Draft Human Health and Ecological Risk Assessment for the Use of Wildlife Damage Management Methods by APHIS-Wildlife Services

Chapter XXV

USE OF 4-AMINOPYRIDINE IN WILDLIFE DAMAGE MANAGEMENT

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EXECUTIVE SUMMARY

The active ingredient 4-aminopyridine or 4-AP in Avitrol products (Avitrol Corporation) is an avian frightening agent formulated as mixed grain or corn bait. Birds that consume treated bait produce distress calls causing flocks of the same species to disperse from an area; the birds that eat treated bait usually die. The USDA-APHIS evaluated the potential human health and ecological risks from Wildlife Services (WS) use of Avitrol to deter target bird species from damage sites.

WS used four Avitrol products to control bird damage from fiscal years 2011–2020: mixed grain (0.5% 4-AP), corn chops (0.5% 4-AP), double strength corn chops (1.0% 4-AP), and whole corn (0.5% 4-AP). A fifth product, double strength whole corn (1.0% 4-AP), is labeled for use to frighten crows. Avitrol products are restricted use pesticides, and only certified applicators or persons under their direct supervision can apply them and only for those uses stated on the labels.

The labels include restrictions to prevent exposure to the public, pets, and nontarget species. They require applicators to prebait sites to ensure target species take the bait and nontarget species are not present. If nontarget species feed on the untreated bait, the label does not allow the use of treated bait at that site. WS often uses bait trays instead of applying bait directly to the ground; this makes it easier for the applicator to remove unused bait. As part of the current registration review cycle, the U.S. Environmental Protection Agency (USEPA) states they intend to amend the labels further to require the use of bait trays at all urban and industrial use sites and agricultural use sites when feasible. In areas accessible to the public, when possible, WS conducts baiting at elevated sites that are out of reach of the public. When applicators cannot treat at elevated sites in publicly accessible areas, the label requires them to remain at the treatment site and remove all dead or dying birds and unused bait before they leave the site. WS prefers to apply treated bait when the fewest people are in the vicinity, as seeing distressed birds can be upsetting. As part of the registration review, USEPA also intends to amend the labels further, requiring applicators to remove all uneaten bait in the application area within 24 hours.

4-AP is a nervous system toxicant and is highly toxic to most vertebrates. 4-AP is acutely toxic through oral, dermal, and inhalation exposure routes (Toxicity Category I for oral and Toxicity Category II for dermal and inhalation). Although the hazard potential for the technical active ingredient could be high, the potential exposure and risk to the public is negligible due to the WS use pattern and label restrictions and requirements, as well as the lack of dietary exposure through food, feed, and drinking water. Exposure is greatest for workers who handle and apply the bait material; however, limiting use to certified applicators and the required personnel protective equipment reduces the potential for exposure and minimizes risk. APHIS is unaware of any reports of exposure to WS personnel or the public from WS's use of Avitrol products.

Label requirements minimize the risks to nontarget species. Exposure to aquatic species is not expected as the label does not permit Avitrol use within 25 feet of permanent water bodies. As part of the registration review, USEPA also intends to amend the labels further to recommend that applicators do not apply the product if rain is predicted within 24 hours to ensure the product does not enter groundwater or surface water sources. Since applicators remove dead and dying birds at the end of the treatment period or sundown, secondary exposure to predatory or scavenging nontarget species is minimized. WS expects some take of target species that ingest 4-AP-treated bait. WS also expects minor take of nontarget species that are attracted to

the bait or distressed and dying birds. The release of 4-AP into the environment is expected to have no or negligible cumulative impacts on nontarget species, the public, and the environment.

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1 INTRODUCTION

The U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Wildlife Services (WS) uses Avitrol bait products (containing the active ingredient 4-aminopyridine or 4-AP, a chemical frightening agent) to deter target bird species from creating problems in certain areas. The Avitrol Corporation currently manufactures five different grain bait end-use products containing 4-AP. These products cannot be used in food crops. This human health and ecological risk assessment provides a qualitative evaluation of the potential risks and hazards to human health and the environment, including nontarget fish and wildlife, from WS' use of 4-AP. The methods used to assess potential human health effects follow standard regulatory guidance and methodologies (National Research Council 1983) and conform to other Federal agencies such as the U.S. Environmental Protection Agency (USEPA) (USEPA 2022). The methods used to assess potential ecological risk to nontarget fish and wildlife generally follow USEPA (2022) methodologies.

The risk assessment has four sections: problem formulation (identifying hazard), toxicity assessment (dose-response assessment), exposure assessment (identifying potentially exposed populations and determining potential exposure pathways for these populations), and risk characterization (determining whether there is adverse human health or ecological risk based on information from the toxicity and exposure assessments). A discussion of the uncertainties associated with the risk assessment and cumulative effects is included.

1.1 Labels and Usage

Avitrol products are classified as restricted-use pesticides because they have a higher potential to cause harm to public health, the environment, and wildlife compared to other pesticides. Only certified applicators or persons under their direct supervision can apply these products, and only for those uses allowed on the labels. Avitrol products are registered for use to control flocking pest birds, specifically European starlings[1], rock doves (feral pigeons), house sparrows, red-winged, yellow-headed and Brewer's blackbirds, great-tailed, boat-tailed, and common grackles, brown-headed and bronzed cowbirds, and American[2] and fish crows. Avitrol bait is applied to nesting, feeding, loafing, and roosting sites on or in structures, feedlots, landfills, and airports across urban, rural, agricultural, and non-agricultural use sites (USEPA 2017b). Five registrations are currently available for use, containing 0.5% or 1.0% 4-AP (Table 1). Section 2(ee) of the Federal Insecticide, Rodenticide, and Fungicide Act (FIFRA) is a provision that presents special circumstances where it is permissible to use a pesticide in a manner for which it is not specifically labeled. For some projects, WS uses Avitrol products at lower ratios than the label allows, which falls under Section 2(ee) of FIFRA.

WS personnel, per the product labels, survey the problem, identify the target pest species and number causing a conflict, and determine the best solution to resolve that particular problem. If it is determined that 4-AP is the best choice, WS personnel determine if 4-AP can be used per the label restrictions, would be low risk (e.g., no access to the public, pets, or livestock) and effective, and where and when the target species are feeding. That site or a nearby site at a

[1] Scientific names are given in the Risk Assessment Introduction Chapter I, unless first time used is in this Chapter.

[2] The American and northern crows were grouped together taxonomically and are now considered one species. Northern crows (*Corvus caurinus*) were allowed on the double strength whole corn label.

safer location is then prebaited. WS personnel adhere to product labels to determine the quantity of Avitrol bait to use based on the number of untreated grains of the same composition as the Avitrol bait consumed by target birds during prebaiting. If target birds are using the site with no nontarget species, then Avitrol bait is put out at the recommended mix (usually 1:9 or greater for most species but house sparrows up to 1:5 depending on the situation) (Table 1). Bait is provided in bait trays or sometimes scattered by hand at the site (usually in small piles). Bait trays make cleanup easier but may require a few more days of prebaiting due to the target species' wariness to the tray. As part of the registration review, USEPA will amend labels to require bait trays to be used at all urban and industrial sites and also at agricultural sites when feasible (USEPA 2020b). In addition, USEPA will require that bait trays are constructed of aged plywood or hardwood with a 1-inch lip to prevent spillage (USEPA 2020b).

Table 1. Summary of Avitrol product labels. All are labeled for use in, on, or in the area of structures, feeding, nesting, loafing, and roosting sites, in such a way that a part of a flock may react and frighten the rest away.

Product Information	**Target Species**	**Dilution ratio (4-AP bait:untreated grains)**
Avitrol Mixed Grains 0.5% 4-AP EPA Reg. No. 11649-4 Label version 9/24/2013	House sparrow	1:5
	Rock pigeon (feral pigeon); red-winged, yellow-headed, rusty[1], and Brewer's blackbirds; great-tailed, boat-tailed, and common grackles; brown-headed and bronzed (*Molothrus aeneus*) cowbirds; and European starling	1:5 (minimum), commonly 1:9
Avitrol Corn Chops 0.5% 4-AP EPA Reg. No. 11649-6 Label version 9/24/2013	House sparrow	1:5
	Red-winged, yellow-headed, rusty[1], and Brewer's blackbirds; great-tailed, boat-tailed, and common grackles; brown-headed and bronzed cowbirds; and European starling	1:5 (minimum), commonly 1:9
Avitrol Double Strength Corn Chops 1.0% 4-AP EPA Reg. No. 11649-5 Label version 9/24/2013	Red-winged, yellow-headed, rusty[1], and Brewer's blackbirds; great-tailed, boat-tailed, and common grackles; brown-headed and bronzed cowbirds; and European starling	1:9 (minimum)
Avitrol Whole Corn 0.5% 4-AP EPA Reg. No. 11649-7 Label version 9/24/2013	Rock pigeon (feral pigeon)	1:29 (common), where other bird food is available, this ratio may be adjusted to 1:19 or 1:14; the minimum dilution rate is 1:5
Avitrol Double Strength Whole Corn 1.0% 4-AP EPA Reg. No. 11649-8 Label version 9/24/2013	American, northern[2], and fish crows	1:9

[1] As a result of a declining population, WS does not target rusty blackbirds. In general, rusty blackbirds are not found in areas where WS treats. Instead, they are primarily found in bottomland hardwoods, where they feed on invertebrates (Greenberg et al. 2011, Avery 2020).

[2] The northern or northwestern crow (*Corvus caurinus*) was grouped taxonomically with the American crow and is no longer a separate species.

On treatment day, WS personnel monitor the presence of people, place baits, and monitor the bait application from a distance to watch bait for target bird activity and nontarget species. Once birds have consumed Avitrol baits and reacted, which often scares other birds away, and feeding stops, the remaining uneaten bait is retrieved and disposed of per label instructions (deep burial or incineration). As part of the registration review, USEPA intends to amend the labels further to require applicators to remove all uneaten bait in the application area within 24 hours (USEPA 2020b). WS typically completes a project by sunset and picks up the remaining bait. WS collects birds that died from treatment and disposes of them through incineration or deep burial.

When an Avitrol bait is ingested, 4-AP causes behaviors similar to an epileptic seizure. 4-AP is a potassium (K) channel blocker. Birds that ingest treated bait emit distress calls that frighten other birds, except feral pigeons, which are mostly silent. Most birds, including pigeons, fly in circles upwards (towering) while emitting distress calls and return to the ground. During this process, the birds are in convulsions and are unaware of their actions. This may include flying erratically, vocalizing, trembling, dilating pupils, and other symptoms which may be offensive to people. An assessment was completed on the humaneness of 4-AP, concluding it was a humane method similar to changes produced by dissociative anesthetics. During this phase, birds do not feel pain (Roswell et al. 1979). No pathological changes to organs or other tissues occurred that would indicate pain and distress, and electroencephalogram results were fairly identical to the use of anesthetics such as ketamine hydrochloride and chloral hydrate. Thus, it was found that while birds may appear in pain and distress, similar to observing an epileptic seizure, all study parameters found that they were not (Roswell et al. 1979).

As far as a repellent, starlings and blackbirds vocalize the most, and flocks disperse relatively quickly from the damage site, often traveling far away. On the other hand, pigeons and house sparrows generally roost nearby and do not vocalize as loudly; they often retreat to their roost or another feeding site and do not disperse as far as the blackbirds. They may come back to feed again, whereas blackbirds and starlings usually leave the area, making it a longer-lasting repellent for them.

1.2 Use Pattern

WS used three Avitrol bait products from FY16 to FY20, including Avitrol Mixed Grains (0.5%) (EPA Reg. No. 11649-4), Avitrol Double Strength Corn Chops (1.0%) (EPA Reg. No. 11649-5), and Avitrol Corn Chops (0.5%) (EPA Reg. No. 11649-6) (Table 2). Avitrol Whole Corn (0.5%) (EPA Reg. No. 11649-7) was used from FY11 to FY15 (Appendix 1: Table 1a). Another product label is available for use to manage crows (Avitrol Double Strength Whole Corn, 1.0%; EPA Reg. No. 11649-8) but was not used by WS. WS applies 4-AP baits by placing the bait into trays or by hand scatter (spot) placement. WS applicators prefer to use bait trays at urban structures and airports because removing the bait at the end of the application is easier. Going forward, EPA will require the use of bait trays at these use sites. WS considers applications at airports as public areas, and applicators remain onsite during the entire application period. At airports and other public areas, applicators use Avitrol baits when the fewest people are in the vicinity because seeing treated birds can be upsetting. Between FY16 and FY20, WS annually used a total of 49 ounces of Avitrol bait (0.5% Avitrol Mixed Grains, 1.0% Avitrol Double Strength Corn Chops, and 0.5% Avitrol Corn Chops) with annual average 1,338 target species killed and 273 repelled in 7 states (Tables 2 and 3). Applicators report the numbers of each species killed and repelled for each application. The number of birds repelled is not always documented due to difficulties in determining the number of birds in the vicinity. Of the birds lethally taken with 4-AP,

92% were house sparrows and 7% feral pigeons, whereas blackbirds (86%) and house sparrows (14%) accounted for all birds repelled.

Table 2. Avitrol products used by WS in WDM from FY16 to FY20, the annual average target species killed and repelled, the amount of product used, and the states where used.

ANNUAL AVERAGE 4-AP BAIT USE BY WS					
Product	**EPA Registration**	**Killed**	**Repelled**	**Ounces Applied**	**States**
Avitrol Mixed Grains (0.5%)	11649-4	1,162	8	21	CT TX
Avitrol Double Strength Corn Chops (1.0%)	11649-5	12	235	3	NH
Avitrol Corn Chops (0.5%)	11649-6	164	30	25	IA KY MO OK
TOTAL	**3 Products Used**	**1,338**	**273**	**49**	**7 States**

Table 3. The annual average number of target species killed and repelled with Avitrol products used by WS in WDM from FY16 to FY20.

ANNUAL AVERAGE 4-AP BAIT USE AND SPECIES TAKE				
Species*	**Killed**	**Repelled**	**Ounces Used**	**States Where Used**
Rock Dove (Feral Pigeon)*	89	-	3	TX
European Starling*	1	-	0.1	KY
House Sparrow*	1,236	38	43	CT IA KY MO OK TX
Red-winged Blackbird	12	235	3	NH
TOTAL (4 sp.)	**1,338**	**273**	**49**	**7 States**

* Introduced species

Between FY16 and FY20, WS averaged 6 projects per year, sometimes with multiple treatments at the same site. WS applied Avitrol grain baits at 5 electrical utilities (4 car parking lots/plug-ins for electric vehicles and 1 electrical substation) to prevent damage to equipment, 5 food plants to prevent contamination and consumption of food items, 4 airports to control birds caught indoors and to prevent flock interference with aircraft, 4 feedlots to reduce consumption of grain, 2 industrial plants and 1 fruit orchard to prevent bird damage to fruit. The average hours spent per treatment site was 2.7 hours, which indicates that relatively little time was spent on the project day waiting for birds to feed, indicating the usefulness of prebaiting. WS applicators stay onsite during the treatment. When birds have been prebaited to an area, the bait and birds generally disappear quickly.

WS conducted fewer projects from FY16 to FY20 (Tables 2 and 3) than from FY11 to FY15 (Appendix 1: Table 1a and 1b). The ounces of Avitrol grain baits applied and take decreased from FY11–15 to FY16–20.

2 PROBLEM FORMULATION

WS uses 4-AP (Avitrol baits) to control bird damage. The following sections cover the chemical description, product use, physical and chemical properties, environmental fate, and hazard identification for 4-AP.

2.1 Chemical Description and Product Use

The active ingredient in Avitrol baits is 4-aminopyridine (4-AP). 4-AP was first registered with USEPA in 1963 as an avicide (USEPA 2020b). Currently, Avitrol products are labeled as poisons with flock alarming properties. 4-AP ($C_5H_6N_2$, CAS No. 504-24-5) is a member of the pyridine family, which acts as a neurotoxin by blocking potassium channels and increasing acetylcholine levels at synapses and neuromuscular junctions. These characteristics result in convulsions, hyperactivity, and seizures (USEPA 2020a). Birds that ingest Avitrol baits will behave distressed and give warning calls that frighten other birds from the area. 4-AP is lethal to most all birds that ingest treated baits as a result of cardiac and respiratory arrest (USEPA 2020a).

2.2 Physical and Chemical Properties

4-AP has a molecular weight of 94.1 grams (g)/mol and a melting point between 155–158˚Celcius (˚C) (USEPA 2016c, Avitrol Corporation nd). It has a vapor pressure of 1.64×10^{-4} to 2.09×10^{-4} torr at 25˚C (USEPA 2016c, NIH 2023) and an estimated Henry's law constant of 2.3×10^{-10} atm-m^3/mol at 20˚C (USEPA 2007b, NIH 2023). Its water solubility is 112 g/Liter (L) at 25˚C (USEPA 2016a). Its octanol/water partition coefficient (log K_{ow}) is 0.146-0.320 at 25˚C (USEPA 2016c, NIH 2023).

2.3 Environmental Fate

The environmental fate describes the processes by which 4-AP moves and degrades in the environment. The environmental fate processes include 1) persistence, degradation, and mobility in soil; 2) movement to air; 3) migration potential to groundwater and surface water; 4) degradation in water; and 5) plant uptake.

Environmental fate data is limited for 4-AP. 4-AP is expected to be persistent in the open environment with an aerobic soil degradation half-life of 3–32 months (USEPA 2020a); it is stable to hydrolysis and photolysis and is stable under anaerobic conditions (USEPA 2007b;2016c). USEPA (2020a) summarized that when 4-AP is washed off treated bait, it may be mobile in soil and dissolve in water. 4-AP would not volatilize in water (estimated air-water partition coefficient or log K_{aw} of 1×10^{-7}), but would rapidly volatilize in field runoff due to the vapor pressure of 1.64×10^{-4} to 2.09×10^{-4} torr, which suggests intermediate to high volatility in the field, and low K_{aw} from surface water (USEPA 2020a). Degradates of 4-AP have not been identified in environmental fate studies.

4-AP is likely to be mobile in soil and has the potential to leach to groundwater or runoff to surface water based on its high solubility in water, low K_{ow}, and low K_{oc} (K_{oc} of 34.6 mL/g) (USEPA 2020a). However, its mobility in soil would decrease because it may also be susceptible to aged sorption (USEPA 2007b).

4-AP has a low potential to bioaccumulate in fish based on low log K_{ow}<3 (USEPA 2007b). Plant uptake is greatly reduced since 4-AP is tied up in a bait formulation. Most of the bait is expected

to be removed by the target species or applicator following a project reducing the amount of 4-AP available for any potential plant uptake.

The primary route of dissipation or transportation of 4-AP appears to be through the food chain, where birds, mammals, or other organisms consume bait products, carry the chemical within their bodies, and move to offsite locations. However, 4-AP toxicity is relatively fast-acting, with treated birds reacting within 5–15 minutes after ingestion (USEPA 2020a). During the period from exposure to mortality, birds that succumb to the toxic effects could become secondary sources for predators and scavengers because not all treated grain may be digested (USEPA 2016d). However, WS applicators are present at the site and can generally pick up many carcasses for disposal. Thus, it is anticipated that secondary risks are minimal.

2.4 Hazard Identification

4-AP is a central nervous system toxicant that is highly toxic to mammals (USEPA 2017b). People ingesting low levels of 4-AP (5–30 milligrams (mg)/day) experienced nervousness, nausea, giddiness or dizziness, memory alteration, cramps, arterial vasospasm, and peripheral paresthesia. In an accidental poisoning case, a person who ingested a high dose (~60 mg) experienced weakness, intense sweating, a feeling of impending doom, labored breathing, agitation and combative behavior, and profound thirst (Spyker et al. 1980).

USEPA (2016a) evaluated human incident reports for 4-AP during the product registration review. USEPA consulted two databases:

- Office of Pesticide Program Main Incident Data Systems (IDS) for pesticide incident data on the active ingredient 4-aminopyridine between January 1, 2011 and June 10, 2020, and
- SENSOR-Pesticides, a pesticide surveillance program and database managed by the Center for Disease Control’s National Institute for Occupational Health for cases involving 4-aminopyridine between 1998 and 2015.

No human adverse effects incident cases were reported for 4-AP in either database during these time periods.

4-AP is the active ingredient in several human drugs. Its potassium channel-blocking property has been used to help patients restore function in nerve fibers that have been traumatically injured and have lost the myelin sheath (USEPA 2007a). Fampridine treats multiple sclerosis and spinal cord injury by blocking potassium channels. The orally administered version of 4-AP, Ampydin, treats chronic functional motor and sensory deficits. Other medicinal uses of 4-AP in humans include reverse neuromuscular blockage resulting from non-depolarizing neuromuscular blocking agents and certain antibiotics and an experimental treatment for botulism, myoneural disorders, and Alzheimer’s disease (USEPA 2016b).

2.4.1 Mode of Action and Metabolism

4-AP is a nervous system toxicant that blocks potassium ion channels and increases acetylcholine levels at synapses and neuromuscular junctions, causing hyperactivity, convulsions, and seizures. Within 5–15 minutes of ingesting 4-AP bait, birds will behave erratically and emit distress calls, causing a distress display that frightens flocks of target bird species away from the treatment site. The distress display can occur for 30 minutes or more (USEPA 2020a). Birds either die or recover within 1–15 hours (USEPA 2020a). Birds are

frightened away from the treatment site, and birds that recover from ingesting 4-AP bait do not usually return to the treatment site (USEPA 2020a).

4-AP is readily absorbed through the skin and gastrointestinal tracts of animals. Human studies showed that 4-AP is quickly eliminated from the body with effects proportional to the serum levels of 4-AP in the body (USEPA 2007a).

2.4.2 Acute Toxicity

4-AP is highly toxic to most vertebrates (USEPA 2007a;2020a). 4-AP has high acute toxicity to mammals by the oral route of exposure (Category I) in rats and the dermal and inhalation routes of exposure (Category II) in rabbits (Table 4) (USEPA 2007a). The acute toxicological effects of 4-AP in animals include hyperexcitability, salivation, tremors, muscular incoordination, clonic and tonic convulsions, cardiac or respiratory arrest, and death.

Table 4. Acute toxicity data of technical and end-use 4-AP formulations.

Test Species	Scientific Name	Test	Technical 4-AP
Rat	*Rattus norvegicus*	Oral LD_{50}[1]	20 mg/kg-bw [2]
Rabbit	*Oryctolagus cuniculus domesticus*	Dermal LD_{50} (0.017% a.i.)	327 mg/kg-bw
Rat	*Rattus norvegicus*	Inhalation LC_{50}[3] (50% a.i.)	0.53 mg/L
Rabbit	*Oryctolagus cuniculus domesticus*	Eye Irritation (1.0% a.i.)	Not irritating
Rabbit	*Oryctolagus cuniculus domesticus*	Dermal Irritation (0.017%	Not irritating
Guinea Pig	*Cavia porcellus*	Dermal Sensitization	Not required

1 LD50 = acute median lethal dose

2 mg/kg = milligrams/kilogram body weight

3 LC50 = acute median lethal concentration

References: (USEPA 2007a, Avitrol Corporation 2018)

2.4.3 Subchronic and Chronic Toxicity

Subchronic animal studies of 4-AP included a 90-day oral toxicity study in rats (MRID 00131328 and 00004026, 1968) and a 90-day oral toxicity study in dogs (MRID No. 00131329 and 00004027, 1968) (USEPA 2007a). The study in rats reported a No Observable Adverse Effect Level (NOAEL) of 0.21 mg/kilogram-body weight (kg-bw)/day and a Lowest Observable Adverse Effect Level (LOAEL) of 2.15 mg/kg-bw/day (males) and 2.54 mg/kg-bw/day (females) based on hyperirritability to noise and touch. The study in dogs reported a NOAEL of 1 mg/kg-bw/day and a LOAEL of 2 mg/kg-bw/day based on occasional minimal salivation and muscular weakness in the hindquarters. USEPA (2007a) considers these studies unacceptable/non-guideline studies that do not meet the current guideline requirements for 90-day studies in rodents and non-rodents due to deficiencies in the test substance characterization.

Subchronic human studies of 4-AP included clinical studies to investigate the safety and efficacy of 4-AP in patients with spinal cord injury and multiple sclerosis (USEPA 2007a). Segal et al. (1999), in a controlled long-term human clinical study (MRID 47093602), tested an oral dose of 30 mg/day for 3 months to treat spinal cord injury patients (both male and female) who were otherwise healthy. The observed common adverse side effects during the study were

nervousness, giddiness or dizziness, and gastrointestinal upset manifested as mild abdominal cramping or nausea.

Grijalva et al. (2003), in a randomized, double-blind, placebo-controlled study (MRID 47093601), tested an initial oral dose of 5 mg/day, increasing to 30 mg/day, for 3 months in patients with long-term spinal cord injury. The observed mild adverse reactions in patients at the dose range of 5–10 mg/day included dry mouth, dizziness, nausea, and gastritis. Only at the 30 mg/day dose did patients show paresthesia (abnormal sensation of tingling or pricking).

Van Diemen et al. (1993) (as cited in (USEPA 2007b;2020c)) in a randomized, double-blind, placebo-controlled study (MRID 47093603) tested intravenous dosing infused gradually up to 5 mg/kg-bw and oral dosing from 5 mg/day up to 30 mg/day of 4-AP in patients with multiple sclerosis for dosage and serum level related to efficacy and safety. Paresthesia occurred at a minimal dose of 1 mg in the intravenous phase. Adverse side effects observed in patients who received a minimum daily dose of 5 mg in the oral phase included paresthesia, dysesthesias, dizziness, lightheadedness, gait instability, nausea, vomiting, restlessness, and anxiety.

2.4.4 Developmental and Reproductive Effects

USEPA (2007a) did not find valid studies for reproductive or developmental toxicity.

2.4.5 Carcinogenicity and Mutagenicity

USEPA (2017b) classified the carcinogenic potential of 4-AP as "not classifiable to human carcinogenicity" based on the lack of human or animal data and the weight of evidence. USEPA determined that chronic or carcinogenicity studies are not required based on the non-food uses of 4-AP and the negative findings in the reverse mutation assays (not mutagenic) in *Salmonella typhimurium* (USEPA 2017a).

2.4.6 Immunotoxicity Effects

A literature review did not identify any 4-AP mammalian studies indicating immunotoxicity.

2.4.7 Endocrine Effects

A literature search did not identify any mammalian studies indicating the potential of 4-AP to affect the endocrine system. USEPA developed a screening program to determine whether certain substances may affect humans' estrogen, androgen, and thyroid hormone systems (USEPA 2017c). 4-AP is not among the chemicals screened under the USEPA Endocrine Disruptor Screening Program. 4-AP is not among the European Union (EU) list of chemicals with the potential to impact the endocrine system (Danish Centre on Endocrine Disrupters 2018). It was excluded in the second literature screening for endocrine disruptor effects due to the lack of endocrine disruptor mode of action. The EU list includes three categories: Category 1 – endocrinal effect recorded at least on one type of animal; Category 2 – a record of biological activity *in vitro* leading to disruption; and Category 3 – not enough evidence or no evidence of data to confirm or disconfirm endocrinal effect of tested chemicals (Hrouzková and Matisova 2012).

3 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 short-term incidental oral, dermal, and inhalation exposures, USEPA (2007a) selected a 5 mg daily dose (0.07 mg/kg-bw/day) as a minimal LOAEL for a point of departure (POD). The LOAEL was based on human clinical studies with 4-AP. A total of 30x uncertainty factor (an uncertainty factor of 10x for individual variability (intraspecies) in the human population, and an additional uncertainty factor of 3x for the use of a POD based on a minimal LOAEL with transient mild adverse effects) applies to the LOAEL yielding a reference dose of 0.002 mg/kg-bw/day. For route-to-route extrapolation, USEPA assumes 100% dermal and inhalation absorption factors. USEPA uses an occupational level of concern of 30 as a margin of exposure (USEPA 2016b).

USEPA did not establish a tolerance for 4-AP because it is not registered for food or agricultural crop uses. The maximum contaminant level has not been established for drinking water.

3.2 Ecological Effects Analysis

This section discusses available ecological effects data for terrestrial and aquatic biota. Available acute and chronic toxicity data are summarized for all major taxa and will be integrated with the exposure analysis section to characterize the risk of 4-AP to nontarget wildlife and domestic animals. Information in this section was gathered from on-line databases and searches for relevant peer-reviewed and other published literature.

3.2.1 Aquatic Species

4-AP has high acute toxicity to freshwater invertebrates and moderate acute toxicity to freshwater fish and amphibians (Table 5). 4-AP is highly toxic to the freshwater juvenile glass shrimp[3] with a 96-h LC_{50} of 0.37 mg active ingredient (ai)/L (USEPA 2020a). The 24-h and 48-h LC_{50} in the water flea are 17 mg/L and 3.2 mg/L, respectively (Marking and Chandler 1981). In the most sensitive fish species tested, channel catfish, 4-AP is moderately toxic, with an acute 96-h LC_{50} of 2.43 in very hard water to 5.8 mg ai/L in soft water (USEPA 2020a). Although exposure to 4-AP did not affect the hatching of leopard frog eggs, it did affect larvae survival (Marking and Chandler 1981). 4-AP has moderate acute toxicity in Southern leopard frog larvae with a 24-h and 96-h LC_{50} of 7.2 and 2.4 mg/L, respectively (Marking and Chandler 1981, USEPA 2020a). Mayfly nymphs were highly sensitive to 4-AP, with a 24-h and 96-h LC_{50} of 5.3 and 0.58 mg/L, respectively (Marking and Chandler 1981). The adult river horn snail had lower sensitivity than other freshwater invertebrates with a 24-h and 96-h LC_{50} of >100 and 62 mg/L, respectively (Marking and Chandler 1981). Similarly, the adult Asiatic clams had lower sensitivity with a 24-h and 96-h LC_{50} of 78 and 45 mg/L, respectively (Marking and Chandler 1981). At the 96-h exposure, sublethal effects were observed in the clams; they could not right themselves or cling to the sidewalls of the vessel (Marking and Chandler 1981). In a study on

[3] Scientific names are given in Table 5 for this section.

marine/estuarine fish, 4-AP has high acute toxicity, with a 72-h LC_{50} of 7.6 mg/L for cowfish and globefish (USEPA 2016d). In the same study, the No Observable Adverse Effect Concentration (NOAEC) for both the cowfish and globefish was 4.6 mg/L, and the Lowest Observable Adverse Effect Concentration (LOAEC) was 6.8 mg/L based on mortality and sublethal effects (USEPA 2016d). No acute or chronic toxicity information is available for marine or estuarine invertebrates.

Table 5. 4-AP acute toxicity values in aquatic species.

Species	Scientific Name	Toxicity Value	Reference
Channel catfish	*Ictalurus punctatus*	96-h LC_{50} 2.43 mg/L (very hard water) 96-h LC_{50} = 5.8 mg/L (soft water)	(USEPA 2020a)
Glass shrimp (juvenile)	*Palaemonetes kadiakensis*	96-h LC_{50} = 0.37 mg/L	(USEPA 2016c)
Water flea	*Daphnia magna*	24-h LC_{50} = 17 mg/L 48-h LC_{50} = 3.2 mg/L	(Marking and Chandler 1981)
Crayfish (juvenile)	*Procambarus acutus*	96-h LC_{50} = 2.2 mg/L	(USEPA 2020a)
Southern leopard frog (larvae)	*Lithobates (Rana) sphenocephala*	24-h LC_{50} = 7.2 mg/L 96-h LC_{50} = 2.4 mg/L	(Marking and Chandler 1981, USEPA 2020a)
Mayfly (nymphs)	*Isonychia sp.*	24-h LC_{50} = 5.3 mg/L 96-hr LC_{50} = 0.58 mg/L	(Marking and Chandler 1981)
Caddisfly (larvae)	*Hydropsyche sp.*	24-h LC_{50} = 30 mg/L 96-h LC_{50} = 15 mg/L	(Marking and Chandler 1981)
River horn snail (adult)	*Oxytrema catenaria*	24-h LC_{50} = >100 mg/L 96-h LC_{50} = 62 mg/L	(Marking and Chandler 1981)
Asiatic clam (adult)	*Corbicula manilensis*	24-h LC_{50} = 78 mg/L 96-h LC_{50} = 45 mg/L	(Marking and Chandler 1981)
Cowfish	*Lactophyrys tricornis*	72-h LC_{50} = 7.6 mg/L	(USEPA 2016d)
Burrfish or Globe fish	*Chilomycterus sp.*	72-h LC_{50} = 7.6 mg/L	(USEPA 2016d)

3.2.2 Terrestrial Species

3.2.2.1 Mammals

4-AP has high acute toxicity in mammals with an acute oral LD_{50} of 28.7 mg/kg-bw in laboratory rats with a very steep dose-response curve and 3.7 mg/kg-bw in dogs (Schafer et al. 1973, USEPA 2020a). No chronic toxicity studies in mammals are available (USEPA 2020a).

3.2.2.2 Birds

4-AP has high acute toxicity in birds with LD_{50} values ranging from 2.4 mg/kg-bw for red-wings blackbirds and 15 mg/kg-bw for bobwhite quail (Table 6). The rose-ringed parakeet had a LD_{50} of 3 mg/kg-bw; the birds gave distress calls at an average of 39 minutes and 15 minutes after gavage with 5 mg/kg-bw and 10 mg/kg-bw, respectively (Sultana et al. 1986). Acute dietary and subchronic studies indicate 4-AP is slightly toxic to birds, with LC_{50} values of 361 and 681 mg/kg-diet for the mourning dove and mallard duck, respectively (USEPA 2020a). One avian chronic toxicity study resulted in a NOAEC of 31.6 mg/kg-diet in coturnix quail (*Coturnix*

coturnix) (USEPA 2020a). Subchronic exposure of dove and coturnix quail to 4-AP did not result in cumulative toxicity (Schafer and Marking 1975). One non-guideline reproductive study indicates some chronic toxicity in Japanese quail based on reductions in male weight gain (NOAEL = 31.6 mg ai/kg-diet, LOAEL = 100 mg ai/kg-diet (Schafer et al. 1975, USEPA 2020a). In birds (pigeons, sparrows, and red-winged blackbirds) that survived ingesting 4-AP bait, incapacitation lasted up to 90 minutes (Frank et al. 1981); during this time, they may be vulnerable to predators.

Table 6. 4-AP acute toxicity values in bird species.

Species	Scientific Name	LD_{50} Value	Reference
Red-winged blackbird	*Agelaius assimilis*	2.4 mg/kg-bw	(USEPA 2016c)
Black-billed magpie	*Pica hudsonia*	2.4 mg/kg-bw	(USEPA 2016c)
Yellow-billed magpie	*Pica nutalli*	2.4 mg/kg-bw	(USEPA 2016c)
European starling	*Sturnus vulgaris*	4.9 mg/kg-bw	(USEPA 2020a)
Northern bobwhite	*Colinus virginianus*	15.0 mg/kg-bw	(USEPA 2016c)
Rock dove	*Columba livia*	2.5 mg/kg-bw	(Sultana et al. 1986)
Mourning dove	*Zenaida macroura*	8.1 mg/kg-bw	(USEPA 2020a)
Rose-ringed parakeet	*Psittacula krameri*	3.02 mg/kg-bw	(Sultana et al. 1986)
House sparrow	*Passer domesticus*	4.2 and 7.5 mg/kg-bw	(Sultana et al. 1986)
White-rumped munia	*Lonchura striata*	2.97 mg/kg-bw	(Sultana et al. 1986)
Mallard duck	*Anas platyrhynchos*	4.36–5.19 mg/kg-bw	(USEPA 2020a)

3.2.2.3 Reptiles and Terrestrial Phase of Amphibians

Acute and chronic toxicity data is unavailable for terrestrial reptiles and amphibians (USEPA 2020a). Based on surrogacy from birds, 4-AP would be toxic to reptiles and amphibians.

3.2.2.4 Terrestrial Invertebrates

Acute and chronic toxicity studies for adult and larval honeybees and other terrestrial invertebrates are unavailable (USEPA 2020a). Bees are not attracted to the bait (USEPA 2020a). The label suggests using bait trays, which reduces bait contact with the ground and potential subsequent exposure to ground- and soil-dwelling invertebrates. Invertebrates are not likely to be harmed by treatments.

3.2.2.5 Terrestrial Plants

Information on the toxicity of 4-AP to terrestrial plants is limited (USEPA 2020a). USEPA (2020a) summarized one study where a reduction in fresh weight (less than 25%) was observed in corn seeds and seedlings after two applications of 4-AP.

4 EXPOSURE ASSESSMENT

4.1 Human Health

The exposure analysis evaluates the potential for exposure of humans to WS use of Avitrol. The exposure assessment begins with the use pattern for Avitrol. An exposure pathway for Avitrol includes (1) a release from an Avitrol source, (2) an exposure point where human contact can occur, and (3) an exposure route such as ingestion, inhalation, or dermal contact. Exposures for the identified human populations are evaluated qualitatively for each identified exposure pathway.

4.1.1 Potentially Exposed Human Populations and Complete Exposure Pathways

Avitrol products are all *"restricted-use pesticides,"* and only certified applicators or persons under their direct supervision may use the product (Avitrol Corporation 2013d;b;a;e;c, USEPA 2017b). The baits are applied by hand using a scoop and cannot be applied by air or mechanical equipment designed to broadcast baits or other pesticides (Avitrol Corporation 2013d;b;a;e;c). The Avitrol products are for non-food or non-agricultural crop use.

WS handlers and applicators (occupational workers) adhere to label requirements as they prepare and apply (including placement, monitoring, and retrieval of) treated baits to prevent contact with themselves and the public directly or through drift. Based on the expected use patterns for Avitrol products, WS applicators are the most likely subgroup of the human population to be exposed to 4-AP.

Exposure of the public to Avitrol products is unlikely when applicators follow label requirements concerning application sites, entry restrictions, use restrictions, and post-treatment cleanup requirements. The product labels require baiting at elevated sites in populated areas and areas open to the public and continuously monitored ground baiting in public areas when baiting at elevated sites is not feasible (Avitrol Corporation 2013d;b;a;e;c). Only certified applicators wearing personal protective equipment (PPE) are allowed in the treatment area during bait application. In ground-baited public areas, applicators must remain onsite during treatment and remove all dead or dying birds and unused bait after treatment. WS applicators dispose of collected birds by burial or incineration. Between FY16 and FY20, WS applicators completed about 6 treatments nationally per year. They spent an average of 2.7 hours at treatment sites, which for Avitrol treatments is enough time to place baits, wait for birds to react and leave the area, and pick up baits and dead birds.

After ground-baiting in public areas, the post-treatment cleanup requirement minimizes the potential for human exposure to uneaten baits. In public areas, WS applicators prefer to place Avitrol bait in bait trays for ease of bait removal after treatment. WS applicators prefer to treat when few people are around because seeing distressed birds can be disturbing. The labels require product containers and unused, spoiled, or unconsumed bait to be disposed of at an approved waste disposal facility, deep burial, or by incineration. The product labels also have restrictions on storage (including temporary placement).

A complete exposure pathway is not identified for dietary exposure. There are no registered 4-AP uses for food or agricultural crops (USEPA 2017b). The Avitrol labels (Avitrol Corporation 2013d;b;a;e;c) prohibit the following:

- applying the treated baits to growing food crops,
- using the treated baits as food, feed, or in any way used such that they could contaminate human food or animal feed,
- feeding, or mixing with grains for livestock or poultry, and
- applying where livestock or poultry may be exposed (users must keep livestock away from the bait storage location and application areas).

A complete exposure pathway is not identified for drinking water because of the use pattern of Avitrol formulations and label requirements not to use bait within 25 feet of permanent water bodies. Bait intake by the target species further reduces the chance of offsite transport via runoff. In addition, in publicly accessible areas that WS ground-treats, the labels require the applicator to retrieve unconsumed bait. Any bait left on the ground after cleanup would be minor. Bait trays reduce the potential runoff of bait should precipitation events occur. WS applicators avoid treating areas when precipitation is forecast to reduce the chance of bait effectiveness being degraded and the need for retreatment, reducing the likelihood of bait runoff. The use patterns preclude contamination of surface and groundwater that could be used for drinking water. During registration review, the label amendments proposed by USEPA will further specify these use restrictions and methods to protect the public and nontarget animals and prevent surface and groundwater contamination.

4.1.2 Human Health Exposure Evaluation and Risk Characterization

This section qualitatively evaluates worker exposure from direct contact while handling and applying bait in the field and re-entering treated sites for post-treatment cleanup activities. Avitrol formulations are restricted-use pesticides handled by certified applicators or persons under their direct supervision. The end-use products are mixed with untreated bait grains of the same composition, so ratios of treated baits to untreated grains are approximately 1:9 or greater for most projects to 1:5 for some. Exposure from direct contact to 4-AP in Avitrol baits for applicators and handlers is minimized under normal conditions with proper worker hygiene and PPE. PPE requirements for all mixers, loaders, applicators, persons picking up the dead birds and unused bait, and other handlers include:

- Long-sleeved shirt and long pants,
- Chemical-resistant gloves, such as those made from waterproof material, and
- Socks and shoes.

Applicators use a scoop when mixing and applying Avitrol products. Following treatment, which at the maximum is at the end-of-the-day or sundown, applicators retrieve dead birds and unused bait and dispose of these appropriately.

Other user safety requirements on the labels include:

- Properly cleaning PPE after use, such as washing in detergent and hot water,
- Keep and wash PPE separately from other laundry,
- Washing hands before eating, drinking, chewing gum, using tobacco, or using the toilet,
- Removing clothing and PPE immediately if pesticide gets inside, washing exposed skin surfaces thoroughly, and putting on clean clothing,
- Removing PPE immediately after handling the product, and
- Washing the outside of gloves before removal.

Accidental exposure may occur during the handling and application of baits. This type of exposure is low since only certified applicators or persons under their supervision who are trained are allowed to use Avitrol products. The infrequent and limited use of Avitrol products reduces the potential for accidental exposure. A quantitative exposure is not further evaluated.

4.2 Ecological Exposure Assessment

USEPA summarized 4-AP incident data for the years 1981–2018 reported in the Ecological Incident Data System (IDS), the USEPA Office of Pesticide Program's database that contains nontarget animal adverse effects incidents reported to the agency. A total of 180 incidents were reported, with 31 incidents related to registered uses, 106 incidents with unknown legality of the application, and 43 incidents that were illegal uses. Take of birds represented 99% of the incidents. No incidents involved aquatic species or plants. Most of the birds taken are listed as target species on the products' labels. No incidents were reported after 2012 (USEPA 2020a). None of the reports in the IDS was from a WS application.

4.2.1 Aquatic Exposure Assessment

Exposure of aquatic species to 4-AP is limited. The 4-AP labels require a minimum 25-foot buffer from permanent water bodies. Due to these label restrictions, runoff into surface or groundwater of 4-AP into aquatic environments is not expected. Using bait trays would reduce the potential for bait to run off during or following a rain event. WS avoids applying bait when precipitation events are predicted due to the chance bait would wash away, requiring them to repeat the treatment. The USEPA (2020a) estimated the amount of bait that would need to enter a waterbody to reach a concentration of 4-AP that would be toxic to freshwater fish and invertebrates is all of >1,000 and >500 applications worth of bait, respectively. These levels are magnitudes greater than what WS uses during applications and their frequency, which is unlikely to pose a risk.

Other potential aquatic exposure scenarios could involve birds dropping or regurgitating bait offsite or poisoned animals dying in a water resource. The labels require applicators to remove dying or dead birds in and around publicly accessible areas to reduce secondary exposure. Removal of these birds would reduce aquatic exposure potential. Additionally, the 4-AP is relatively fast acting (5–15 minutes), which limits the areas where birds can travel.

The label language, WS' use patterns, and aquatic exposure scenarios indicate exposure of aquatic vertebrates, invertebrates, and plants to 4-AP is not expected.

4.2.2 Terrestrial Exposure Assessment

Exposure to terrestrial species is through the consumption of 4-AP bait. Based on the formulation, exposure through dermal and inhalation routes are not significant exposure pathways. Wildlife attracted to the grains used in the Avitrol products are most at risk of exposure. As aquatic exposure is not expected, as previously discussed, ingestion of water containing 4-AP is not an expected route of exposure for wildlife. Honeybees and other pollinators are not attracted to the 4-AP baits (USEPA 2020a). USEPA waived the requirements for acute and chronic toxicity tests for the honeybee due to this lack of exposure. WS' use patterns result in minimal exposure to terrestrial plants and no exposure to plants for human consumption, as the label restricts applications in areas where food crops grow. For example, WS treated red-winged blackbirds on the periphery of an orchard instead of within the orchard.

4-AP presents a primary hazard to nontarget birds and mammals because of its acute toxicity, lack of selectivity, and attractiveness of the Avitrol grain baits. All but two of the IDS incident reports between 1981 and 2018 involved birds; 129 incidents were primary exposure of nontarget songbirds and one eagle (USEPA 2020a). None of the incident reports in the IDS were from WS applications, and WS has no reports of a nontarget bird or mammal taken through its use of 4-AP (Tables 2 and 3, Appendix 1: Tables 1a and 1b).

A search of the ASPCA Animal Poison Control Center database from 2002 to 2011 found 29 exposures of nontarget species to 4-AP (none of these were from WS applications): 89% were dogs, 10% cats, and 3% bovines (McLean and Khan 2013). The animal's outcome was known in 6 of the cases; all but one animal lived after veterinary care. The amount of 4-AP ingested in these exposures was unknown.

The current Avitrol product labels impose requirements to mitigate the risk to nontarget species. The labels require prebaiting in the proposed treatment area to determine that no nontarget birds feed on the prebait and to ensure the target species will take the bait where it is placed. Treated bait is not applied if the target species do not feed on the prebait or if nontarget species feed on it. In areas accessible to the public that are ground-treated, the label instructs the applicator to remain on site until all dead and dying birds and unused bait are retrieved from the site. This reduces the potential for primary and secondary poisoning of nontarget birds and other animals that may be attracted to the bait and potentially affected and prevents the public from attempting to rescue a bird.

4.2.3 Secondary Exposure

Predators and scavengers are at risk of exposure to undigested or unassimilated gut contents of species poisoned with 4-AP while intoxicated or after dying. USEPA (2020a) summarized incident data reported in the Incident Data System for 1981-2018. Seven incidents involved raptors. Two of these (Cooper's hawk and peregrine falcon) likely involved ingesting birds poisoned with 4-AP. One lethal incident involved the primary exposure of one eagle; however, WS suspects this poisoning was not from primary exposure because corn is not known to be part of the eagle diet (scavenger). The other 3 raptors that died had no necropsy done. One raptor (not identified) fed on mourning doves which had concentrations of strychnine and may not have been poisoned by 4-AP (USEPA 2020a). One incident involved mammals; however, 4-AP may not have been the cause of death. The incident involved a dog mortality (the dog's weight was not provided) that had consumed a poisoned dove; however, strychnine was detected in the dove, and 4-AP was not mentioned in the necropsy report (USEPA 2020a). None of these incidents were the result of WS applications. From the summarization by USEPA (2020a), it appears the incidents involved mostly strychnine and not 4-AP.

Studies on secondary exposure risk are limited. In a laboratory study evaluating secondary poisoning, 2 out of 20 kestrels died after exposure to red-winged blackbirds that fed on 1% Avitrol bait diluted 1:9 (Holler and Schafer 1982). All kestrels in the study consumed gut contents. Sharp-shinned hawks displayed no treatment-related effects (Holler and Schafer 1982). USEPA (2020a) reviewed one study where blackbirds killed with 4-AP were fed to dogs, American kestrels, and red-tailed hawks. No effects in the study were observed; however, the estimated amount of 4-AP ingested by the blackbirds was not provided, and secondary exposure concentrations were unknown (USEPA 2020a). In another study, no effects were observed in the adult male beagle and adult female beagle-coyote hybrid, magpies, rats, and three species of hawks fed 4-AP killed red-winged blackbirds (Schafer et al. 1974). The estimated amount of 4-AP ingested by eating red-winged blackbirds was 5.8 mg/kg-bw and 8.2

mg/kg-bw for the adult male beagle and the adult female beagle-coyote hybrid, respectively (Schafer et al. 1974). In the rat, no symptoms were observed at the highest dose, estimated at 67 mg/kg-bw based on the amount of red-winged blackbirds given to the rats (Schafer et al. 1974). Similarly, magpies displayed no effects at the highest dose of 7.5 mg/kg-bw (estimated). The female sharp-shinned hawk and American kestrels exposed to an estimated 6.4 mg/kg-bw and 5.5-6.1 mg/kg-bw 4-AP per day through consumption of 4-AP-poisoned red-winged blackbirds did not display symptoms (Schafer et al. 1974). The authors conclude the lack of effects is due to the rapid metabolizing of 4-AP in red-winged blackbirds.

USEPA (USEPA 2007b;2020a) found that 4-AP could be a risk to nontarget predators and scavengers, particularly bird species, in areas where 4-AP is used due to 4-AP's mode of action and toxicity to birds. The removal of dead or dying birds from the treatment area at the end of the project or at sundown would reduce secondary exposure. WS has no reports of secondary exposure from their use of 4-AP. This does not mean that no take of nontarget predators or scavengers has occurred, as some target birds may fly off and die offsite. In one study, 10 dead or dying herring gulls poisoned with 4-AP were collected up to 5 km away from the treatment site with 4-AP residues of 2.2-92 mg/kg-bw detectable in the crop and gut contents (the amount of 4-AP detected was for all herring gulls, not specifically for those collected at 5 km) (Frank et al. 1981).

5 RISK CHARACTERIZATION

5.1 Human Health Risks

Risks to human health are characterized qualitatively in this section. WS' use of Avitrol products is limited (Table 2), and applications are extremely controlled to prevent exposure. Under WS' use patterns, Avitrol baits should pose minimal risks to human health.

Adherence to label requirements regarding PPE minimizes risk to WS workers who handle and apply Avitrol products. Although 4-AP is a hazard to humans due to its acute toxicity via the ingestion, dermal, and inhalation routes, the low potential for exposure to 4-AP when following label requirements during handling and application of bait formulations suggest adverse health risks to workers are not expected. Any exposure and risk would be short-term based on the methods for baiting and the low quantity of Avitrol baits used by WS. Exposure of the general public to 4-AP is not anticipated based on the limited use pattern (e.g., entry restriction and pre-operation monitoring for bait disappearance rate), and the post-treatment cleanup requirements (e.g., remove unconsumed baits, monitor the bait area periodically and collect dead/dying birds for proper disposal). Therefore, adverse health risk to the public is not expected, which is supported by the lack of adverse incidents that have been reported to date.

4-AP is rapidly metabolized in birds and excreted in the urine in the target species (Extoxnet 1996). Therefore, the amount of chemical that remains in killed birds is unlikely to present a hazard to people. A person would have to ingest the internal organs of birds found dead from 4-AP ingestion to have any chance of receiving even a minute amount of the chemical into their system. This is highly unlikely to occur. In addition, people do not commonly consume the species of birds that are the target of baiting with Avitrol products. No reports of poisoning in humans from 4-AP exposure were documented by USEPA (2020c).

5.2 Ecological Risks

WS assumes birds that are attracted to Avitrol bait and those that ingest the bait will likely ingest enough 4-AP to receive a toxic dose. Secondary exposure is a concern for predators and scavengers of birds poisoned with 4-AP. The label requirements to prebait the treatment area with untreated grains of the same composition reduces exposure to nontarget birds and other wildlife. In treatment areas accessible to the public where ground-baiting occurs, the removal of leftover bait and dead or dying birds at the end of the project or sundown reduces exposure to nontarget species, including scavengers and predators. However, WS expects some predators and scavengers will enter the treatment area before cleanup, but the typical treatment site is not conducive to many raptors and other scavengers. WS uses Avitrol products to treat a sub-population of flocking birds to create a frightening response and agitation disturbance to cause the flock of birds to disperse. The entire flock of birds does not ingest treated baits. In a field study, researchers observed 82 dead birds with estimated flocks of 30,700 after broadcast treating cornfield experimental plots (total of 89 acres) with a 1:99 dilution rate of 3% 4-AP chopped corn baits (Besser and DeGrazio 1985). Avitrol products are poisons with flock alarming properties. WS dilutes baits further than the label requirements for large flocks to reduce mortality rates. WS expects the target birds that ingest Avitrol baits will die, although this is not always the case. Birds that do not receive a lethal dose may still be at risk of predation because of the neurological effects that may make them susceptible to predators.

Mammals in the treatment area attracted to the Avitrol bait are also at risk of lethal exposure. Although WS prebaits the treatment area and will not apply the Avitrol bait if nontarget species take the untreated bait, there is still a possibility for nontarget species to be present during treatment. In treatment areas accessible to the public where ground-baiting occurs, removing leftover bait and dead or dying birds at the end of the project or sundown reduces exposure to other nontarget species, including mammals. This would reduce the exposure risk to domestic pets, such as dogs, as pet owners are aware of the area’s hazards.

Although 4-AP is toxic to freshwater, marine, and estuarine fish and freshwater invertebrates, label restrictions, and WS’ use patterns result in a low exposure potential. Chronic and subchronic toxicity studies are lacking for aquatic species; USEPA waived these studies due to lack of aquatic exposure because of label mitigations. The overall risk to aquatic species from WS uses of 4-AP products is negligible.

The risk of nontarget species ingesting water contaminated with 4-AP is also negligible. 4-AP bait is not expected to impact terrestrial and aquatic plants due to lack of exposure and 4-AP’s mode of action.

6 UNCERTAINTIES AND CUMULATIVE IMPACTS

The uncertainties associated with this risk assessment arise primarily from a lack of recent information about the effects of 4-AP, its product formulations, and potential mixtures to nontarget organisms that can occur in the environment because much of the information came from studies when 4-AP products were first registered. These uncertainties are not unique to this assessment but are consistent with uncertainties in human health and ecological risk assessments with any environmental stressor.

Another potential uncertainty in this risk assessment is the potential for cumulative impacts on human health and the environment from the use of Avitrol products. The potential for cumulative impacts is expected to be low based on the low amount of Avitrol baits that WS uses. WS used an annual average of 49 ounces of Avitrol baits from FY16 to FY20 and 221 ounces between FY11 and FY15. Areas, where cumulative impacts may occur include: 1) repeated worker and environmental exposures to 4-AP from program activities and other sources; and 2) exposure to other chemicals with a similar mode of action.

Repeated exposures that could lead to significant risk from 4-AP are not expected due to label requirements that prevent significant exposure and reduce use. Accidental exposure may occur from improper use of PPE, but the potential for this is unlikely because Avitrol products are used only by certified applicators or those under their direct supervision.

Cumulative impacts may occur from 4-AP use in relation to other chemicals with a similar mode of action, as well as others with a different mode of action but could result in synergistic, additive, or antagonistic effects. This is an area of uncertainty since it's unknown what other stressors, including chemicals, humans, and nontarget wildlife, may be exposed to during a 4-AP application.

From a human health perspective, WS' low volume and minor uses of Avitrol products is expected to result in negligible cumulative impacts and low potential for cumulative impacts from exposure to other chemicals. Avitrol products are restricted use of pesticides, and only certified applicators and those under their direct supervision may use these products. Avitrol products are not sold to the public. Avitrol products are not registered for use on food crops and are unlikely to impact surface or groundwater, so risks are negligible for the public. Treatments may occur in areas accessible to the public. During these applications, the certified applicator remains onsite to ensure the public and pets do not enter the treatment area or consume baits. The lack of exposure and risk to the public suggests that cumulative impacts would also be incrementally negligible when factoring in other stressors.

7 SUMMARY

WS uses Avitrol products to reduce bird nuisance and damage. The WS use pattern and their classification as restricted use pesticides result in negligible risk for the public. The dietary risk from 4-AP exposure to the public is negligible since Avitrol products have no registered food uses and do not pose a threat to drinking water. The risk to WS applicators is low because they receive training in the products' use, are certified by the State pesticide regulatory agencies to use restricted-use pesticides, and follow label instructions, including the use of appropriate PPE. WS expects some take of target species that ingest Avitrol baits. WS also expects minor take of nontarget species that are attracted to the baits or to distressed and dying birds. The minimal release of 4-AP into the environment is expected to have no or negligible cumulative impacts on nontarget species, the public, and the environment.

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9 PREPARERS

9.1 APHIS WS Methods Risk Assessment Committee

Writers for "Use of 4-Aminopyridine in Wildlife Damage Management Risk Assessment":

Primary Writer: Jim Warren
Position: USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Environmental Toxicologist, Little Rock, AR
Education: B.S. Forest Ecology and M.S. Entomology – University of Missouri; Ph.D. Environmental Toxicology – Clemson University
Experience: Sixteen years of experience working for APHIS preparing ecological risk assessments and providing assistance on environmental compliance. Prior experience before joining APHIS includes other government and private sector work regarding ecological risk assessments related to various environmental regulations.

Primary Writer: Andrea Lemay

Position: USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Biological Scientist, Raleigh, NC
Education: B.S. Plant and Soil Science (Biotechnology) - University of Massachusetts; M.S. Plant Pathology - North Carolina State University
Experience: Fifteen years of service in APHIS conducting risk analysis. Seven years of experience in preparing environmental analyses in compliance with the National Environmental Policy Act.

Writer: Thomas C. Hall
Position: USDA-APHIS-WS, Operational Support Staff, Staff Wildlife Biologist, Fort Collins, CO
Education: BS Biology (Natural History) and BA Psychology – Fort Lewis College; MS Wildlife Ecology – Oklahoma State University
Experience: Special expertise in wildlife biology, identification, ecology, and damage management. Thirty-seven years of service in APHIS Wildlife Services including operations and research in CO for research and OR, GU, CA, OK, and NV for operations conducting a wide variety of programs including bird damage research and management, livestock protection (predators and birds), invasive species management, wildlife hazard management at airports, property and natural resource protection including waterfowl, brown tree snake, feral swine, rodent, and beaver damage management. Researched, applied, and supervised the use of 4-AP.

Editors/Contributors for "Use of 4-Aminopyridine in Wildlife Damage Management Risk Assessment":

Editor/Contributor: Shelagh DeLiberto
Position: USDA-APHIS-WS Operational Support Staff, Environmental Management Coordinator, Fort Collins, CO
Education: BA Biology and Environmental Science – Ithaca College; MS Wildlife Biology – Colorado State University
Experience: Nineteen years of service in APHIS conducting wildlife research. Six years of experience in preparing categorical exclusions and environmental analyses in compliance with the National Environmental Policy Act.

Editor/Contributor: Michael McCaskill
Position: USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Toxicologist, New Market, MD
Education: B.S. Environmental Science – University of Florida; MPH Industrial Hygiene-University of South Carolina, Ph.D. Toxicology-Florida Agriculture and Mechanical University
Experience: Ten years of experience conducting human toxicological research at Florida Agriculture and Mechanical University, University of Nebraska Medical Center, and Tulane University. Four years of experience conducting human health and environmental toxicological risk assessments and assisting environmental compliance programs at the Florida Department of Health, Commonwealth of Pennsylvania, and USDA.

Editor/Contributor: Emily Ruell
Position: USDA-APHIS-WS, NWRC, Registration Specialist, Fort Collins, CO
Education: B.S. Zoology and Biological Aspects of Conservation – University of Wisconsin - Madison; M.S. Ecology – Colorado State University (CSU); M.A. Political Science – CSU

Experience: Nine years of experience with WS NWRC preparing and reviewing vertebrate pesticide registration data submissions and other registration materials and providing pesticide regulatory guidance to WS, WS NWRC, and collaborators. Prior experience before joining APHIS includes seven years of conducting field and laboratory wildlife research at CSU and environmental policy research for the U.S. Geological Survey.

Editor: Ryan Wimberly
Position: USDA-APHIS-WS, Operational Support Staff, Staff Wildlife Biologist, Madison, TN
Education: BS Wildlife Management and Ecology – Northwest Missouri State University
Experience: Special expertise in wildlife biology, ecology, and damage management. Seventeen years of service with APHIS Wildlife Services, including operations and research, conducting a wide variety of programs, including bird damage research and management, livestock protection, invasive species management, wildlife hazard management at airports, property and natural resource protection. Expert in preparing environmental documents for WS programs to comply with the National Environmental Policy Act and the Endangered Species Act.

9.2 Internal Reviewers

Reviewer: David Marks
Position: USDA-APHIS-WS, Assistant State Director, Missouri and Iowa
Education: BS in Wildlife Biology and MS in Environmental Science and Policy, University of Wisconsin Green Bay
Experience: Twenty years experience with APHIS Wildlife Services in Wisconsin, Michigan, and Iowa. Specialized experience in all levels of WS Operations, including pesticide use, NEPA, FOIA, ESA, predator control, feral swine damage management, wildlife hazards at airports, wildlife disease sampling, invasive reptiles, and urban wildlife damage. Pesticide experience mostly with avian species including pigeons, European starlings, and house sparrows using DRC-1339 and Avitrol.

Reviewer: Joshua A. Janicke
Position: USDA-APHIS-WS, Wildlife Biologist, Concord, NH
Education: BS Wildlife Management, University of New Hampshire
Experience: Twenty-five years of service with USDA-APHIS-Wildlife Services in New Hampshire. Experience includes urban wildlife damage management, wildlife hazards at airports, wildlife disease sampling, invasive species control, controlled material inventory tracking, restricted-use pesticides, NEPA and ESA. Supervisory pesticide applicator license holder in NH. Train WS-NH employees on procedures for use of DRC-1339 and Avitrol within NH. Conducted bait efficacy trials for pesticide work with blackbirds in sweet corn fields. Experience with DRC-1339 to control damage caused by European starlings and Red-winged blackbirds. Experience with Avitrol to control damage caused by red-winged blackbirds.

Reviewer: John Cummings
Position: EDM International Inc, Wildlife Biologist, Fort Collins, CO. Retired Wildlife Biologist from USDA National Wildlife Research Center, Fort Collins, CO
Education: B.S. in Wildlife Biology (Research), Colorado State University. Completed Ornithology graduate courses. Colorado State University.
Experience: At the National Wildlife Research Center, as a research biologist and project leader, was responsible for research leadership and supervision for projects addressing agriculture crop depredations from birds, bird hazards to aircraft, predation on endangered

and threatened species and bird ecology. Was involved in developing Avitrol as a bird frightening agent for agriculture crops, specifically sunflowers and DRC-1339 for staging area baiting. The research was designed to provide an ecological understanding of bird species, develop management tools, improve existing management techniques and provide sound data in support of the Environmental Protection Agency registration issues. Since 2014, worked on a variety of projects with Southern California Edison, PPL/PSEG, Rockwood Lithium, Xcel Energy, Alabama Power, PNM New Mexico, National Park Service and state wildlife agencies. Projects ranged from developing and evaluating wildlife deterrent tools, developing wildlife mitigation plans, avian protection plans, impact analysis of aircraft on wildlife, telemetry of bald eagles, raptor monitoring and development of repellent tools for woodpecker damage to utility poles. A Certified Wildlife Biologist and a Certified Airport Wildlife Biologist.

9.3 Peer Review

The Office of Management and Budget requires agencies to have peer review guidelines for scientific documents. The APHIS guidelines were followed to have "Use of Carcass Disposal in Wildlife Damage Management" peer reviewed. WS worked with the Association of Fish and Wildlife Agencies to have experts review the documents.

9.3.1 Peer Reviewers Selected by the Association of Fish and Wildlife Agencies

South Dakota Game, Fish and Parks

Louisiana Department of Wildlife and Fisheries

Michigan Department of Natural Resources

9.3.2 Comments

1. I found 1 typographical error. P.10 3.2.2.2, the paragraph above the table denotes "morning dove" instead of "mourning dove."

   Response: We have corrected this error.

2. While it is useful and appreciated that the risk assessment provided exposure information in non-target species from the ASPCA Animal Poison Control Center database and the USEPA Ecological Incident Data System, it would be beneficial to include information from state wildlife agencies that perform necropsies and ancillary diagnostic testing such as toxicology. State veterinary diagnostic laboratories with a toxicology service will also have useful results that could be included in future risk assessments. Collectively, this will capture more information about exposure and toxicosis in free-ranging wildlife species.

   Response: We appreciate this comment and agree that results from state veterinary diagnostic laboratories may be informative regarding exposure of 4-aminopyridine to free-ranging wildlife species. However, state veterinary diagnostic laboratory testing results are not readily available without contacting individual laboratories for such data. In addition, the Risk Assessment covers WS use and risk associated with the use of 4-

Aminopyridine, not the use of the product by the general public or other pesticide applicators. We provide the ASPCA Animal Poison Center and USEPA Ecological Incident Data System exposure information as a comparison to the exposure due to use by WS.

Comments received not requiring a response.

1. This document provides thorough coverage of the use of 4-Aminopyridine (Avitrol) in Wildlife Damage Management. We have no comments except to say we appreciate the opportunity to participate in the review process.

2. The document was thorough and fully informative, addressing all aspects of my concern including but not limited to: toxicity to non-target bird species, toxicity to scavengers and predators of poisoned birds, human toxicity, environmental toxicity, and past accidental exposure histories.

3. Due to the small amount of use of this product, I see it of little impact to the overall health and well-being of wildlife. Additionally, the product is a very useful tool to have in situations where large flocks of birds can cause agricultural damage or threaten human life.

4. The authors explained the methodology of efficient use very well. This concise explanation should lead to good results with the product while ameliorating negative effects. In addition, the authors explained assumptions and limitations of the product as well.

5. The methodologies of application protect the user, non-target mammalian species, and amplify the non-lethal frightening effect of the bait.

6. The references seemed complete and supported many facets of the document.

7. The risk assessment provided information on the purpose and consequences of using Avitrol. This product is a restricted use pesticide utilized to control flocking pest birds such as passerines and corvids as a poison with flock alarming properties. It is lethal to most all birds that ingest treated baits, resulting in seizures/ convulsions/ hyperactivity, cardiac and respiratory arrest. The use pattern is clearly defined and includes allowing only certified applicators to use the product, bait trays, occupational workers remaining on site during the application period and post-treatment cleanup (e.g., removing unused bait and dead or dying birds) and proper disposal of carcasses. The standard operating procedures and mitigations to prevent adverse impacts are defined and include pre-baiting to ensure target species take the bait and nontarget species are not present, and in-person monitoring of the site to reduce the potential for primary and secondary poisoning of nontarget birds and other animals. Assumptions and uncertainties are stated in the risk assessment, such as the expectation that target birds that ingest Avitrol baits will die but recognizing that some birds will display neurological signs and may be at increased risk of predation. The assessment also acknowledges that there are uncertainties due to a lack of recent scientific studies regarding the effects of Avitrol, effects of co-occurring toxic exposures, and cumulative or repeated impacts to people and animals. The selection of references in the risk assessment seemed appropriate.

Appendix 1. Additional 4-Aminopyridine Use Data.

Additional data is given for FY11 through FY15 because of the limited use of Avitrol products. Generally, for the risk assessments, only five years are summarized. The data for the two five-year time spans was similar, except that four products (Table A1) were used from FY11 to FY15, and more starlings were targeted during projects (Table A2). Additionally, brown-headed cowbirds were targeted but apparently left the area, so the treatment was not successful. In FY16–FY20, red-winged blackbirds were targeted (Table 3) but were not during FY11–FY15 (Table A-2). It should be noted that birds hazed may not necessarily be documented and cannot be estimated.

Table 1a. Avitrol labels used by WS in WDM from FY11 to FY15, the annual average target species killed and repelled, the amount of product used, and the states where used.

ANNUAL AVERAGE 4-AP PRODUCT USE BY WS					
Product	EPA Registration No.	Killed	Repelled	Oz. Applied	States
Avitrol Mixed Grains (0.5%)	11649-4	2,226	2,455	138.6	MA MD NC OR TN TX VA
Avitrol Double Strength Corn Chops (1.0%)	11649-5	0.2	2	11.2	MA
Avitrol Corn Chops	11649-6	811	287	50.7	IL KY MA OK TN WA
Avitrol Whole Corn	11649-7	4	7	20.4	MA
TOTAL	4 Products Used	3,041	2,751	220.9	11 States

Table 1b. The annual average number of target species killed and repelled with Avitrol products used by WS in WDM from FY11 to FY15.

ANNUAL AVERAGE 4-AP PRODUCT USE AND SPECIES TAKE				
Species*	Killed	Repelled	Oz. Used	States Where Used
Rock Dove (Feral Pigeon)*	24	7	39.6	MA OR TX
European Starling*	1,137	2,682	75.8	KY MA MD OR TN VA
House Sparrow*	1,880	62	104.3	IL MA NC OK OR TN TX VA WA
Brown-headed Cowbird	0	0	1.2	VA
TOTAL (4 sp.)	3,041	2,751	220.9	11 States

* Introduced species