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Draft Human Health and Ecological Risk Assessment for Diazinon in Exotic Fruit Fly 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 is proposing the continued use of diazinon in its fruit fly cooperative eradication program. Diazinon is an organophosphate insecticide applied as a soil drench to containerized nursery stock in commercial nurseries to kill exotic fruit fly larvae.

USDA-APHIS evaluated the potential human health and ecological risks from the proposed use of diazinon soil drenches and determined that the risk to human health and the environment is negligible. The use pattern and label requirements substantially reduce the potential for exposure to humans and the environment. USDA-APHIS does not expect adverse health risks to workers based on the application method and label requirements, such as the use of personal protective equipment, which results in a low potential for exposure to diazinon. USDA-APHIS quantified the potential risks associated with accidental exposure of diazinon for workers during mixing, loading, and application based on the proposed use. The quantitative risk evaluation indicates no concerns for adverse health risks to program workers from diazinon applications. The risk to the general public from diazinon exposure associated with soil drench applications is also expected to be minimal based on the proposed use pattern and lack of dietary exposure.

Diazinon is toxic to terrestrial and aquatic non-target organisms; however, the proposed use pattern and its use in commercial nurseries reduces the potential for significant exposure. The environmental fate of diazinon and its proposed use pattern in the program also reduces the potential for impacts to air, soil, and water quality.

1.0 INTRODUCTION

This human health and ecological risk assessment (HHERA) is a qualitative and quantitative evaluation of the potential risks and hazards to human health, non-target fish, and wildlife as a result of exposure to diazinon. Diazinon is an organophosphate insecticide used to eradicate various species of exotic fruit flies (e.g., Mediterranean fruit fly, Mexican fruit fly, oriental fruit fly, etc.) when they are detected in the United States. Organophosphate insecticides affect nervous system function in animals.

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

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

2.0 PROBLEM FORMULATION

Fruit flies in the family Tephritidae are among the most destructive and well-publicized pests of fruits and vegetables around the world. Exotic fruit flies in the genera *Anastrepha*, *Bactrocera*, and *Ceratitis* pose a significant risk to U.S. agriculture. Tephritid fruit flies spend their larval stages feeding and growing on over 400 host plants. Introduction of these pest species into the United States causes economic losses from destruction and spoiling of host commodities, costs associated with implementing control measures, and loss of market share due to quarantines and restrictions on shipment of host commodities. The extensive damage and wide host range of tephritid fruit flies become obstacles to agricultural diversification and trade when exotic fruit fly species establish where host plants occur (USDA APHIS, 2013).

Diazinon is an organophosphorous insecticide used to control insects on various fruits, vegetables, nuts, ornamental plants grown outdoors in nurseries, and in cattle ear tags. Diazinon was widely used in residential settings prior to 2000; however, the registrant and USEPA agreed to cancel all residential uses for diazinon products due to potential human health risks. Sales of all residential use products ceased in 2004 (USEPA, 2008a). Currently, there are no registered residential uses for diazinon (USEPA, 2016b).

The USDA-APHIS fruit fly cooperative eradication program uses diazinon applied as a soil drench to kill tephritid fruit fly larvae and pupae in containerized nursery stock in commercial nurseries. Currently, diazinon is registered under a Special Local Need (SLN) Section 24(c) registration in California. When fruit flies are detected, USDA-APHIS uses trapping to delimit the extent of the population and will implement various control measures until there is eradication of all fruit fly populations from that area. Diazinon may be used when the quarantine area includes commercial nurseries that grow containerized host plants. Exotic fruit fly treatments vary temporally and spatially each year based on need. Typically, an eradication program lasts two to three months.

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

2.1 Chemical Description and Product Use

Diazinon (CAS No. 333-41-5, $C_{12}H_{21}N_2O_3PS$) is the common name for O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate. The chemical structure is illustrated in Figure 2-1.

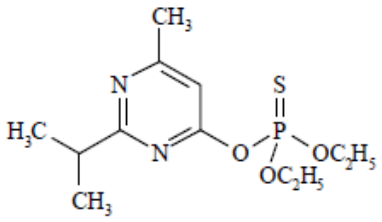

Figure 2-1 The chemical structure of diazinon

USEPA first registered diazinon as a pesticide in 1956 to control soil insects and pests of fruit, vegetables, forage and field crops (USEPA, 2006a). The program proposed formulation (Diazinon AG500®) (EPA Reg. No. 66222-9) contains 48% diazinon as an active ingredient (a.i.) and 52% inert ingredients (4 pounds diazinon per gallon) (Makhteshim Agan of North America, Inc., 2017). The program makes applications in accordance with the requirements of the Diazinon AG500® and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 24(c) labels to control fruit flies. California is currently the only state where diazinon is used as part of the fruit fly cooperative eradication program (SLN No. CA-050002). Diazinon AG500® is a restricted use pesticide due to avian and aquatic toxicity. It is for retail sale to and used only by certified applicators, or persons under their direct supervision, and only for those uses covered by the certified applicator's certification (Makhteshim Agan of North America, Inc., 2017; California Department of Food and Agriculture, 2015).

2.2 Physical and Chemical Properties

Diazinon is a colorless oil. It has a molecular weight of 304.3 g/mol and a vapor pressure ranging between 6.6×10^{-5} and 7.22×10^{-5} torr at 25 ºC. The estimated Henry's law constant is 1.1×10^{-7} at 23 ºC and 4.4×10^{-7} atm-m^3/mol at 25 ºC. Technical diazinon (> 90% pure) is an amber to brown liquid with a boiling point of 83–84°C. Diazinon has a water solubility ranging between 59.5 and 65.5 mg/L at 25°C. It is soluble in petroleum oils, and is miscible in organic solvents such as acetone, benzene, and ethanol (USEPA, 2006a; 2008b; 2016c). The octanol-water partition coefficient (Kow) is 4,898 (log Kow of 3.69) at 24 ºC and 6,393 (log Kow of 3.8) at 25 ºC, (USEPA, 2016c). It has a boiling point of 190 ºC, a vapor pressure of 9.0×10^{-5} torr at 25 ºC, and a water solubility of 60 mg/L at 20 ºC (Makhteshim Agan of North America, Inc., 2014).

Diazoxon (CAS No. 962-58-3, $C_{12}H_{21}N_2O_4P$, Phosphoric acid, diethyl 6-methyl-2-(1-methylethyl)-4-pyrimidinyl ester) is an oxon degradate of diazinon. Diazoxon has a molecular weight of 288.28 g/mole, an estimated vapor pressure of 1.1×10^{-5} torr at 25ºC, an estimated Henry's law constant of 1.89×10^{-10}, and a Kow of 117 (log Kow of 2.07) (USEPA, 2016c).

2.3 Environmental Fate

The environmental fate section describes the processes by which diazinon moves and transforms 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. Diazinon is typically not persistent in the environment with half-lives of less than 60 days in soil and water, and less than 2 days in air (USEPA, 2016c). Diazinon in soil degrades by photolysis and microbial metabolism with representative aerobic half-lives ranging from 9 to 57 days (USEPA, 2016c). A previous USEPA environmental fate evaluation includes soil photolysis half-lives of 2.8 to 8.8 days and an anaerobic soil half-life of 17 days (USEPA, 2008b). Diazinon may move to the atmosphere as a vapor or in particulate form. Diazinon in the atmosphere degrades by reaction with hydroxyl radicals (a half-life of 4 hours) or by photolysis (a half-life of greater than 1 day) (Munoz et al., 2011). The estimated atmospheric degradation half-lives estimated for the hydroxyl radicals in the troposphere were 1.3 hours at 40ºC for diazinon and

4.1 hours at 30ºC for diazoxon (USEPA, 2016c). Terrestrial field dissipation studies show diazinon half-life values ranging from 5 to 20 days in the top 6 inch soil layer.

In aquatic environments, diazinon degrades by hydrolysis under acidic conditions with half-lives of 2 days (pH 4) and 12 days (pH 5), but is more stable under neutral and alkaline conditions with abiotic hydrolysis half-lives ranging from 62 to 139 days between pH 7 and pH 9. Diazinon also degrades by microbial metabolism with aerobic aquatic metabolism half-life values ranging from 10 to 16 days in water-soil and 6 to 41 days in surface water. The anaerobic aquatic metabolism half-life is 24.5 days. Diazinon is stable to photolysis in water. Laboratory and field studies indicate that diazinon breaks down to degradates such as oxypyrimidine and diazoxon. The oxidation product diazoxon is a strong cholinesterase inhibitor; however, diazoxon hydrolyzes faster than diazinon with a half-life of 25 days at pH 7.4 (30 ºC) (USEPA, 2008b). Diazinon is classified as moderately to slightly mobile in soils according to the Food and Agriculture Organization of the United Nations (FAO) classification system (FAO, 2000) with Kocs ranging from 138 to 3,779 L/kg (USEPA, 2016c). Diazinon has the potential to reach surface water through runoff and soil erosion especially in low organic matter soil types. Soil column leaching studies observed oxypyrimidine and diazinon residues in the leachate at 30 cm in a soil column, indicating a potential for movement of diazinon from soil to ground water (USEPA, 2008b). The maximum depth of leaching in the terrestrial field dissipation studies was 48 inches (USEPA, 2016c). Diazinon can reach groundwater especially in soils that are highly permeable and with low organic-carbon content and/or the presence of shallow groundwater tables. The U.S. Geological Service (USGS) detected diazinon in surface and ground water samples from 2004 and 2006 with detectable diazoxon residues in surface water samples collected between 2002 and 2005 (USGS, 2008). More recent monitoring data indicates diazinon is detected less frequently in U.S. streams and rivers, due to the reduction of diazinon use related to additional label restrictions (Stone et al., 2014, Wang, et al., 2017).

Diazinon is not expected to bioaccumulate in aquatic organisms based on the low octanol-water partition coefficient (Log Kows of 3.69 to 3.8), reported bioconcentration factor (BCF) values in aquatic species (3 to 82 µg/kg wet weight per µg/L in aquatic invertebrates and 18 to 213 µg/kg wet weight per µg/L in fish), and the rapid elimination of accumulated residues in fish once they are placed in clean water (USEPA, 2008b. Aggarwal et al., 2013; USEPA, 2016c). A bioconcentration study in bluegill sunfish reported a BCF of 542x for whole fish; however, 96% of the diazinon residues were eliminated from fish tissue within 7 days once fish were moved to clean water (USEPA, 2008b). In this study, 67 to 95% of total residue in fish was oxypyrimidine, 2.3 to 10% of residue was diazinon, and diazoxon was not detected (USEPA, 2016c). Bioaccumulation of diazinon in air-breathing organisms may occur based on the estimated log octanol-air partition coefficient of 9.1 (USEPA, 2008b; Kelly et al., 2007). However, bioaccumulation is limited because diazinon metabolizes to oxypyrimidine and other degradates that would not bioaccumulate or be of toxicological concern (USEPA, 2008b).

2.4 Hazard Identification

Diazinon is a hazard to human health because it can cause cholinesterase inhibition and overstimulate the nervous system. Symptoms of neurotoxicity include nausea, dizziness, and confusion. Other adverse health impacts of diazinon include excessive secretions (e.g.,

salivation, lacrimation, and rhinorrhea); neuromuscular effects (e.g., muscle twitching, tremor, weakness, and incoordination); cardiovascular effects (e.g., slow heart rate, which may lead to cardiac arrest and hypotension); gastrointestinal effects (e.g., abdominal pain, vomiting, and diarrhea); and respiratory effects (e.g., difficulty in breathing due to bronchospasm, and productive cough from bronchorrhea) (USEPA, 2016b; d). Exposure to high levels of diazinon from events such an accident or major spill can result in pulmonary edema, respiratory insufficiency from respiratory muscle paralysis, asphyxia, and death (USEPA, 2016d).

2.4.1 Toxicological Effects

Similar to other organophosphate (OP) pesticides, the mode of action for diazinon involves inhibition of the enzyme acetylchlolinesterase (AChE) through phosphorylation of the serine residue at the active site of the enzyme, which leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (USEPA, 2016b). AChE inhibition (AChEI) requires the bioactivation of diazinon to an oxon metabolite (diazoxon). AChEI is the most sensitive endpoint for multiple species and exposure pathways. For both diazinon and diazoxon, red blood cell (RBC) AChEI was generally more sensitive than brain AChEI; females rats were generally more sensitive than males; and pups were generally more sensitive than adults (USEPA, 2016b).

2.4.2 Absorption, Distribution, and Excretion

Diazinon absorbs and distributes rapidly with extensive metabolism and no accumulation in tissue. A rat metabolism study showed 58.2% (females) and up to 93.3% (males) of the ^{14}C label recovered in the urine, and <2.5% in the feces in the first 24 hours of exposure. After 7 days, there was 97 to 100% recovery with 87–95% in the urine, 2–3% in feces, and 1–2% remained in the tissues. The highest level of residues was in the blood. The major urinary metabolites, diazoxon and hydroxydiazinon, indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted (USEPA, 2016b).

2.4.3 Human Incidents

This section summarizes reviews by the USEPA/OPP Health Effect Division (HED) on acute and chronic health effects potentially associated with diazinon exposure, as well as additional online searches (USEPA, 2016d). The HED's review of information sources included human toxicological reviews, medical case reports, epidemiological studies, and human incident databases such as Incident Data System database (2003 to 2013), National Pesticide Information Center (2001 to 2012), California's Pesticide Incident Surveillance Program (2005 to 2010), and National Institute for Occupational Safety and Health SENSOR-Pesticides (1998 to 2010). These sources reveal a decrease in the number of diazinon incidents over time. There were fewer reports of exposures after a series of USEPA regulatory decisions limiting use sites and adding additional safety language to the label to reduce exposure. These decisions included (a) cancellation of residential uses, (b) increased restricted entry intervals (REI), (c) prohibition of foliar application on most vegetables, (d) elimination of aerial application and granular uses, and (e) additional engineering controls.

The HED's review of the incident database found that the acute health effects of diazinon are typical of OP toxicity including primarily neurological (such as headaches and dizziness), gastrointestinal, and respiratory effects. These OP-related effects are generally mild to moderate and resolve rapidly or, with primary medical intervention, are reversible.

The HED's review of medical literature for diazinon poisonings found that diazinon can cause AChEI related symptoms, airway hyper reactivity, and an increase in oxidative stress inside the brain. Diazinon poisoning can also cause acute pancreatitis, kidney failure, and development of amorphous crystalluria. There were also acute poisonings that resulted in severe negative health effects, some life threatening, and even death from accidental exposure of diazinon that occurred in foreign countries.

The HED's review on occupational and environmental epidemiological investigations indicates a potential role for diazinon in the cause of several cancer and non-cancer health effects. However, the investigations on cancer effects did not observe a positive association between the development of prostate, breast, colorectal, pancreatic, or pediatric cancers or glioma or cutaneous melanoma and diazinon exposure. The evidences of the association of diazinon exposure with lung cancer and non-Hodgkin lymphoma identified in the Agricultural Health Study (AHS, https://aghealth.nih.gov/) (Jones et al., 2015; Alavanja et al., 2014) are insufficient to conclude a causal or clear associative relationship (USEPA, 2016c). Pahwa et al., (2011) reported a significant, positive association of diazinon exposure with soft tissue sarcoma; however, the positive association has not yet been replicated in other populations (USEPA, 2016d).

There is suggestive evidence of an association between diazinon exposure and respiratory effects such as rhinitis (Slager et al., 2009; Slager et al., 2010). However, the HED's review concluded the evidence is insufficient to reach causal conclusions without additional studies. There is little to no relationship between other non-cancer health effects such as Parkinson's disease, diabetes, neurological effects, myocardial infarction, retinal degeneration, thyroid disease, and mental hygiene (suicide, depression) and diazinon exposure in the current AHS database.

Additional online open literature searches for recent human incident cases did not identify new studies associated with diazinon exposure.

2.4.4 Acute Toxicity

Diazinon has low acute toxicity (Toxicity Category III) via the oral and dermal exposure routes and very low acute toxicity (Toxicity Category IV) via the inhalation route. The acute oral median lethality doses (LD_{50}) in rats are 1,340 mg/kg (males) and 1,160 mg/kg (females). The acute dermal LD_{50} in rabbits exceeds 2,020 mg/kg. The acute inhalation median lethality concentration (LC_{50}) in rats exceeds 2.33 mg/L in a 4-hour exposure. Diazinon is a mild irritant to the eye and in dermal exposures in rabbits, but is not a dermal sensitizer in the guinea pig (USEPA, 2016b).

The Diazinon AG500® formulation has moderate acute oral (Toxicity Category II), low acute dermal (Toxicity Category III), and very low acute inhalation (Toxicity Category IV) toxicity. The safety data sheet (SDS) (Makhteshim Agan of North America, Inc., 2014) reported an acute oral LD_{50} of 66 mg/kg in rats, an acute dermal LD_{50} of >2,150 mg/kg in rats and 3,600 mg/kg in rabbits, and an acute inhalation LC_{50} of >2.33 mg/L for 4-hour exposure in rats.

2.4.5 Subchronic and Chronic Toxicity

A 90-day oral toxicity study in rats reported a No Observable Effect Level (NOEL) of 0.04 mg/kg/day and a Lowest Observable Effect Level (LOEL) of 0.3 mg/kg/day based on plasma cholinesterase inhibition in both sexes and RBC AChEI in females. The inhibition of RBC AChE in males, brain AChE in females, and brain AChE in males occurred at 15 mg/kg/day, 19 mg/kg/day, and 168 mg/kg/day, respectively. The study also reported a systemic NOEL of 19 mg/kg/day and a LOEL of 168 mg/kg/day based on observed systemic effects including hypersensitivity to sound and touch, aggressiveness, deceased body weight, decreased feed consumption, decreased hemoglobin and hematocrit, increased liver weight (absolute and relative), and hepatocellular hypertrophy (USEPA, 2016b).

A 90-day oral toxicity study in dogs reported a No Observable Adverse Effect Level (NOAEL) of 0.020/0.0037 mg/kg/day (males/females), and a Lowest Observable Adverse Effect Level (LOAEL) of 5.9 mg/kg/day and 5.6 mg/kg/day based on decreased RBC and brain AChE, respectively, in both sexes. The study also observed a systemic effect of decreased body weight at 5.6 mg/kg/day (USEPA, 2016b).

A 21-day dermal toxicity study in rabbits reported a NOAEL of 1 mg/kg/day and a LOAEL of 5 mg/kg/day based on decreased brain AChE levels in females. The study also reported decreased RBC and brain AChE at 50 mg/kg/day in both sexes, as well as systemic effects such as death related to cholinergic inhibition at 100 mg/kg/day (USEPA, 2016b).

A 90-day dermal toxicity study in rats reported a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day based on decreased brain and RBC AChE in females, but no inhibition was observed in males at 10 mg/kg/day. The study also observed decreased brain AChE in males at 25 mg/kg/day, but no decreased RBC AChE was observed in males. There was no adverse systemic effect observed (USEPA, 2016b).

A 21-day inhalation toxicity study in rats reported a LOAEL of 0.1 µg/L based on decreased RBC AChE in males without a NOAEL. There was decreased brain and RBC AChE activity observed in both sexes at 1 µg/L and above (USEPA, 2016b).

A 98-week chronic toxicity study in rats reported a NOAEL of 0.005 mg/kg/day and a LOAEL of 0.06 mg/kg/day based on plasma cholinesterase inhibition. The study also reported a systemic NOAEL of greater than 12 mg/kg/day with no LOAEL established (USEPA, 2016b).

A 52-week chronic toxicity study in dogs reported a NOAEL of 0.015/0.020 mg/kg/day (males/females) and a LOAEL of 4.7/4.5 mg/kg/day in males/females based on decreased brain

and RBC AChE, decreased body weight gain, decreased food consumption, and increased serum amylase activity (USEPA, 2016b).

2.4.6 Nervous System Effects

Neurotoxicity (AChEI) is the most sensitive endpoint for diazinon and its oxon, diazoxon, in all species, routes, and life stages (USEPA, 2016b). An acute neurotoxicity screening battery study in rats reported a NOAEL of 2.5 mg/kg/day and a LOAEL of 150 mg/kg/day based mainly on abnormal gait, decreased body temperature, decreased rearing count, stereotypy (all in females); decreased fecal consistency, stained fur in females; and decreased RBC AChE (USEPA, 2016b). A subchronic neurotoxicity study in rats reported a NOAEL of 0.018 mg/kg/day, and a LOAEL of 1.8 mg/kg/day based on reduced RBC AChE in both sexes and cerebral cortex/hippocampus AChE in females. There was reduced brain AChE activity observed in both sexes at 18 mg/kg/day, and decreased body weight gain, deceased food consumption, muscle fasciculation, hyper-responsiveness and tremors, and decrease in grip strength at 180 mg/kg/day (USEPA, 2016b).

A developmental neurotoxicity study in rats reported a maternal NOAEL of 0.026 mg/kg/day and a LOAEL of 2.36 mg/kg/day based on reduced RBC and brain AChE. There was no maternal systemic toxicity observed at the highest dose tested (a NOAEL of 2.36 mg/kg/day). The study also reported an offspring NOAEL of 0.026 mg/kg/day, and a LOAEL of 2.36 mg/kg/day based on reduced RBC AChE in both sexes, as well as an offspring systemic NOAEL of 2.36 mg/kg/day and a LOAEL of 24.2 mg/kg/day based on reduced body weight and body weight gain and delayed sexual maturation in males and females. However, USEPA classified this study as non-guideline because of inadequacies in the assessment of offspring motor activity (USEPA, 2016b).

2.4.7 Reproductive or Developmental Effects

A multi-generation reproduction study in rats reported a parental NOAEL of 0.67/0.77 mg/kg/day (male/female), and a LOAEL of 6.69/7.63 mg/kg/day (male/female) based on decreased body weight gains. The offspring NOAEL and LOAEL were the same and the LOAEL was based on decreased pup body weight gains and pup mortality. The study reported a reproduction NOAEL of 6.69/7.63 mg/kg/day, and a LOAEL of 35/41 mg/kg/day (males/females) based on tremors in females, decreased male and female mating and fertility indices (second parental group), and increased gestation length (USEPA, 2016b).
The prenatal developmental toxicity study in rats (administered at doses of 0, 10, 20, and 100 mg/kg/day) reported a maternal NOAEL of 20 mg/kg/day and a maternal LOAEL of 100 mg/kg/day based on reduced body weight gains. The fetal NOAEL was 100 mg/kg/day, and a fetal LOAEL was not observed (USEPA, 2016b).

The prenatal developmental toxicity study in rabbits (administered at doses of 0, 7, 25, and 100 mg/kg/day) reported a maternal NOAEL of 25 mg/kg/day and a maternal LOAEL of 100 mg/kg/day based on deaths with tremors and convulsions, reduced body weight gains, and gastro-intestinal hemorrhages and erosions. The fetal NOAEL was 100 mg/kg/day, and a fetal LOAEL was not observed (USEPA, 2016b).

Prenatal developmental toxicity studies in rats and rabbits did not reveal evidence of increased susceptibility of rat or rabbit fetuses based on AChEI effect following *in utero* exposure to diazinon. The offspring sensitivity observed in the reproduction study was based on offspring effects that occurred at high doses without AChE measurements. If AChE measurements had been included in the reproduction study, AChE inhibition would have occurred at lower doses in both parental and juvenile rats and resulted in no concern for potential offspring sensitivity. Therefore, there was no indication of susceptibility of the fetus or pregnant female to diazinon. There are no fetal or pregnant female data available for diazoxon. It is expected that diazoxon has the same qualitative toxicity profile as diazinon because of the bioactivation of diazinon to the oxon. However, USEPA retains the Food Quality Protection Act (FQPA) safety factor of 10X for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios because there is uncertainty in the human dose-response relationship for neurodevelopmental effects (USEPA, 2016b).

2.4.8 Carcinogenicity and Mutagenicity

The International Agency for Research on Cancer (IARC) concluded diazinon is probably carcinogenic to humans (Group 2A) based on limited evidence in experimental animals and in humans with a positive association observed for non-Hodgkin lymphoma, leukemia, and cancer of the lung (IARC, 2016).

USEPA classified diazinon as “not likely to be carcinogenic in humans” based on the lack of evidence of carcinogenicity and mutagenicity in rats and mice (USEPA, 2016b). A 103-week carcinogenicity toxicity study in rats observed no evidence of compound related tumors. There were no systemic effects with a systemic NOAEL of 40 mg/kg/day and no LOAEL observed (AChEI not measured). The second 103-week carcinogenicity toxicity study in mice observed no evidence of carcinogenicity. There were no systemic effects with a systemic NOAEL of 29 mg/kg/day and no LOAEL observed (AChEI not measured). A chronic carcinogenicity toxicity study in rats reported no evidence of carcinogenicity and no systemic toxicity. The study reported a NOAEL of 0.06/0.07 mg/kg/day and a LOAEL of 5/6 mg/kg/day (males/females) based on decreased brain and RBC AChE. Mutagenicity studies (such as bacterial and mouse gene mutation, chromosome aberration in mice, and other *in vivo* and *in vitro* mutagenicity assays) are not supportive of mutagenic concern.

2.4.9 Endocrine System Effects

Diazinon was one of 52 chemicals to undergo Tier 1 screening for endocrine disruptor potential under the USEPA Endocrine Disruptor Screening Program (EDSP) (USEPA, 2015). Based on the Tier 1 assay data, and other scientifically relevant information including general toxicity data and open literature studies of sufficient quality, USEPA (the EDSP Tier 1 Assay Weight of Evidence Review Committee of the USEPA/OPP and the Office of Science Coordination and Policy) performed a weight-of-evidence assessment of the potential interaction of diazinon with the estrogen, androgen, or thyroid hormone signaling pathways. The weight-of-evidence analysis concluded there was no convincing evidence for potential interaction of diazinon with the estrogen or thyroid pathways, and the totality of the evidence does not support a potential

interaction of diazinon with the androgen pathway. As a result, mammalian and wildlife EDSP Tier 2 testing was not recommended (USEPA, 2015).

2.4.10 Immune System Effects

Immunosuppression effects or immunotoxicity effects have been reported in the open literature at 25 mg/kg intraperitoneally in a 28-day exposure (Neishabouri et al., 2004), 50 mg/kg in a 30-day oral exposure (Alluwaimi and Hussein, 2007), and 300 mg/kg dietary via food consumption in a 45-day exposure study (Handy, et al., 2002). However, the USEPA acceptable guideline immunotoxicity study in mice did not observe immunotoxicity. The study reported an immunotoxicity NOAEL of 400 parts per million (ppm) (equivalent to 75 mg/kg/day) without the establishment of the immunotoxicity LOAEL (>400 ppm). The study reported systemic effects such as reduced body weight with a systemic NOAEL of 160 ppm (32 mg/kg/day) and a LOAEL of 400 (75 mg/kg/day) (USEPA, 2016b).

2.4.11 Toxicity of Other Ingredients

The Diazinon AG500® formulation contains aromatic petroleum hydrocarbons (Makhteshim Agan of North America, Inc., 2014). The acute oral LD_{50} for aromatic petroleum hydrocarbons is 8,970 mg/kg in rats, which is much higher than the acute oral LD_{50} of 66 mg/kg for the active ingredient diazinon previously discussed in Section 2.4.4. The safety data sheet (SDS) states that the product may be harmful to skin, harmful if swallowed, toxic if inhaled, and may cause cancer (Category 1B for carcinogenicity). The SDS also states to avoid contact with eyes.

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. For the OP pesticides, USEPA uses a steady state approach to evaluate chronic exposure because the degree of AChE inhibition comes into equilibrium with the production of new, uninhibited enzymes after repeated dosing at the same dose level. USEPA calculates a benchmark dose (BMD) and a benchmark dose lower bound (BMDL) for each exposure scenario for AChE-inhibiting compounds. The BMD_{10} is the estimated dose where 10% AChE inhibition occurs compared to background AChE levels. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. USEPA uses the BMDL as the point of departure (PoD), which is the dose-response point that marks the beginning of a low-dose extrapolation (USEPA, 2012a).

The established acute population adjusted dose (aPAD) or acute reference dose (aRfD) is 0.003 mg/kg/day for the general population including the subgroup of females aged 13-49 years old based on RBC AChE inhibition as the endpoint for the PoD. The aRfD was calculated by applying an uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects) to estimate a $BMDL_{10}$ of 3.0 mg/kg/day. The FQPA safety factor protects children from exposures that may cause neurodevelopmental effects such as delays in mental development in infants (24–36 months), attention problems, autism spectrum disorder in early childhood, and intelligence decrements in school age children identified in epidemiology studies. The FQPA safety factor may be excluded for the population subgroup of adults 50–99 years old (USEPA, 2016b).

The established chronic steady state reference dose (ssRfD) is 0.00035 mg/kg/day by applying an uncertainty factor of 1000X to the $BMDL_{10}$ of 0.35 mg/kg/day (RBC AChE inhibition was the endpoint for the PoD). The FQPA safety factor of 10X may be excluded for the sub-population of adults 50–99 because the safety factor is based on incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (USEPA, 2016b).

For dermal exposure, USEPA selected a steady state dermal PoD from a route-specific rat 90-day dermal toxicity study based on RBC AChE inhibition (NOAEL of 3.0 mg/kg/day and LOAEL of 10.0 mg/kg/day) in the female rat. For inhalation exposure, USEPA selected a steady state inhalation PoD from a route-specific 21-day inhalation toxicity study in female rats based on RBC AChE inhibition ($BMDL_{10}$ of 0.816 mg/m^3/day; 0.22 mg/kg/day; BMD_{10} of 0.988 mg/m^3/day) (USEPA, 2016b).

To account for the increased toxicity from exposure to the diazinon degradate diazoxon, USEPA applies a toxicity adjustment factor of 12 in the acute studies and 9 in the repeat-dose studies, which means diazoxon is 12 or 9 times more toxic than diazinon.

USEPA classified diazinon as “not likely to be carcinogenic in humans”, and did not derive a toxicity value for diazinon.

3.2 Ecological Dose-Response Assessment

3.2.1 Wild Mammal, Avian and Reptile Toxicity

The acute and chronic toxicity of diazinon to mammals is characterized in section 2.4 of this risk assessment. Additional mammalian toxicity information is included in this section. Diazinon is classified as moderately toxic to the house mouse, and moderately to slightly toxic to the Norway rat in acute exposures (table 3-1).

Table 3-1. Acute oral toxicity of diazinon to mammal test species.

Test Organism	LD_{50} (mg/kg bw)	Reference
House mouse, *Mus musculus*	66.6–81.7	USEPA, 2017
Norway rat, *Rattus norvegicus*	472.5–2,549.5	USEPA, 2017

Sublethal effects of diazinon in subchronic and chronic exposures using the Norway rat (14, 90, 365, and 730 days) and domestic dog (90 days) indicate plasma AChE is the most sensitive endpoint (table 3-2). A 12-day subchronic toxicity study with diazinon using the wild goat reported a NOAEL of 3.19 mg/kg body weight (bw) based on AChE inhibition without an estimated LOAEL (USEPA, 2017).

Diazinon is considered very highly toxic to birds such as the red-winged blackbird, young European starling, and domestic fowl after acute exposure (table 3-3). Adult European starlings appear to be more resistant to diazinon (Wolfe and Kendall, 1998). Subacutely, diazinon is also very highly toxic to the mallard duck and red-winged blackbird, and highly toxic to northern bobwhite quail. Diazinon is significantly more toxic to Canada goose goslings in outdoor tests compared to laboratory tests (Vyas et al., 2006).

Sublethal effects from diazinon subchronic and chronic exposure includes decreased reproduction, hatching, egg production, and AChE inhibition (table 3-4). Sauter and Steele (1972) reported a LOEL/LOAEL of 0.1 ppm based on hatch and reproductive success, a NOAEL of 1 ppm based on mortality, and a NOAEL/LOAEL of 3 mg/kg and 6 mg/kg based on AChE inhibition using domestic fowl chicks. A study using the mallard reported a No Observed Adverse Effect Concentration (NOAEC) and Lowest Observable Adverse Effect Concentration (LOAEC) of 8.3 and 16.33 ppm, respectively, based on hatching (Marselas 1989). A chronic study using the northern bobwhite quail, *Colinus virginianus*, reported a NOAEC and LOAEC of 35 and >35 ppm, respectively, based on food consumption, hatchability, and egg production (Stromborg, 1981).

Table 3-2. Subchronic and chronic oral toxicity of diazinon to mammal test species.

Test Organism	NOAEL/LOAEL (mg/kg bw) (Effect Measures)	Reference
Subchronic:		
Norway rat, *Rattus norvegicus*		
• 14 days	0.044/3.9561 (Plasma cholinesterase) 3.9561/39.5609 (Buterylcholinesterase and RBC cholinesterase)	43543902, USEPA, 2017
• 90 days	0.0659/0.6593 (Plasma cholinesterase and RBC cholinesterase) 0.8791/41.7588 (Buterylcholinesterase) 32.9675/369.2355 (Cholesterol, aggression, total white blood cell count, weight, weight gain, and delayed type hypersensitivity) 41.7588/465.9401 (Chloride, hemoglobin, phosphorus content, sodium content, and serum glutamic pyruvic transaminase)	40815003, USEPA 2017
Domestic dog, *Canis familiaris* • 90 days	0.0194/0.104 (Plasma cholinesterase) 30.91/78.5847 (Buterylcholinesterase, RBC cholinesterase) 29.3383/ 78.5847 (weight, weight gain, diarrhea)	40815004, USEPA, 2017
Chronic:		
Norway rat, *Rattus norvegicus*		
• 365 days	0.0088/0.4396 (Plasma cholinesterase) 0.4396/10.3298 (Buterylcholinesterase, RBC cholinesterase, total protein, and calcium uptake)	41942001, USEPA, 2017
• 730 days	0.011/0.1538 (Plasma cholinesterase) 0.1538/13.187 (Buterylcholinesterase and RBC cholinesterase)	41942002, USEPA, 2017

Table 3-3. Acute and subacute oral and dietary toxicity of diazinon to various avian test species.

Test Organism	LD_{50} /LC_{50}	Reference
Acute:		
Red-winged blackbird, *Agelaius phoeniceus*	2.4 (0–3 days) –9.1 (adult) mg/kg	Wolfe and Kendall, 1998
European starling, *Sturnus vulgaris*	5–10 mg/kg 12.7 (0–3 days) –602 (adult) mg/kg	Parker and Goldstein, 2000, Wolfe and Kendall, 1998
Domestic fowl, *Gallus domesticus*	6.32–9.2 mg/kg	Mohammad et al., 2008, Al-Zubaidy, et al., 2011, Al-Zubaidy and Mohammad, 2007
Subacute:		
Mallard duck, *Anas platyrynchus* (14 days)	3.54 mg/kg	Hudson et al., 1984
Red-winged blackbird, *A. phoeniceus* (14 days)	4.33 mg/kg	Hudson et al., 1984
Northern bobwhite quail, *Colinus virginianus* (7 days)	10–17 mg/kg	Hill and Camardese, 1984, Hill et al., 1984
Canada goose, *Branta canadensis* (8 days)	3.6 (outdoor)/ 263 (laboratory) a.i. ppm	Vyas et al., 2006

Table 3-4. Subchronic and chronic toxicity of diazinon to various avian test species.

Test Organism	NOAEL, NOAEC, NOEL LOAEL, LOAEC, LOEL (Effect Measures)	Reference
Domestic fowl, *G. domesticus*	LOEL, LOAEL: 0.1 ppm (hatch, reproductive success, progeny) NOAEL: 1 ppm (Mortality) NOAEL/LOAEL: 3 / 3-6 mg/kg (ChE)	Sauter and Steele, 1972
Rock dove, *Columba livia*	NOAEL: 1 mg/kg (Migration)	Brasel et al., 2007
Canada goose, *B. canadensis*	LOAEL: 2.8 ppm (AchE)	Vyas et al., 2006
Mallard duck, *A. platyrynchus*	NOAEC: 8.3 ppm LOAEC: 16.33 ppm (Hatching)	431229-01 (Marselas 1989), USEPA, 2008
Northern bobwhite quail, *C. virginianus*	NOEL: 35 ppm (food consumption and hatchability) LOEL: >35 ppm (egg production)	Stromborg, 1981

Diazinon toxicity to reptiles is not well studied. Oral or dietary dosing studies do not appear to be available. USEPA uses available toxicity data for birds as a surrogate for reptiles (USEPA, 2017). However, the actual sensitivity of reptiles to diazinon compared to birds is unknown. Ortiz-Santaliestra et al. (2017) indicates that homeothermic vertebrates are not suitable surrogates for toxicity on reptiles based on the absence of correlation in the toxicity indicators in the terrestrial environment between reptiles and birds or mammals.

3.2.2 Terrestrial Invertebrate Toxicity

Diazinon is considered very highly toxic to terrestrial invertebrates, including pollinators (table 3-5). Contact toxicity to the honey bee (*Apis mellifera*) is high with a reported 24-hour LD_{50} value of 0.22 µg a.i./bee (Stevenson, 1968; USEPA, 2008). Other reported LD_{50} values in the honey bee range between 0.0065 µg/bee (24-hour) and 0.372 µg/bee (48-hour) (USEPA, 2017). Honey bee larvae are more sensitive to diazinon than adults with an LD_{50} value of 1.2×10^{-4} µg/larva and an LD_{10} of 1.2×10^{-7} µg/larva administered for an unspecified duration with technical grade diazinon (88.4% ai) (Atkins and Kellum, 1986; USEPA, 2017). Toxicity is also high for other bee species such as the alfalfa leafcutter bee (*Megachile rotundata*) and alkaline

bee (*Nomia melanderi*). There were effects on colony maintenance and feeding behavior with a reported LOAEL of 0.005 µg/bee and 0.0075 µg/bee, respectively with a NOAEL of 0.0056 µg/bee for feeding behavior. USEPA's search of the Ecological Incident Information System identified three reports of adverse effects on honey bees, and one report of adverse effects on butterflies potentially associated with diazinon use. These incidents consisted of two in California in 1995 and one in Washington in 1998 for the honey bee, and one in Florida for butterflies. These incidents were not related to soil drench treatments. There were no terrestrial invertebrate incidents reported to USEPA for diazinon subsequent to the implementation of the mitigations with certain altered use patterns related to the 2006 registration eligibility decision (USEPA, 2017).

Table 3-5. Diazinon toxicity to terrestrial invertebrates (24 to 48 hours).

Species	LD_{50}, NOAEL, LOAEL (µg/bee)	Reference
Honey bee, *Apis mellifera*	LD_{50}: 0.0065–0.372	Atkins and Kellum, 1986, USEPA, 2017
	LOAEL: 0.005 (Colony maintenance) NOAEL/LOAEL: 0.005625/0.0075 (Feeding behavior)	Valdovinos-Nunez et al., 2009, USEPA, 2017
Stingless bee, *Nannotrigona perilampoides*	0.12	Mayer, 1999, USEPA, 2017
Alfalfa leafcutter bee, *Megachile rotundata*	0.121	Valdovinos-Nunez et al., 2009, USEPA, 2017
Stingless bee, *Melipona beecheii*	0.185–0.24	Valdovinos-Nunez et al., 2009, USEPA, 2017
Alkali bee, *Nomia melanderi*	0.456	USEPA, 2017

3.2.3 Terrestrial Plant Toxicity

Available terrestrial plant laboratory toxicity testing indicates that oats are the most sensitive monocot plant, and that the carrot is the most sensitive dicot plant species when evaluating plant seedling emergence (table 3-6). Onion is the most sensitive monocot and cucumber is the most sensitive dicot plant when measuring vegetative vigor (USEPA, 2012b) (table 3-6). Field studies using diazinon as a foliar spray on carrots (*Daucus carota*) for control of the carrot weevil (*Listronotus oregonensis* (Coleoptera: Curculionidae)) showed no effects at an application rate of 0.5 lb a.i./acre (Bonham, 2009).

Table 3-6. Diazinon toxicity to non-target terrestrial plants.

Species	% a.i.	EC_{25}/EC_{05} (lbs a.i./acre) Endpoint Effected	Reference
Plant seedling emergence			
Monocot - Oat	87.7	5.26/0.17 Shoot height	408030-01 (Pan-Agricultural Labs 1988), USEPA, 2012b
Dicot - carrot	87.7	9.03/1.58 Shoot height	408030-01 (Pan-Agricultural Labs 1988), USEPA, 2012b
Vegetative vigor			
Monocot - Onion	87.7	≥7.0/7.0 Shoot height	408030-02 (Pan-Agricultural Labs 1988) USEPA, 2012b
Dicot - cucumber	87.7	3.23/1.27 Shoot height	408030-02 (Pan-Agricultural Labs 1988) USEPA, 2012b

3.2.4 Aquatic Vertebrates Toxicity

Diazinon is slightly to very highly toxic to freshwater fish and moderately to very highly toxic to marine fish in acute exposures (table 3-7). Among freshwater fish, diazinon is very highly toxic to rainbow trout (96-hour LC_{50} of 0.09 mg/L), highly toxic to bluegill (LC_{50} of 0.136 mg/L) and brook trout (LC_{50} of 0.45 mg/L), moderately toxic to fathead minnow (LC_{50} of 4.7 mg/L) and Japanese medaka (LC_{50} of 9.64 mg/L), and slightly toxic to green swordtail (LC_{50} of 14.3 mg/L) and chinook salmon (LC_{50} of 29.5 mg/L). Cold water species such as the trout are more sensitive to diazinon compared to warm water species such as the bluegill. Among marine fish, diazinon ranges from being very highly toxic to the turbot (LC_{50} of 0.00185 mg/L) to moderately toxic to the inland silverside (LC_{50} of 1.1232 mg/L) and sheepshead minnow (LC_{50} of 1.5 mg/L).

Table 3-7. Acute oral toxicity of diazinon to freshwater and marine fish species.

Test Organism	Toxicity Endpoint EC_{50}/LC_{50} (mg/L)	Reference
Freshwater fish:		
Rainbow trout, *Oncorynchus mykiss*	LC_{50}: 0.09	Mayer and Ellersieck, 1986 /USEPA, 2008, MRID: 400946-02 (Johnson and Finley, 1980)
	EC_{50}: 0.00231	Do Hong et al., 2004
Sunshine bass, *Morone saxatilis ssp. x chrysops*	EC_{50}: 0.0152	Gaworecki et al., 2009
Snake-head catfish, *Channa striata*	EC_{50}: 0.03	Van Cong et al., 2006
Sacramento splittail, *Pogonichthys macrolepidotus*	EC_{50}: 3.7275	Teh et al., 2004
Bluegill, *Lepomis macrochirus*	LC_{50}: 0.136	Beliles R, 1965
Brook trout, *Salvelinus fontinalis*	LC_{50}: 0.45-1.05	Allison and Hermanutz, 1977
Fathead minnow, *Pimephales promelas*	LC_{50}: 4.7	Dyer et al, 1993
Japanese medaka, *Oryzias latipes*	LC_{50}: 9.64-33.45	Hamm et al., 2001
Green swordtail, *Xiphophorus helleri*	LC_{50}: 14.3-61.6	Khalili, et al., 2012
Chinook salmon, *O. tshawytscha*	LC_{50}: 29.5-545	Viant, et al., 2006
Marine Fish:		
Turbot, *Psetta maxima*	LC_{50}: 0.00185-8	Mhadhbi and Boumaiza, 2012
Striped mullet, *Mugil cephalus*	LC_{50}: 0.15	USEPA, 2017 (MRID: 40228401, Mayer, 1986)
Hirame flounder, *Paralichthys olivaceus*	LC_{50}: <0.2-<0.4	Menendez and Ishimatsu, 1993
Inland silverside, *Menidia beryllina*	LC_{50}: 1.123-3.043	Thursby and Berry, 1988
Sheepshead minnow, *Cyprinodon variegatus*	LC_{50}: 1.5	USEPA, 2017 (MRID: 40228401, Mayer, 1986)

Sublethal effects for freshwater and marine fish from chronic diazinon exposure include decreased growth, reproduction, and behavior. The most sensitive sublethal endpoints include: (NOEC/LOEC of <0.55/0.55 µg/L), reproduction (NOEC/LOEC of <0.47/0.47 µg/L), and feeding behavior (NOEC/LOEC of 0.1/1 µg/L) (table 3-8).

Table 3-8. Chronic toxicity of diazinon to freshwater and marine fish.

Test Organism	Toxicity Endpoint (NOAEC/LOAEC) µg/L/(Measures)	Reference
Freshwater fish:		
Brook trout, *S. fontinalis*	<0.55/0.55 (length/weight)	Allison and Hermanutz, 1977
Chinook salmon, *O. tshawytscha*	0.1/1 (feeding behavior)	Scholz et al., 2000
Fathead minnow, *P. promelas*	<3.2/3.2 (hatch)	Allison and Hermanutz, 1977,
	285/>285 (dry weight/survival)	Norberg-King, 1989
Snake-head catfish, *Channa striata*	4/8 (cholinesterase)	Van Cong et al., 2006
	74/350 (weight/specific growth rate)	Van Cong et al., 2009
Zebrafish, *Danio rerio*	913.05/3,043.5 (swimming and acetylcholinesterase activity)	Yen et al., 2011
	3,043.5-9,000 (survival)	
Marine Fish:		
Sheepshead minnow, *C. variegatus*	<0.47/0.47 (egg production)	USEPA, 2017 (MRID 40914801, Goodman et al., 1979, and MRID: 44244802, Sousa, 1997)
	4.3/8 (weight/length)	
Turbot, *Psetta maxima*	200/400 (hatch)	Mhadhbi and Boumaiza, 2012

Diazinon is very highly toxic to slightly toxic to various species of freshwater amphibians in acute exposures (table 3-9). The bronze frog is the more sensitive species to diazinon with LC_{50} values ranging from 0.0028 to 0.05 mg/L compared to the Asian common toad and African clawed frog with LC_{50} values ranging from 5.36 mg/L to 12.64 mg/L. Sublethal effects include decreased growth with a NOAEC of 0.4965 mg/L, and a LOAEC of 4.965 mg/L in bronze frog, and AChEI with a NOAEC of 1 mg/L, and a LOAEC of 3 mg/L in the snouted tree frog.

Table 3-9. Acute and chronic toxicity of diazinon to freshwater amphibians.

Test Organism	Toxicity Endpoint (mg/L) (measures)	Reference
Bronze frog, *Lithobates clamitans ssp. clamitans*	EC_{50}: 0.0059–0.014 LC_{50}: 0.0028 -0.05	Harris et al., 1998
Foothill yellow-legged frog, *Rana boylii*	LC_{50}: 0.76–7.488 NOAEC/LOAEC: 0.4965/4.965 (length)	Sparling and Fellers, 2007 Kerby, 2006
Leopard frog, *L. pipiens*/ Gray tree frog, *Hyla versicolor*	NOAEC/LOAEC: 0.0021 (survival, weight, and metamorphosis)	Relyea, 2009
Gray tree frog, *H. versicolor*/Bullfrog, *R. catesbeiana*/American toad, *Bufo americanus*	NOAEC/LOAEC: 1/2 (weight gain/mortality)	Relyea, 2004
Snouted tree frog, *Scinax fuscovarius*	NOAEC/LOAEC: 1/3 (acetylcholinesterase inhibition)	Leite et al., 2010
Asian common toad, *Duttaphrynus melanostictus*	LC_{50}: 6.2–7.5 NOAEC/LOAEC: 4/400 (mortality)	Sumanadasa et al., 2008
African clawed frog, *Xenopus laevis*	EC_{50}: 5.36–6.79 $LC_{50:}$ 9.84–12.64 NOAEC/LOAEC: 0.9/12 (length)	Modra et al., 2011

3.2.5 Aquatic Invertebrates Toxicity

Diazinon is considered very highly toxic to aquatic invertebrates in acute exposures based on the most sensitive toxicity endpoints (table 3-10). Freshwater cladocerans are the most sensitive test species with LC_{50} values of 0.21 µg/L to 3.2 µg/L and median effective concentration (EC_{50}) values of less than 0.8 µg/L. Marine invertebrates are less sensitive with a reported LC_{50} values of approximately 2 to 8 µg/L in general and an EC_{50} value of 880 µg/L for the eastern oyster (table 3-10).

Table 3-10. Acute diazinon toxicity for various freshwater and marine invertebrates (48 to 96 hour exposures).

Test Organism	EC_{50} or LC_{50} (µg/L)	Reference
Freshwater:		
Cladoceran, *Ceriodaphnia dubia*	LC_{50}: 0.21–0.66	Norberg-King, 1987, Banks et al., 2005
Cladoceran, *Daphnia magna*	LC_{50}: 0.52–3.2	USEPA, 2017 (MRID: 121283, Morrissey, 1978), Matsumoto et al., 2009
Amphipoda, *Gammarus pulex*	LC_{50}: 4.1–12.9 EC_{50}: 0.8	Ashauer et al., 2010, Mayer and Ellersieck, 1986
Plecoptera, *Pteronarcys californica*	LC_{50}: 25–155	Mayer and Ellersieck, 1986
Marine:		
Amphipod, *G. fasciatus*	LC_{50}: 2–8	Mayer and Ellersieck, 1986
Mysid, *Americamysis bahia*	EC_{50}: 4.2 LC_{50}: 4.82–8.736	USEPA, 2017 (MRID: 40625501, Suprenant, 1988) Nimmo et al., 1981, Thursby and Berry, 1988
Ploimida, *Brachionus plicatilis*	EC_{50}: 600/1000 LC_{50}: 26,901	Marcial and Hagiwara, 2007 Marcial et al., 2005
Eastern oyster, *Crassostrea virginica*	EC_{50}: 880	USEPA, 2017 (MRID: 40625502, Suprenant, 1988)

Sublethal toxicity from chronic exposure to diazinon resulted in reduced reproductive effects in freshwater invertebrates (table 3-11). Deanovic et al. (2013) reported a reduction in fecundity in *C. dubia* with a LOEC of 0.228 µg/L and a NOEC of 0.123 µg/L. There was also a statistically significant increase in mortality observed at a LOEC of 0.228 µg/L for fecundity (USEPA, 2017).

Sublethal effects from chronic exposure to diazinon for estuarine/marine invertebrates includes a reduction in dry weight in *A. bahia* at 0.42 µg/L (the most sensitive LOEC), with a corresponding NOEC of 0.23 µg/L (table 3-11). There was no statistically significant increase in mortality at the observed LOEC for growth (i.e., 0.42 µg/L) (USEPA, 2017).

Table 3-11. Chronic diazinon toxicity for various freshwater and marine invertebrates.

Test Organism	Toxicity Endpoint (µg/L)	Reference
Freshwater:		
Cladoceran, *C. dubia*	NOEC/LOEC: 0.123/ 0.228	Deanovic et al., 2013
Cladoceran, *D. magna*	NOEC/LOEC: 4.95/7.92	Jemec et al., 2007
Cladoceran, *D. pulex*	NOEC: 0.62	Stark, 2005
Marine:		
Mysid, *A. bahia*	NOEC/LOEC: 0.23/ 0.42 NOEC/LOEC: 2.1/4.4	USEPA, 2017 (MRID: 44244801, Sousa, 1997), Berry, 1989
Ploimida, *Brachionus plicatilis*	NOEC/LOEC: 100/1000 5,000/10,000	Marcial and Hagiwara, 2007

3.2.6 Aquatic Plants Toxicity

The effects of diazinon to aquatic plants is determined based on the EC_{50} values associated with growth effects of nonvascular plant species. Aquatic plant testing using diazinon showed that the green algae, *Selenastrum capricornutum,* and the blue-green algae, *Anabaena flos-aquae*, are less sensitive to diazinon compared to the green algae, *Chlorella vulgaris* (table 3-12).

Table 3-12. Aquatic plant toxicity for diazinon.

Test Organism	Toxic Endpoint (mg/L)	Reference
Green algae, *Chlorella vulgaris* (96-hours)	EC_{50}: ≤0.742 NOEC/LOEC: 0.17/0.31	Natal-Da-Luz et al., 2012
Green algae, *Selenastrum capricornutum* (7-days)	EC_{50}/EC_{05}: 3.7/0.06	MRID 40509806, USEPA, 2008
Blue-green algae, *Microcystis flos-aquae, Anabaena flos-aquae* (96-hours)	EC_{50}: 11.5 EC_{50}: 21.3	Ma et al., 2005
Green algae, *Scenedesmus quadricauda* (96-hours)	NOEC/LOEC: 0.5/0.95	Ma et al., 2005
Green algae, *S. capricornutum* (7-days)	NOEC/LOEC: 0.98/1.83	MRID 40509806, USEPA, 2008

3.2.7 Ecological Incidents

The long history of diazinon use shows a high level of bird mortality that substantially decreased after regulatory changes occurred in 2002 (USEPA, 2006; 2008). Nevertheless, each year there are incidents of field observable effects from diazinon exposure. Specifically, USEPA's review of the Ecological Incident Information System (EIIS) indicates a total of 494 reported ecological incidents associated with the use of diazinon over the period of 1950 to 2005 (USEPA, 2008). Between 1994 and 1998, diazinon had the highest number of bird mortality incidents (58) caused by any pesticide with the highest total number per million acres treated (USEPA, 2006). The majority of incidents on known sites have occurred on lawns and other turf. The number of these reported incidents decreased since that time as a result of restrictions placed on use sites and patterns (such as cancellations of granular formulations and residential uses, aerial application limited to lettuce, and reduced application rates) that are a high risk to birds. USEPA's additional review of EIIS for incidents of avian mortality since 2006 identified four avian mortality incidents associated with diazinon with the number of dead birds ranging from 1 to 100. The locations, birds species, and year of the incidents are Moses Lake, WA (Canada goose) in 2006; Lake Shafer, IN (Canada goose and mallard duck) in 2006; Black River, VA (mallard duck) in 2009; and Salem Co., NJ (brown headed cowbirds, common grackles, red-winged blackbirds) in 2013. Although the detailed information on diazinon formulation and application rate is not available, the certainty index associated with diazinon for these incidents was "highly probable". Diazinon was quantified in birds, with 91–93% AChE inhibition reported in the 2009 incident, and diazinon was quantified in collected tissues in the 2013 incident (USEPA, 2017).

4.0 EXPOSURE ASSESSMENT

4.1 Human Health Exposure Assessment

The exposure assessment estimates the potential exposure of humans to diazinon. Beginning with the use and application method for diazinon, a complete exposure pathway includes (1) release from a diazinon source, (2) an exposure point where contact can occur, and (3) an exposure route such as ingestion, inhalation, or dermal contact. The potentially exposed human populations and complete exposure pathways were identified, and then exposure was qualitatively or quantitatively evaluated for the identified human populations, and exposure pathways.

4.1.1 Identification of Potentially Exposed Human Populations and Complete Exposure Pathways

The program applies the Diazinon AG500® formulation as a soil drench treatment. Drift from the soil drench application is minimal because large coarse droplets are applied directly to containerized nursery stock. Based on the application method, workers (i.e., certified applicators, or persons under their direct supervision) in the program are the most likely human population segment to be exposed to diazinon. The potential exposure pathways for these workers include direct contact (i.e., incidental ingestion, inhalation, and dermal contact) to diazinon during application. However, direct contact exposures are minimized with the use of personal protective equipment (PPE). Accidental exposure may occur during mixing, loading, and application. The occurrence for accidental exposure is unlikely with well-trained certified applicators, and recommended safety measures on the label and SDS. However, the potential exposure and risk are further quantified for the worker scenario.

The general public, including nearby residents, are not recognized as a potentially exposed population group during application. APHIS uses diazinon only for fruit fly pests subject to state quarantine action, with applications occurring in commercial nurseries (all containerized nursery stock) (CDFA, 2015). Second, the label requires restricted entry to the treated areas within the restricted-entry interval of 2 days following the application. Third, there is no complete exposure pathway identified for dietary consumption of fruit from fruit bearing trees because the label requires removal of all fruits from plants before application. Lastly, diazinon is not systemic so no residues are expected in any plant parts. The FIFRA Section 24(c) SLN label for California requires applications to be made by certified applicators or persons under their direct supervision and only for those uses covered by the applicator's certification (CDFA, 2015).

A complete exposure pathway associated with direct contact to diazinon from soil drench applications is not identified for the general public. Exposure to diazinon for a resident child is not expected in the treatment area because the soil treatments are made in commercial nurseries, and the label requires keeping children off treated areas until the material has dried. However, the potential exposure and risk for an unusual exposure scenario when diazinon treated soil is placed at a location where a resident child may contact treated soil via pica behavior are further quantified. Pica behavior, generally seen in young children, is a pattern of eating non-food

materials, such as dirt or paper. Ten to 32 percent of children ages 1 to 6 exhibit this type of behavior (MedlinePlus, 2014).

A complete exposure pathway is not identified for the groundwater medium. Although diazinon is moderately mobile in soil and leaching studies observed oxypyrimidine and diazinon residues in the leachate at a 30 cm depth in soil (see Section 2.3), diazinon tends to remain in the upper 10 cm of the soil with the majority of the chemical found in the upper 1 cm when applied as a soil drench (APHIS, 2011). As a result, leaching into groundwater from soil by the soil drench application is not expected.

A complete exposure pathway is not identified for the surface water medium. Significant surface runoff is not expected to occur from the soil drench application based on the program and label requirements for diazinon. The label (Makhteshim Agan of North America, Inc., 2017) specifies not to apply within 100 feet upslope of "sensitive aquatic sites" such as any irrigation ditch, drainage canal, or body of water that may drain into a river or tributary unless a suitable method is used to contain or divert runoff waters. In addition, the label states that applications should not be made to the point of runoff, which mitigates significant residues from contaminating surrounding soils.

4.1.2 Exposure Evaluation

This section quantitatively evaluates worker exposure from dermal and inhalation exposure pathways while mixing, loading, and applying diazinon based on the application rate for the soil drench scenario. The section also quantitatively evaluates the potential exposure to diazinon in soil for a child from ingesting soil (pica behavior). The exposure scenario for a child is not anticipated to occur under normal use conditions because applications are only made to containerized plants in commercial nurseries where children would not be expected to occur. Containerized plants that are treated and then sold to the public could result in potential exposure to children. Therefore, a conservative approach assuming children who exhibit pica behavior was used to estimate exposure to this population subgroup.

Under the FIFRA Section 24(c) label for Diazinon AG500® (CDFA, 2015), the application rate for soil treatment is 0.12 lb a.i. per 1,000 square feet (ft^2) (3.67 fl. oz. of product per 1,000 ft^2), which is equivalent to 5 lb a.i. per acre (1.25 gallons of product per acre). The formulation is added to the water buffered to pH 6.5 or less, and applied in 130 gallons of water per acre or 3 gallons of water per 1,000 ft^2. It is applied as a topical soil treatment to containerized nursery stock suspected or known to be infested with fruit fly larvae or pupae (Tephritidae spp.) as part of a quarantine. The label allows one to three applications at a minimum 14-day interval. APHIS fruit fly eradication efforts do not occur in exactly the same time and location each year. The duration for a typical eradication is normally two to three months.
Direct exposure of diazinon to workers during application is not expected to occur under normal conditions with proper worker hygiene and properly functioning PPE. The label requires PPE for mixers, loaders, applicators, and other handlers using engineering controls (such as a closed system or an enclosed cab) include long sleeved shirt and long pants, shoes plus socks, protective gloves (chemical resistant gloves made of barrier laminate or butyl rubber, nitrile rubber, or viton ≥14 mils if mixing or loading), and a chemical resistant apron if mixing or loading. The SDS

(Makhteshim Agan of North America, Inc., 2014) also recommends splash goggles or a face shield for eye and face protection as well as suitable respiratory equipment in case of inadequate ventilation or engineering controls are not feasible to prevent inhalation of mist or vapors. The occupational exposure limits (8-hour time weighted average) for diazinon are 0.01 mg/m^3 (inhalable fraction and vapor; skin) (the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value) (ACGIH, 2017) and 0.1 mg/m^3 for skin (the National Institute for Occupational Safety and Health Recommended Exposure Limit) (CDC, 2016).

APHIS quantified the potential exposure from dermal and inhalation pathways during mixing, loading, and application for workers using the following equation (USEPA, 2016b):

> Dermal Dose = Dermal Unit Exposure (µg/lb a.i.) × Conversion Factor (0.001 mg/µg) × Application Rate (lb a.i./ft^2) × Area Treated (ft^2/day) ÷ Body Weight (kg)
>
> Inhalation Dose = Inhalation Unit Exposure (µg/lb a.i.) × Conversion Factor (0.001 mg/µg) × Application Rate (lb a.i./ft^2) × Area Treated (ft^2/day) ÷ Body Weight (kg)

The mixer/loader/applicator, manually-pressurized handwand exposure scenario in the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (USEPA, 2016e) is the closest to the program soil treatment mixing, loading, and application exposure scenario. The dermal unit exposure of 365 µg/lb a.i. (the double layer, gloves PPE level), and inhalation unit exposure of 30 µg/lb a.i. (no respirator PPE level) of the mixer/loader/applicator, manually-pressurized handwand exposure scenario were used for the exposure estimations. Based on the program use and the Diazinon AG500 24(c) label requirements, the following assumptions are used for the exposure estimations:

- Area treated for the program is 1,000 ft^2 per day;
- An application rate of 0.12 pounds of diazinon per 1,000 ft^2; and
- Body weight of 69 kg for a woman was used.

To quantify the potential exposure to diazinon in soil for a child exhibiting pica behavior, an upper bound soil concentration was estimated using the label application rate for a soil drench scenario based on the following assumptions:

- A single maximum rate of 0.12 pounds of diazinon per 1,000 ft^2 of soil surface from the Diazinon AG500® 24(c) label;
- Top 1 inch of soil depth containing diazinon based on 0.5 to 1 inches of soil drench; and
- Default soil bulk density of 1.4 g/cm^3 for sandy loam and loam soil type (USDA NRCS, 2014).

The acute exposure intake value was calculated using the following USEPA soil ingestion exposure intake equation:

> Acute Exposure Intake = (Soil Concentration x Soil Ingestion Rate)/ (Body Weight)

Chronic exposure is not expected because of the rapid degradation of diazinon in soil. Information on exposure parameters such as soil ingestion rate and body weight, and the calculated acute exposure intake value are presented in Appendix A.

4.2 Ecological Exposure Assessment

4.2.1 Terrestrial Exposure Assessment

Terrestrial exposure was not quantified due to the low probability that significant exposure could occur under the proposed use pattern. Applications are made directly to soil in containerized nursery stock. Applications occur using a coarse low pressure spray where drift would not be expected. Label requirements state that treatments should not be made to the point of runoff reducing the potential for off-site transport. Exposure to birds and mammals could only occur during foraging for soil borne invertebrates or consuming soil within the containers which would be unlikely. Containerized plant stock in commercial nurseries is highly managed in disturbed areas where wild mammals and birds would not be expected to forage and nest due to management activities. In addition, the amount of food items within containerized nursery stock, such as soil invertebrates, would be low and not favorable areas for prey foraging. Diazinon residues in host plants and any fruits or flowers within the treated containerized nursery stock would not be expected because the insecticide is non-systemic, and any fruits are removed prior to treatment.

4.2.2 Aquatic Exposure Assessment

Aquatic exposure was also not quantified due to the low probability of detectable diazinon residues occurring in water as a result of the proposed treatments. As previously stated, applications are made to containerized plants in commercial nurseries. Drift to aquatic resources are not anticipated because a large, coarse droplet applied directly to soil will mitigate off-site drift. Runoff into aquatic environments is also not expected because of the use of a 100-foot application buffer from aquatic areas and avoiding drench applications beyond the point of runoff as part of the label requirements for use.

5.0 RISK CHARACTERIZATION

Risks associated with potential adverse effects are characterized qualitatively and quantitatively in this section. Results from the risk characterization suggests that the use of diazinon as a soil drench treatment to containerized nursery stock for the fruit fly eradication program will pose minimal risks to human health for all population segments, and ecological risks would be negligible or incidental and localized.

5.1 Human Health

This section qualitatively and quantitatively characterizes risk of adverse impacts to human health. Fruit fly quarantines are infrequent and usually do not occur every year in the same location. The diazinon treatment is infrequently used by the program (only 6 times since 1997). Under the APHIS program, the use of diazinon as a soil drench treatment for the fruit fly eradication program should pose minimal risks to human health.

The adverse health risk to workers (i.e., certified applicators) exposed to diazinon via oral, inhalation, and dermal routes during application is not expected due to minimized exposure because of the application method, the use of PPE, and adherence to other label requirements such as re-entry intervals after treatment. Diazinon is a hazard to humans because of acute AChE depression through ingestion, inhalation, or dermal exposure. However, the low potential for significant exposure from the program use of diazinon suggests there are minimal risks to workers. Accidental exposure during mixing, loading, and application may occur. The exposure frequency is considered low for this exposure scenario because only certified applicators working with State and Federal agencies, or persons under their guidance, will be making applications. APHIS quantified the risks from potential dermal and inhalation exposure for workers and calculated an acute hazard quotient (HQ) using the following USEPA risk estimation equation for non-carcinogens:

Acute HQ = Acute Exposure Intake / Acute Reference Dose

Only non-cancer risk was evaluated because USEPA has classified diazinon as “not likely to be carcinogenic to humans”. The calculated dermal HQ of 0.2, inhalation HQ of 0.2, and a dermal and inhalation combined HQ value of 0.4 (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-1.

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

Parameter	**Dermal Exposure**	**Inhalation Exposure**
Acute exposure intake (mg/kg-day)	6.3E-04	5.2E-05
Acute reference dose (mg/kg-day)	0.003	0.00022
Acute HQ	**0.2**	**0.2**
Combined dermal and inhalation HQ = 0.4		

The risk to the public from diazinon exposure associated with soil drench applications is minimal because (1) the program only uses diazinon for fruit fly pests subject to state quarantine action occurring in commercial nurseries (only containerized nursery stock), and (2) implementation of the label requires restricted-entry intervals. There are no risks associated with dietary consumption of fruit from treated fruit-bearing trees because all fruit is removed from treated nursery stock prior to soil treatment. The drinking water risk is also low based on the method of application and the proposed use pattern that will mitigate residues of diazinon that could occur in drinking water resources from runoff or drift.

The risks associated with residential children being accidentally exposed to treated soil through pica behavior are extremely low because (1) pica behavior is reported in only 10 to 32 % of children ages 1 to 6, (2) children of this age and with this disorder primarily are under adult supervision, and (3) the proposed treatments will occur in commercial nurseries where children would not be expected to frequent. However, APHIS quantified the risk for a child (age 1–6) from exposure to soil through pica behavior as a conservative approach to estimate risks to this subgroup where treated stock could be planted after leaving a nursery, and in a setting where children could gain access, such as in residential areas.

The calculated acute HQ value of 4 (table 5-2) is above the USEPA's level of concern (HQ=1) suggesting potential adverse health risks from exposure through soil ingestion behavior (pica) by children. However, the soil concentration used for the calculation was conservatively estimated based on the application rate on the label without consideration of any degradation. The actual soil concentration should be much less when considering degradation after 2 days (the post-harvest interval) and the time when a treated plant would be moved to an area such as a residential setting where a child could be exposed. Measured soil concentrations from actual program treatments ranged from 0.5 to 5 mg/kg using the same application rate (APHIS, 2011). Using the maximum soil concentration of 5 mg/kg as the exposure concentration for a child, the calculated acute HQ is 1, which indicates no concerns for adverse health risks. The risk calculations are included in Appendix A-2.

Table 5-2. Hazard quotients estimated for child exposure to soil from pica behavior.

Parameter	**Upper Estimation**	**Estimation using Monitoring Data**
Soil concentration	16 mg/kg (estimated)	5 mg/kg (maximum detected concentration)
Acute exposure intake	0.001 mg/kg-day	0.003
Acute reference dose	0.003 mg/kg-day	0.003
Acute HQ	**4**	**1**

5.2 Terrestrial and Aquatic Risk Characterization

The risk to terrestrial non-target wildlife from diazinon exposure will be low. Diazinon is toxic to various terrestrial wildlife, but the potential for exposure is very low because applications are restricted to soil in containerized nursery stock at commercial nurseries. Applications are made

with a large droplet size that is applied directly to the soil, reducing the potential for any off-site drift. Birds and mammals would not be expected to forage in the containerized plants. There would be risks to terrestrial invertebrates, but this would be localized to soil invertebrates within the containerized plants. Pollinator risks would be low because applications are not made directly to the plants, including flowers, and diazinon is not systemic so no residues would be anticipated in pollen and nectar or other plant parts that could result in exposure to pollinators.

The risk to aquatic organisms is low based on the proposed method of application and label restrictions designed to protect aquatic organisms. Drift to aquatic sites is not anticipated because applications are made directly to soils in containerized nursery stock, requiring a large, coarse droplet applied under low pressure. Significant runoff is also not expected due to label restrictions such as a 100-foot application buffer from water bodies. Runoff from the treated containers is also not anticipated because the label requires that applications should not be made to the point that runoff will occur.

6.0 UNCERTAINTIES AND CUMULATIVE IMPACTS

The uncertainties associated with this risk evaluation arise primarily from lack of information about the effects of the diazinon formulation, metabolites, and potential mixtures on non-target organisms that can occur in the environment. These uncertainties are not unique to this assessment but are consistent with uncertainties in HHERAs with any environmental stressor. In addition, there is uncertainty in where and how often exotic fruit fly detections may occur within a specific state, and throughout the rest of the United States. There is uncertainty regarding the extent of diazinon use during any given infestation because its use is based on site-specific factors and detection of larval stages. However, diazinon treatments have been used by the program only six times since 1997 and are not expected to increase in frequency.

There is uncertainty relating to the fact that this risk assessment did not evaluate potential cancer risk because USEPA classifies diazinon as “not likely to be carcinogenic in humans”. However, there is a positive association of non-Hodgkin lymphoma, leukemia, and lung cancer with diazinon exposure, and the IARC classifies diazinon as “probably carcinogenic to humans”. Based on short-term and infrequent use of diazinon in the fruit fly program, acute health risk is the main concern, which is evaluated in the risk assessment.

Another area of uncertainty is the potential for cumulative impacts to human health and the environment including: 1) repeated worker and environmental exposures to diazinon from program activities in conjunction with exposure from other crop use sources, and 2) co-exposure to other chemicals with a similar mode of action.

Diazinon is currently registered for use to control foliage and soil insects and pests on a variety of agricultural crops. The total annual use of diazinon by the top ten counties (Monterey, Los Angeles, Fresno, Imperial, Stanislaus, Kern, Sutter, Tulare, Santa Clara, and San Benito) in California decreased from 329,264 kg (725,903 lbs) in 2000 to 47,390 kg (104,477 lbs) a.i. in 2009 (Aggarwal et al., 2013). The APHIS contribution to these totals was zero because no diazinon soil applications related to the program were made during that time in California and only a total of six diazinon applications have been made since 1997.

Cumulative impacts may occur from diazinon use in relation to other chemicals used in the program that have a similar or different mode of action, and can result in synergism, potentiation, additive, or antagonistic effects. The potential for co-exposure to other pesticides within the program or outside the program with the same toxic action may also occur. The other pesticides used in the fruit fly eradication program include spinosad, lambda-cyhalothrin, naled, DDVP, and malathion. Spinosad over-activates the central nervous system of insects via the nicotinic acetylcholine receptors. Lambda-cyhalothrin disrupts normal nerve function by inhibiting the closing of the voltage-gated membrane sodium channels of nerve cells. Naled, DDVP, and malathion are also OP pesticides with the same toxic mode of action as diazinon. All of the program insecticides have other uses that could occur in areas where fruit fly treatments may occur. The spatial and temporal variability in these other uses relative to treating sporadic exotic fruit fly outbreaks make it difficult to quantify cumulative impacts from the additional use of program insecticides such as diazinon. However its very low frequency of use in the program and label requirements does not support the potential for cumulative impacts.

The results of USEPA's Organophosphorate Cumulative Risk Assessment (2006b) present exposure and risk data from food, water, and residential use to the U.S. population, and support a reasonable certainty of a no harm finding as required by the FQPA. Cumulative impacts from the proposed uses of diazinon, malathion, naled, and DDVP are expected to be incrementally minor due to the proposed use patterns of these pesticides, adherence to individual pesticide label requirements for risk mitigation measures, and the historical low frequency of exotic fruit fly detections. In addition, cumulative impacts to human health from ingesting diazinon residues would not be anticipated because all fruits are removed prior to treatment, and exposure to drinking water is not expected due to the environmental fate, use pattern, and label requirements for diazinon use. In the case of naled and DDVP, they are used in traps and would not result in any dietary exposure to treated commodities or in drinking water.

Water quality data in the United States, including areas where fruit fly program activities may occur, show pesticide mixtures to be a common occurrence in surface water, with varying impacts to aquatic organisms (USGS, 2006). Some of these bodies of water may be listed as impaired under Section 303(d) of the Clean Water Act due to pesticides, or some another abiotic or biotic stressor. The USGS conducted a comparison study from two decades (1992–2001 and 2002–2011) of monitoring for pesticides in U.S. streams and rivers. The study showed that in the second decade of the study, diazinon was among the pesticides detected less frequently in streams, and there was a lower percent of streams exceeding chronic aquatic life benchmarks (Stone et al., 2014). There is also a downward trend of diazinon concentrations and exceedance frequencies in California's surface waters, with the detected diazinon concentrations posing a de minimis risk to aquatic organisms in 2012 to 2014 (Wang et al., 2017). The impact to water bodies from any diazinon residues that could occur from use in the fruit fly program is expected to be incrementally negligible to water bodies that may already be impacted by other contaminants. The proposed method of application for containerized nursery stock and label requirements minimizes potential water quality impacts from drift and runoff. The impacts of potential mixtures at any concentration are an area of uncertainty due to the potential types of chemical mixtures that could occur, and the spatial and temporal variability in their occurrence. However, the impacts are expected to be minimal based on the program use, and adherence to label mitigation measures.

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Appendix A-1

Risk Estimates of Dermal and Inhalation Exposures for Workers

Appendix A-1 includes equations and assumptions used for risk estimations of dermal and inhalation exposures for workers.

Equations:

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

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

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

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

Assumptions for daily acreage and application rate: assumed 1,000 ft^2 per day for the program application, and an application rate of 0.12 pounds of diazinon per 1,000 ft^2 based on the Diazinon AG500 24(c) label.

Assumptions for risk estimation:

Input Parameters	Values	Sources
DUE (μg/lb a.i.)	365	USEPA, 2016e[3]
IUE (μg/lb a.i.)	30	USEPA, 2016e[4]
Conversion Factor (mg/μg)	0.001	
Application Rate (lb a.i./1000 ft^2)	0.12	CDFA, 2015[1]
Area treated (ft^2/day)	1000	CDFA, 2015[2]
BW (kg)	69	USEPA, 2016b[5]
Dermal Dose (mg/kg-day)	6.3E-04	Calculated
Inhalation Dose (mg/kg-day)	5.2E-05	Calculated
Dermal RfD (mg/kg-day)	0.003	USEPA, 2016b
Inhalation RfD (mg/kg-day)	0.00022	USEPA, 2016b
DHQ	**0.2**	calculated
IHQ	**0.2**	calculated
Combined HQ (DHQ + IHQ)	**0.4**	

Notes:

1 0.12 lb a.i. mixed in 3 gallon water per 1000 ft^2 based on the label.
2 Based on the program application of 1000 ft^2 per day.
3 Double layer, gloves PPE level for the mixer/loader/applicator, manually-pressurized handwand exposure scenario.
4 No respirator PPE level for the mixer/loader/applicator, manually-pressurized handwand exposure scenario.
5 Body weight for women.

Appendix A-2

Risk Estimates for Soil Ingestion in Children (ages 1–6) with Pica

Appendix A-2 includes equations and assumptions used for risk estimations of soil ingestion in children (ages 1–6) with pica behavior.

Equations:

Acute Exposure Intake or Dose = (C x IR) / BW

Hazard Quotient (HQ) = Exposure Intake / RfD

Where:

Exposure Intake – mg/kg/day
HQ - unitless
C – Soil concentration (mg/g)
IR – Ingestion rate (g/day)
BW – Body weight (kg)
RfD – Reference dose (mg/kg/day)

Assumptions for soil concentration estimation: Based on the Diazinon AG500 24(c) label, a single maximum rate of 0.12 pounds of diazinon per 1,000 ft^2 of soil surface was used for the soil concentration calculation.

Parameters	Input Values
Amount of diazinon per 1000 ft^2	0.12 lb (54431.04 mg)
Soil surface area	1000 ft^2
Depth of surface soil (assumed top 1 inch)	1 inch (0.083 ft)
Soil volume (soil surface area x depth)	83.3333 ft^3 (2359736.27 cm^3)
Soil bulk density*	1.4 g/cm^3
Soil weight (soil volume x density)	3303.63078 kg
Estimated soil concentration (mg a.i./kg soil)	16 mg/kg

* Default soil bulk density for sandy loams and loams (USDA NRCS, 2014)

Assumptions for risk estimation:

Input Parameters	Estimates	Sources
Estimated soil concentration (mg/kg)	16	Calculated
The maximum detected soil concentration (mg/kg)	5	APHIS, 2011
Acute IR g/day	10	USEPA, 2000
BW (kg)	15	USEPA, 2002
Acute Exposure Intake (mg/kg-day) (upper)	1.1E-02	Calculated
Acute Exposure Intake (mg/kg-day) (central)	3.3E-03	Calculated
Acute RfD (mg/kg-day)	0.003	USEPA, 2016
Acute HQ (upper)	**4**	calculated
Acute HQ (central)	**1**	calculated