day)		1.9E-03	Calculated
		5.1E-03	Calculated
Inhalation Dose (mg/kg-day)		3.8E-04	Calculated
		1.0E-03	Calculated
Dermal RfD (mg/kg-day)		0.02	USEPA, 2015
Inhalation RfD (mg/kg-day)		0.02	USEPA, 2015
DHQ	Average	0.1	Calculated
	Maximum	0.3	Calculated
IHQ	Average	0.02	Calculated
	Maximum	0.05	Calculated
Combined HQ (DHQ + IHQ)	**Average**	**0.1**	Calculated
	Maximum	**0.3**	Calculated

Notes:

1. Average application rate: 0.006 lb a.i. per acre for APHIS average RAATs rate.
2. Maximum application rate: 0.016 lb a.i. per acre for APHIS full rate.
3. Assumed the program application of 20,000 acre per day.
4. Single layer, no gloves PPE levels for the mixing/loading liquids exposure scenario.
5. No respirator PPE level for the mixer/loader/applicator, manually-pressurized handwand exposure scenario.
6. 0.5% of dermal absorption.
7. Body weight for women.

Appendix B-1. Diflubenzuron acute aquatic fish toxicity values

Test Organism	Endpoint/Length	Toxicity Value	Reference
Yellow perch *Perca flavescens*	96-hour LC_{50}	25 mg/L	Johnson and Finley, 1980
Bluegill sunfish* *Lepomis macrochirus*	96-hour LC_{50}	129 mg/L	USEPA, 2018
Rainbow trout *Onchorynchus mykiss*	96-hour LC_{50}	136 mg/L	USEPA, 2018
Cutthroat trout *Oncorynchus clarki*	96-hour LC_{50}	>60 mg/L	Mayer and Ellersieck, 1986
Atlantic salmon *Salmo salar*	96-hour LC_{50}	>50 mg/L	Mayer and Ellersieck, 1986
Brook trout *Salvelinus fontinalis*	96-hour LC_{50}	>50 mg/L	Mayer and Ellersieck, 1986
Flathead catfish *Ictalurus punctatus*	96-hour LC_{50}	>100 mg/L	Johnson and Finley, 1980
Fathead minnow *Pimepheles promelas*	96-hour LC_{50}	>500 mg/L	US FS, 2004

*The lowest LC_{50} value for the bluegill sunfish is reported above. Values as high as 660 mg/L have been reported

Appendix B-2. Diflubenzuron acute aquatic invertebrate toxicity values

Test Organism	Endpoint/Length	Toxicity Value	Reference
Aedes nigromaculatum	48-hour EC_{50}	0.5 µg/L	Miura and Takahashi, 1974
Chironoumus plumosus	48-hour EC_{50}	0.56 µg/L	Julin and Sanders, 1978
Palaemontes pugio	96-hour LC_{50}	0.64 µg/L	USEPA, 2018
Streptocephalus sudanicus	48-hour EC_{50}	0.74 µg/L	Lahr et al., 2001
Tanytarsus dissimilis	120-hour LC_{50}	1.02 µg/L	Hansen and Garton, 1982a
Ceriodaphnia dubia	48-hour EC_{50}	1.7 µg/L	US FS, 2004
Daphnia magna	48-hour EC_{50}	1.84 µg/L	Hansen and Garton, 1982a
Hyallela azteca	96-hour LC_{50}	1.84 µg/L	Hansen and Garton, 1982a
Mysidopsis bahia	96-hour LC_{50}	2.0 µg/L	USEPA, 1997
*Eurytemora affinis**	48-hour LC_{50}	2.2 µg/L	Savitz et al., 1994
*Callinectes sapidus**	96-hour LC_{50}	18.5 µg/L	Rebach, 1996
Gammarus sp.	96-hour LC_{50}	30 µg/L	US FS, 2004
Gammarus pseudolimnaeus	96-hour LC_{50}	45 µg/L	USEPA, 2018
Orthemis sp.	168-hour LC_{50}	50 µg/L	Miura and Takahashi, 1974
Hydrophilus triangularis	48-hour EC_{50}	100 µg/L	Miura and Takahashi, 1974
Anisops sardius	48-hour EC_{50}	1,937 µg/L	Lahr et al., 2001
*Crassostrea virginica**	96-hour LC_{50}	130 mg/L	USEPA, 1997

* Formulation studies

Appendix B-3. Diflubenzuron acute sublethal and chronic aquatic toxicity values

Test Organism	Endpoint/Length	Toxicity Value	Reference
Fundulus heteroclitus	96-hour NOEC	29.86 mg/L	Lee and Scott, 1989
Pimepheles promelas	35-day NOEC	0.10 mg/L	USEPA, 2018
Onchorynchus mykiss	30-day NOEC (growth/survival)	>45 µg/L	Hansen and Garton, 1982a
Daphnia magna	21-day NOEC (reproduction)	0.04 µg/L	USEPA, 1997
Mysidopsis bahia	28-day NOEC (reproduction)	0.045 µg/L	USEPA, 1997
Ceriodaphnia dubia	7-day NOEC (reproduction)	0.25 µg/L	US FS, 2004
Chironomus tentans	NOEC (porewater/sediment (growth)	14.03 µg/L /13.67 µg/kg	USEPA, 2018
Leptochirus plumulosus	10-day NOEC (porewater/sediment (survival)	0.87 µg/L/ 1.24 µg/kg	USEPA, 2018