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

Chapter XI

The Use of GonaCon in Wildlife Damage Management

August 2017

Peer Reviewed Final
July 2022

USE OF GONACON IN WILDLIFE DAMAGE MANAGEMENT

EXECUTIVE SUMMARY

Gonadotropin releasing hormone (GnRH) is a naturally occurring hormone that stimulates production of sex hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH regulate gamete and steroid hormone production by the ovaries and testes and are critical in the reproduction of vertebrates. USDA APHIS Wildlife Services (WS) has developed an immunocontraceptive vaccine called GonaCon, which includes the active ingredient GnRH conjugated to a mollusk-derived carrier protein, against endogenously produced GnRH. When injected into a target animal, GonaCon induces the body to make antibodies against its own GnRH, causing infertility. GonaCon has been shown to be an effective tool in managing fertility in wild and feral mammal species. GonaCon is registered for use in female wild or feral equids, white-tailed deer, and prairie dogs.

GonaCon is delivered to the target animal by using preloaded syringes injected by hand or jab stick or remote delivery dart for equine and white-tailed deer. Delivery by jab stick or remote darting has a greater potential for exposure to human health and the environment due to syringes or darts becoming dislodged from the target animal or in the case of remote darting where the applicator misses the target animal. The potential for exposure is low because the label requires the applicator to attempt to collect syringes or remote darts that become dislodged from the animal, or if a remote dart misses the target animal. GonaCon in syringes and darts that aren't located are not anticipated to result in significant exposure to human health and the environment. The frequency of GonaCon use is low, the amount of GnRH in the syringes and darts is low and is subject to rapid degradation in the environment.

WS evaluated the potential human health and ecological risks from the proposed use of GonaCon and determined that the risks to human health and the environment are negligible. Risks to workers as well as the general population, including hunters who may harvest injected animals, are low based on the method of application, the mode of action of GonaCon, and label requirements. Similarly, risks are negligible for nontarget fish and wildlife based on how GonaCon is applied, its likely environmental fate, and label requirements.

Table of Contents

1 INTRODUCTION

GonaCon is an immunocontraceptive vaccine that was developed and is used by the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Wildlife Services (WS) in the management of certain wildlife and feral vertebrate animal populations. This risk assessment provides a qualitative evaluation of potential risks and hazards to human health, nontarget fish and wildlife as a result of exposure to GonaCon under the proposed uses in the APHIS and WS Program. The results of this human health and ecological risk assessment will help WS determine an appropriate risk management strategy to achieve its program management goal.

The methods used to assess potential human health effects follow standard regulatory guidance and methodologies (National Research Council 1983, USEPA 2022). The methods used to assess potential ecological risk to nontarget fish and wildlife follow U.S. Environmental Protection Agency (USEPA) methods, as well as other published methodologies where appropriate. Data used in this risk assessment were obtained from USEPA registration-related and other peer-reviewed documents, other published literature, and online searches for relevant data.

The following risk assessment is divided into four sections: problem formulation (identifying hazard), toxicity assessment (the dose-response assessment), exposure assessment (identifying potentially exposed populations and determining potential exposure pathways for these populations), and the integration of the exposure and toxicity assessments, or risk characterization.

2 PROBLEM FORMULATION

Wildlife and feral animals can reach population levels that are harmful to ecosystems or the human environment. WS employs several lethal and nonlethal methods for managing these populations depending on the particular problem. GonaCon is one nonlethal population control option -- an immunocontraceptive vaccine that renders female animals temporarily infertile. To date, APHIS has obtained USEPA pesticide registrations for use of GonaCon to control populations of white-tailed deer[1], wild and feral horses (*Equus caballus*) and burros (*Equus asinus*), and for black-tailed prairie dogs, white-tailed prairie dogs, and Gunnison's prairie dogs. APHIS is also investigating the potential for obtaining USEPA registrations to use GonaCon to manage populations of bison and feral swine. In experimental studies, GonaCon has also been shown to prevent pregnancy in other species including elk, domestic cats, California ground squirrels, and brown (*Norway*) rats (Miller et al. 2008).

2.1 Chemical Description and Product Use

GonaCon is an injectable immunocontraceptive vaccine, containing the active ingredient mammalian gonadotropin releasing hormone (GnRH), developed by the WS National Wildlife Research Center (NWRC) (Eisemann et al. 2006). GnRH is a 10 amino acid peptide hormone with the same amino acid sequence conserved across most mammals (USEPA 2009a). Initially, GonaCon was regulated by the U.S. Food and Drug Administration (USFDA) as an investigational new animal drug. However, after interagency discussions between USFDA and USEPA Office of Pesticide Programs, responsibility for regulatory approval was moved to the USEPA once research and development of the product by APHIS WS moved toward use of the product as a

[1] Scientific names are given in the Risk Assessment Introduction Chapter I,or given if not in that Chapter.

wildlife population control tool. USEPA regulates oral and injectable contraceptives when used for population control of wild and feral animals (USEPA 2009a). APHIS is currently the registrant for three GonaCon end-use products:

- USEPA Reg. No. 56228-40: GonaCon –Deer (for white-tailed deer; registered in November 2015)[2]
- USEPA Reg. No. 56228-41: GonaCon – Equine (registered in November 2015)[2]
- USEPA Reg. No. 56228-64: GonaCon – Prairie Dogs (registered in March 2022)

All three products are GnRH-based water-in-oil emulsions with the same active ingredient (0.032% GnRH) and inert ingredients (99.968%). GnRH (also known as luteinizing hormone-releasing hormone (LHRH)) is a reproductive hormone produced in the arcuate nuclei of the hypothalamus. GnRH stimulates production and secretion of two gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) by the anterior pituitary gland. LH and FSH regulate gamete and steroid hormone production by the ovaries and testes (i.e., estrogen, progesterone, and testosterone).

The formulation is comprised of two primary components that are mixed together to form an emulsion for injection. The first component is AdjuVac (a mineral oil-based adjuvant that contains killed *Mycobacterium avium*) to induce a localized inflammatory response that triggers a rapid, strong, and sustained immune response. The second is a mollusk stabilizing buffer (Gionfriddo et al. 2011) containing GnRH conjugated to a mollusk-derived carrier protein (i.e., keyhole limpet hemocyanin or blue protein) (Bender et al. 2009). Three additional amino acids are added to GnRH to act as a spacer and to facilitate conjugation to the carrier protein. Despite GnRH being a "self" protein, GnRH conjugated to the mollusk carrier protein causes the body to recognize GnRH as "foreign," stimulating an immune response and production of specific antibodies against it. This immune response prevents GnRH from stimulating production of additional sex hormones (LH and FSH), which blocks ovulation. The target animal becomes temporarily infertile, and because the production of sex steroids is also reduced, reproductive behaviors are also often suppressed (USEPA 2009b, Killian et al. 2006).

For fertility control in white-tailed deer, single 1-milliliter (mL) doses of GonaCon – Deer (USEPA Reg. No. 56228-40) are packaged and pre-loaded in 3-mL plastic syringes. Applicators, who are limited to APHIS WS personnel, state wildlife management personnel, or persons working under their authority, administer GonaCon by hand injection at least 2 to 3 months prior to the onset of rut (USEPA 2009b). The vaccine then induces temporary infertility in female white-tailed deer. Application by hand-injection into a large muscle mass is done by using a 1.5-inch 18-gauge or 19-gauge stainless steel hypodermic needle (USEPA 2009b). All vaccinated deer must be tagged. A second application can be done by hand injection or remote darting. Application by remote darting is done by using a 2 cubic centimeter (cc) dart with a 1.25- or 1.5-inch 14-gauge gelatin barb needle. Applicators transfer 1-mL of GonaCon-Deer from the preloaded syringe into the dart. In studies, researchers injected GonaCon into the upper hind limb of white-tailed deer and found that a single vaccination can induce infertility for multiple years (Gionfriddo et al. 2011). The risks of using remote darting as an application method for GonaCon – Deer would be similar to those discussed below for the equine label, and in the Use of Immobilization and Euthanasia and Firearms Risk Assessments.

GonaCon – Equine (USEPA Reg. No. 56228-41) is approved for fertility control in female wild or feral horses and burros. Horses and burros receive a single dose (2 mL) of GonaCon – Equine at

[2] Labels can be found @ https://ems-team.usda.gov/sites/aphis-ws/PSD/_layouts/15/start.aspx#/Pesticide%20Labels.

least 2 to 3 months prior to the onset of breeding. A single vaccination of GonaCon – Equine can induce infertility for multiple years in equids. It has shown similar results in other ungulates, but it is not registered for these species (Gray et al. 2010, Fagerstone et al. 2010). GonaCon – Equine is administered by hand injection, jab stick, or remote delivery (darting) under the following application directions:

- **Hand Injection**: Inject 2 mL of GonaCon by intramuscular injection into a large muscle mass (e.g., rump, neck) using the preloaded syringe and a 1.5-inch 18-gauge or 19-gauge stainless steel hypodermic needle
- **Jab-Stick Delivery**: Transfer 2 mL GonaCon from the preloaded syringe. Inject intramuscularly using a 1.5-inch 14-gauge stainless steel hypodermic needle
- **Remote Darting**: Recommended dart specifications are 2 cc dart with a 1.25 or 1.5-inch 14-gauge gelatin barb needle. The 2 mL of GonaCon in a preloaded syringe must be transferred into the dart. Deliver intramuscularly using the appropriate projection device.

If remote delivery is used, the applicator must make every attempt to recover the dart, whether it missed or fell out of the equid. If possible, all darts that are discharged and dropped from the horses at the shooting site must be recovered before another darting occurs. In the event that spent darts cannot be located due to inclement weather, darkness, or safety concerns, the site of a lost dart may be noted and marked, and recovery efforts made at a later date.

GonaCon – Prairie Dogs (USEPA Reg. No. 56228-64) is approved for fertility control of black-tailed, white-tailed, and Gunnison prairie dogs. GonaCon – Prairie Dogs is administered by intramuscular injection into a large muscle in the thigh of individual female prairie dogs. Pre-loaded syringes are used to administer 0.4 mL of the GonaCon- Prairie Dogs formulation using a 20- or 23-gauge stainless steel hypodermic needle. The initial injection is administered at least two to three months prior to the onset of breeding. A second vaccination (0.4 mL) can be administered after 90 days from the initial injection for a total of two vaccinations per individual prairie dog per year. The label recommends that applicators mark the fur of vaccinated prairie dogs to ensure that they are not unintentionally reinjected during the same application period.

GonaCon - Deer is classified by USEPA as a restricted-use pesticide. All users must be certified pesticide applicators or be under the supervision of a certified pesticide applicator. Use of the white-tailed deer label is further restricted to USDA APHIS WS or state wildlife management agency personnel or persons working under their authority. GonaCon – Equine is a general use pesticide that is for use only by employees of federal agencies, federally recognized Indian Tribes, state agencies responsible for wild or feral horse and burro management, public and private wild horse sanctuaries, research scientists and veterinarians treating wild or feral horse and burro populations, or persons working under their authority. GonaCon – Prairie Dogs is a general use pesticide that is for use only by employees of USDA APHIS WS or state wildlife management agency personnel, or persons working under their authority. All three product labels specify that applicators keep these products away from humans, domestic animals, and pets. The labels prohibit GonaCon from direct use in water, in areas where surface water is present, or in intertidal areas below the mean highwater mark.

Use of all pesticide products also requires a State pesticide registration by individual States. As of June 2022, Maryland, New Jersey, and North Carolina have approved the use of the GonaCon - Deer (USEPA Reg. No. 56228-40), and Arizona, California, Colorado, Idaho, North Dakota, New Mexico, Nevada, Oregon, Pennsylvania, Utah and Wyoming have registered GonaCon - Equine (USEPA Reg. No. 56228-41). GonaCon – Prairie Dogs (USEPA Reg. No. 56228-64) is approved

for use in Colorado and New Mexico. The labels also specify that users must consult State regulations to determine whether they need additional permits or approval prior to use.

2.2 Physical and Chemical Properties

The GnRH (CAS Number: 9034-40-6, and molecular formula: $C_{55}H_{75}N_{17}O_{13}$) peptide used in GonaCon is a white odorless powder, solid at room temperature (USEPA 2009b), with a molecular weight of 1182.31 (Merck 2013). Melting point, boiling point, stability to normal and elevated temperatures, metal and metal ions, oxidation/reduction action, flammability, explodability, and vapor pressure are not available (USEPA 2009b, Merck 2013). Preliminary testing of the GnRH peptide indicates that it is very water-soluble (≥100 mg/mL) (Warren and Stephens 2008). GonaCon is a white odorless liquid, the pH is 6.46, and the storage stability is 6 months (USEPA 2009b).

2.3 Environmental Fate

As part of the data package required by USEPA for registration of GonaCon, APHIS submitted waivers for the environmental fate studies because, when used according to label instructions, there is limited potential for environmental release from direct injection of the product into the target animal. USEPA granted waivers for environmental fate studies including hydrolysis, photolysis, soil dissipation, aerobic soil metabolism, and adsorption/desorption due to the low potential for release to soil and water (USEPA 2009b).

2.4 Hazard Identification

The role of GnRH within the reproductive system has been intensively studied. However, mammalian toxicology data on GnRH is limited to a few acute toxicity studies. The toxicity study in deer performed during the safety and toxicity evaluation of GonaCon showed no significant contraindications or toxic effects in female white-tailed deer in weeks following vaccination with GonaCon, except for the formation of granulomata at the injection site (Killian et al. 2006). Behavioral studies in white-tailed deer showed that treated animals are not permanently sterilized, but they exhibit fewer breeding behaviors due to the decline in serum sex steroids (Killian and Miller 2001). A field study in free-roaming feral horses showed that GnRH vaccine can significantly reduce fertility for several years with a single injection. However, no significant effects were noted from contraceptive treatment on the sex ratio of foals, birthing season, or foal survival (Gray et al. 2010). With elk, male precopulatory behavior rates toward cows treated with a GnRH vaccine was greater than controls and could be problematic; treatment did not affect existing pregnancies or calf survival (Powers et al. 2011). However, currently, GonaCon is not registered for use in elk.

Acute oral and dermal studies in the rat showed that all tested animals survived a 1-mL GonaCon exposure. A primary eye irritation study for GonaCon in rabbits did not show corneal opacity or iritis. Treated eyes exhibited conjunctival redness and discharge within one-hour after treatment, but there were no “positive” grade irritations at 24 hours. Rabbits were free of all eye irritation after 72 hours. A primary skin irritation study for GonaCon in rabbits did not show swelling at any treated site. Initially, treatment resulted in a very slight superficial reddening of skin that dissipated within 72 hours. For these reasons, USEPA classified GonaCon as a Toxicity Category IV (no precautions required) for acute oral/dermal toxicity and eye and skin irritation exposures (USEPA 2009b). Chronic toxicity of GnRH is not expected since it is rapidly metabolized in animals.

When GonaCon is used according to the label, human exposure is unlikely. First, certified applicators deliver GonaCon while wearing personal protective equipment, which includes long-

sleeved shirts, long pants, gloves, and shoes with socks. Secondly, GonaCon is pre-packaged in syringes and the preloaded syringes significantly reduce exposure or transferring it to jab stick syringes or darts presents minimal potential for exposure. Lastly, certified applicators apply GonaCon through hand injection (most equids are actually injected using a syringe since they are in chutes following roundups) or remote delivery. As a result of these attributes, certified applicators are unlikely to have dermal contact with GonaCon or inhale it during its intended use. Thus, USEPA waived several study requirements, including:

- The acute inhalation study in the rat because inhalation is unlikely to occur;
- The dermal sensitization study because dermal contact is not expected;
- The studies on gene mutation, structural chromosomal aberration, and other genotoxic effects because the intended use precludes human exposure;
- The acute delayed neurotoxicity study in the hen, because GonaCon is not an organophosphate pesticide and its structure is not similar to products causing delayed neurotoxic effects; and
- The chronic dietary toxicity studies for mammalian and non-mammalian species, because GonaCon use will not result in repeated human exposure during its intended use.

The previously described use pattern for GonaCon also resulted in the waiver of ecological effects studies required by USEPA for pesticide registration including (USEPA 2009c):

- Seedling Germination/Vegetative Vigor (Guideline 122-1)
- Aquatic Plant Growth (Guideline 122-2)
- Avian Oral Toxicity (LD50) (Guideline 850.1200)
- Avian Dietary Toxicity (LC50) (Guideline 850.2200)
- Acute Toxicity Freshwater Invertebrates (EC50) (Guideline 850.1010)
- Freshwater Fish Toxicity (LC50) (Guideline 850.1075)

USEPA granted waivers for these studies due to the low potential for environmental release of GnRH from the proposed use pattern in this assessment.

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. USEPA did not establish a reference dose for GnRH since it is not considered a food use product and will not accumulate in the tissues of treated animals. USEPA assigned GonaCon a Category IV rating for acute oral, dermal, inhalation, and ocular exposure routes. A category IV rating means that GonaCon is considered practically non-toxic. USEPA waived the requirement for an acute inhalation study during the registration of GonaCon (USEPA 2009b); thus, these studies are not available. With the use pattern of GonaCon, inhalation exposure is not expected to occur.

3.2 Ecological Exposure Dose-Response Assessment

USEPA waived the aquatic and terrestrial ecological effects data requirements for GonaCon due to its method of application, mode of action, and lack of potential exposure to nontarget fish and wildlife. Currently the only available toxicity data applicable to the effects analysis for nontarget wildlife is an acute oral limit toxicity study using the rat. No lethal or sublethal effects were noted

during a 14-day period at a dose of 1-mL solution containing 0.03% GnRH (Eurofins 2008). GnRH belongs to a large group of peptide-based endocrine-related hormones that are present in all vertebrates and are critical for proper reproductive function (Somoza et al. 2002). Sublethal effects would be expected in nontarget vertebrates under the appropriate exposure pathway and in cases where GnRH is non-specific to binding receptors; however, this is unlikely in nontarget fish[3] and wildlife since exposure would have to occur through intramuscular injection. GnRH and similar peptides have been noted in some invertebrates; however, their role in reproduction and other physiological functions is not fully understood (Tsai 2006). Studies regarding these peptides are conducted *in-vitro* and no dose-response data for invertebrates appear to be available in the literature.

4 EXPOSURE ASSESSMENT

4.1 Human Health Exposure Assessment

Exposure assessment estimates the potential exposure of humans to GnRH. The exposure assessment begins with the use and application methods of the GnRH products. A complete exposure pathway for GnRH includes (1) release from a GnRH source, (2) an exposure point where human contact can occur, and (3) an exposure route for the contact such as ingestion, inhalation or dermal contact (USEPA 1989). In this way, the potentially exposed human populations and complete exposure pathways are identified and qualitatively evaluated.

4.1.1 Potentially Exposed Human Populations and Exposure Pathways

Exposure of certified pesticide applicators to GonaCon or GnRH is unlikely during proper use; however, there are potential exposures for trained applicators during an accidental event, or if the product is not used according to label directions and precautions. There is the potential for accidental exposure during hand injection or remote darting. The GonaCon labels provide caution statements about preventing accidental injection. Accidental exposure may also occur through faulty darts that discharge accidentally or break during use. This type of exposure to applicators is minimized by inspecting darts prior to use and ensuring they are loaded properly. Exposure to GonaCon is further reduced by wearing personal protective equipment (PPE) that is intended to reduce dermal exposure. PPE for all three GonaCon labels includes long-sleeved shirt and long pants, chemical resistant gloves, and shoes plus socks.

The public would not have access to GonaCon. Exposure through consumption of treated animals by the public or hunters who consume a recently injected animal is unlikely because GnRH is rapidly metabolized and has a short half-life (under one hour) so dietary ingestion of GnRH from treated animals is expected to be minimal (see discussion below in Exposure Evaluation for additional information on oral exposure). If remote delivery is used, the label requires that applicators make every attempt to recover all darts. In addition, the applicators examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its vaccine content. Therefore, the potential for the general public to encounter a loaded dart, either from failing to recover darts that fall out of treated animals or missing the animal with the dart, is low.

Release of GonaCon or GnRH into soil is unlikely because the vaccine is contained within syringes and is injected directly into target animals. The lack of product reaching the soil means that subsequent movement and impacts to groundwater via leaching, surface water via runoff, or plant uptake are not expected. This excludes the exposure pathway for soil, groundwater, and

[3] Fish as well as other non-mammalian animals produce different forms of GnRH, which reduces the risks even further.

surface water media or plant uptake. Loaded darts may occasionally fall out of or miss target animals and remain on the ground if applicators fail to locate and remove them. If this happens, a dose may leak onto the soil, but the volume released would be small. These events would be infrequent because not all animals are treated using remote delivery methods such as darts, but when they are, the chance that WS employees would miss their target is small because employees are trained and skilled in remote delivery methods.

4.1.2 Exposure Evaluation

This section qualitatively evaluates the worker exposure in direct contact pathways associated with applying GnRH formulations. It also discusses exposure through dietary consumption for hunters.

As discussed in Sections 2.4 and 3.1, GonaCon has low toxicity (Category IV) via the oral, dermal, ocular, and inhalation routes of exposure. Direct contact exposure from incidental ingestion, inhalation, and dermal contact to trained workers wearing (PPE) are minimal. In addition, the label prohibits pregnant women from handling or injecting GonaCon. Acute and chronic exposure to applicators is negligible. All GonaCon products are contained within pre-loaded syringes eliminating the possibility of exposure under labeled use. There is the potential for exposure under accidental injection into an applicator during application or during loading a jab stick or a dart. This exposure potential is reduced through proper training and handling of animals during field operations using any of the GonaCon products.

People could eat a GonaCon-treated animal harvested through hunting. The risk from this type of exposure is negligible since the label requirement for GonaCon-Deer requires all vaccinated deer to be tagged. This will notify the public that any harvested white-tailed deer have been vaccinated. Equine and prairie dogs that are vaccinated with GonaCon are not required to be tagged but are not anticipated to be harvested for human consumption. However, if somebody harvests and consumes a tagged white-tailed deer, the likelihood of exposure through ingestion is expected to be very low for humans, based on the short half-life (less than 1 hour) of GnRH in the animal relative to the harvest date, and degradation in the digestive tract prior to absorption. The half-life of synthetic GnRH was reported as 4 to 12 minutes (Warren 2006). A short half-life indicates that GnRH is rapidly metabolized in treated animals and would not be available for human exposure by the time of dietary consumption. The half-life of the conjugated GnRH is expected to be longer at the injection site when compared to GnRH, but conjugated GnRH would not be biologically active and would degrade prior to the animal being harvested. Even if a human consumed a treated game animal shortly after administration, it is unlikely that he or she would be adversely affected because the active ingredient GnRH is a protein that is digested into its component amino acids instead of absorbed intact in the digestive tract of mammals. Therefore, oral exposure to GonaCon products is not an effective exposure route for humans and animals compared to the injection route (USEPA 2009a).

It is possible that the public could encounter a dart that has fallen on the ground from a targeted animal (either the dart falls out of the animal or the applicator misses the animal with the dart); however, GonaCon would likely be contained within the syringe or have been evacuated as a result of contact.

4.2 Ecological Exposure Assessment

Aquatic exposure to GnRH is unlikely based on the method of application and short half-life once animals are injected. In a scenario where an animal is injected and subsequently dies, due to

other causes, no residues are expected that could runoff or leach into sediment or water. Secondary exposure to terrestrial nontarget wildlife should also be considered. The extremely short half-life and the lack of effects from ingestion of GnRH due to breakdown in the gut would not result in a direct or secondary exposure pathway for non-target vertebrates. The short half-life would also reduce the potential for exposure to any invertebrates that may feed on injected animals or carcasses. Loaded darts may fall out of or miss target animals and remain on the ground if applicators fail to locate and remove them. Loaded darts that fall out of an animal would not be expected to contain GnRH since it would most likely have been discharged when the dart contacted the target animal. In cases where the contents from a remote delivery are not discharged, for example if the target animal is missed, the probability of exposure would also be low since it would be unlikely that nontarget wildlife would ingest the syringe and it is likely the contents would have been evacuated when the dart strikes the ground or other object.

GonaCon has caused injection-site and lymph node reactions, which include abscesses, nodules, swelling and stiffness from the water-in-oil emulsions containing mycobacteria such as AdjuVac (Gionfriddo et al. 2011), but not in all studies (Gray et al. 2010). Curtis et al. (2008) noted granulomas in virtually all deer that were vaccinated with GnRH. Vacuoles in the lymph nodes were found in cytoplasm or among macrophages and multinucleated giant cells, which were likely mineral oil droplets from the AdjuVac. However, injection site reactions to the vaccine did not result in observed differences in an animal's range of movement or locomotor patterns. Thus, a side effect can be injection site reactions, but these did not have any noted effects on mobility. Injection site and lymph node reactions may be necessary immune system responses that precede infertility (Gionfriddo et al. 2011).

The method of drug delivery may be responsible for some injection-site reactions. More injection-site reactions were observed in remote delivery compared to syringe injection with porcine zona pellucida (PZP) (Roelle and Ransom 2009), another immunocontraceptive agent. Rifle darts caused less injuries than blowpipes. Roelle and Ransom (2009) determined that the method of delivering the drug was likely the cause of injuries since hand injection resulted in few injuries whereas dart trauma was much higher.

5 RISK CHARACTERIZATION

This section qualitatively characterizes risks associated with human health and nontarget fish and wildlife. Under the anticipated uses, GonaCon will pose minimal risks to human health as well as nontarget fish and wildlife.

GonaCon products contain only 0.032% GnRH as active ingredient, and the remaining 99.968% of the formulations are other ingredients that cause an immune response and enhance the stability of the vaccine in the treated animal. Applicators administer the vaccine by injection (hand, jab stick, or remote darting). Trained applicators must use required PPE and follow other label directions to minimize exposure and risk. GonaCon has a Toxicity Category IV for the registered uses regarding acute oral, dermal, inhalation, and ocular and skin irritation toxicities. The low potential for exposure to GonaCon during intended use combined with the use of PPE and low toxicity suggest that adverse health risk to applicators is not expected.

Risks to consumers of hunted game animals are minimal based on the exposure evaluation discussed in Section 4.1.2.

GonaCon products pose negligible risk to terrestrial and aquatic nontarget plants and animals. The lack of ecological risk is due primarily to the proposed use pattern of GonaCon, which

includes hand injection, jab stick, or remote darting, which greatly reduces the potential for any exposure to nontarget fish and wildlife either directly or from residues on soil, water, or plant material. The requirement for intramuscular injection for activation as well as the short half-life further reduces the risk to nontarget organisms. Direct risk to nontarget fish and wildlife and any impacts to habitat or prey items (indirect risk) would not be expected to occur under the proposed use pattern for GonaCon.

6 UNCERTAINTIES AND CUMULATIVE IMPACTS

The uncertainties associated with this risk evaluation arise primarily from the unpredictability associated with human behavior and can only be discussed qualitatively. Accidental release of a small amount of GonaCon from a hand application may occur when GonaCon in the preloaded syringe is not accurately delivered to the target animal or the loaded syringe becomes detached. Accidental self-injection when administering GonaCon to the target animal may also occur. However, the potential for these accidental exposures is very low with trained and experienced applicators. Accidental exposure from transferring the contents of a preloaded syringe into a jab stick hypodermic needle or a dart could occur with similar risks as accidental self-injection. These risks are expected to be very low. Finally, accidental injection could occur as a result of the dart missing its target. However, this would be negligible since WS applicators are trained to use firearms (certified) and know what their backstop is should the dart miss the intended target animal.

WS does not necessarily record the application method (hand injection, jab stick, or dart) used to treat target animals with GonaCon, just that it was treated with GonaCon. As this is unknown, and data is unavailable on the frequency with which darts fall from or miss target animals, and how often applicators are able to recover these darts, APHIS WS cannot exactly determine how much GnRH would end up in the environment. However, the amount is expected to be small because APHIS applicators make every attempt to recover all darts. In addition, the low volume of GnRH in each syringe, the expected short half-life, and the infrequent occurrence of a remote delivery miss where the dart is not collected, would equate to minimal amounts of GnRH in the environment; in all likelihood discharges in the environment would be expected to quickly result in undetectable residues. Any GnRH that would occur in the environment from this type of release would be localized to the area immediately adjacent to a compromised syringe and would be expected to quickly dissipate.

The independent potential impacts to human health and the environment of the inert ingredients in the GonaCon formulation have not been determined in toxicity studies. Previously discussed inert ingredients in the formulation occur in minor quantities. Other inert materials that occur in larger quantities have been evaluated and determined to be practically nontoxic to humans and nontarget organisms. In addition, potential exposure of humans and nontarget organisms to the formulation, due to the low volume and method of application, as discussed is low, and therefore the risk from the formulation is expected to be negligible.

Potential cumulative effects could be associated with: (1) repeated worker exposure to GonaCon or GnRH, (2) co-exposures to other pesticides within the program with respect to their toxicity, and (3) exposures to other chemicals affecting the toxicity of GnRH. Repeated exposure to GonaCon or GnRH by applicators wearing appropriate PPE is not expected. In addition, vaccinations are injected using prefilled syringes. An accidental exposure may occur if a syringe breaks and the contents spill. However, this occasional accidental exposure will not lead to accumulation in the human body. WS does not use other pesticides with the same active ingredient as GnRH, so exposure by applicators to multiple pesticides with the same mode of

action will not occur. Cumulative effects involving other chemicals that can affect the endocrine system are possible for human and ecological exposures. However, it is highly unlikely for WS personnel to be simultaneously exposed to GonaCon and these other types of agents. Similarly, the low potential for GnRH to occur in soil, water, or plants makes cumulative impacts from exposure to other endocrine modulating chemicals and GnRH highly unlikely for nontarget fish and wildlife.

7 SUMMARY

This risk assessment has determined that the human health and ecological risks from the proposed use of GonaCon are negligible. Risks to workers as well as the general population, including hunters who may harvest treated animals, are low based on the method of application, the mode of action of GnRH, and label requirements. Similarly, risks are negligible for nontarget fish and wildlife based on how GnRH is applied, its fate, and label requirements.

8 LITERATURE CITED

Bender, B. C., D. L. Bergman, K. M. Wenning, L. A. Miller, C. E. Rupprecht, D. Slate, and F. R. Jackson. 2009. No adverse effects of simultaneous vaccination with the immunocontraceptive GonaCon™ and a commercial rabies vaccine on rabies virus neutralizing antibody production in dogs. Vaccine 27:7210-7213.

Curtis, P.D., M.E. Richmond, L.A. Miller and F. W. Quimby. 2008. Physioloigical effects of gonadotropin-releasing hormone immunocontraception on white-tailed deer. Human-Wildlife Interactions. 2(1):68-79.

Eisemann, J. D., K. A. Fagerstone, and R. Jeanette. 2006. Wildlife contraceptives: a regulatory hot potato. Proc. Vert. Pest Conf. 22:63-66.

Eurofins. 2008. Acute oral toxicity – limit dose procedure in rats. Eurofins Product Safety Laboratories, Lab. Study No. 23211. 28 pp.

Fagerstone K. A., L. A. Miller, G. Killian, and C. A Yoder. 2010. Review of issues concerning the use of reproductive inhibitors, with particular emphasis on resolving human-wildlife conflicts in North America. Integr Zool 5:15–30.

Gionfriddo, J. P., A. J. Denicola, L. A. Miller, and K. A. Fagerstone. 2011. Health effects of GnRH immunocontraception of wild white-tailed deer in New Jersey. Wildl. Soc. Bull. 35:149-160.

Gray, M. E., D. S. Thain, E. Z. Cameron, and L. A. Miller. 2010. Multi-year fertility reduction in free-roaming feral horses with single-injection immunocontraceptive formulations. Wildlife Research 37:475-481.

Killian, G., and L. A. Miller. 2001. Behavioral observations and physiological implications for the white-tailed deer treated with two different immunocontraceptives. Proc. Wildl. Damage Manage. Conf. 9:283-291.

Killian, G., J. Eisemann, D. Wagner, J. Werner, D. Shaw, R. Engeman, and L. Miller. 2006. Safety and toxicity evaluation of GonaCon immunocontraceptive vaccine in white-tailed deer. Proc. Vert. Pest Conf. 22:82-87.

Merck. 2013. Gonadotropin-Releasing Hormone. Royal Society of Chemistry, The Merck Index Online. *Accessed 08/18/2022* @ https://www.rsc.org/Merck-Index/monograph/m5831/gonadotropinreleasing%20hormone?q=authorize

Miller, L. A., J. P. Gionfriddo, K. A. Fagerstone, J. C. Rhyan, and G. J. Killian. 2008. The single-shot GnRH immunocontraceptive vaccine (GonaCon) in white-tailed deer: Comparison of several GnRH preparations. Am. J. Reprod. Immunol. 60: 214-223.

National Research Council. 1983. Risk assessment in the Federal government: Managing the process. NRC Comm. Inst. Means for Assessment of Risks to Public Health. National Academies Press. 190 pp.

Powers, J. G., D. L. Baker, T. L. Davis, M.M. Conner, A. H. Lothridge, and T. M. Nett. 2011. Effects of gonadotropin-releasing hormone immunization on reproductive function and behavior in captive female Rocky Mountain elk (*Cervus elaphus nelsoni*). Biol. Reprod. 85(6):1152-1160.

Roelle, J. E., and J. I. Ransom. 2009. Injection-site reactions in wild horses (*Equus caballus*) receiving an immunocontraceptive vaccine. U.S. Geol. Survey Scientific Investigation Report 2009-5038. 15 pp.

Somoza, G. M., L. A. Miranda, P. Stobl-Mazzulla, and L.G. Guilgur. 2002. Gonadotropin-Releasing Hormone (GnRH): from fish to mammalian brains. Cell. and Mol. Neurobiol. 22(5/6): 589-609.

Tsai, P. S. 2006. Gonadotropin-releasing hormone in invertebrates: structure, function, and evolution. Gen. Comp. Endocrinol. 148:48-53.

United States Environmental Protection Agency (USEPA). 1989. Risk Assessment Guidance for Superfund: Human Health Evaluation Manual. Vol. I Part A. Interim Final. Office of Emergency and Remedial Response, USEPA, EPA/540/1-89/002. December. Wash., DC.

_____ USEPA. 2009a. Memorandum on GonaCon™ Immunocontraceptive Vaccine for Use in White-Tailed Deer. USEPA, Section 3 Registration. August 4.

_____ USEPA. 2009b. Pesticide Fact Sheet: Mammalian Gonadotropin Releasing Hormone (GnRH), New Chemical, Nonfood Use, USEPA Office of Pesticide Programs, Pesticides and Toxic Substances. Sept.

_____ USEPA. 2009c. Memorandum on Section 3 New Chemical Review for Use of GonaCon™ (Gonadotropin Releasing Hormone, GnRH) in Deer. USEPA-Environmental Effects and Fate Division. July 22.

_____ USEPA. 2022. Overview of Risk Assessment in the Pesticide Program. USEPA, Office Pesticide Programs. *Accessed 8/18/2022* @ https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program

Warren, J. 2006. Summary of metabolism data for GnRH: GonaCon™ Immunocontraceptive. Unpublished Report OPPTS 870.7485. USDA-APHIS-WS National Wildlife Research Center, Fort Collins, CO. 68p.

Warren, J., and S. Stephens. 2008. Waiver Request: GonaCon™ Water Solubility. Submitted by USDA-APHIS to USEPA Office of Pesticide Programs to meet Guideline OPPTS 830.7840 and 830.7860.

9.0 PREPARERS

9.1 APHIS-WS Methods Risk Assessment Committee

Writers for "Use of GonaCon in Wildlife Damage Management Risk Assessment":

Primary Writer: Fan Wang-Cahill
Position: USDA-APHIS-Policy and Program Development (PPD), Environmental and Risk Analysis Services (ERAS), Environmental Health Specialist, Riverdale, MD
Education: BS Biology and M.S. Hydrobiology - Jinan University, Guangzhou, China; Ph.D. Botany (Ultrastructure/Cell Biology) – Miami University

Experience: Joined APHIS in 2012, preparing human health risk assessments and providing assistance on environmental compliance. Prior experience before joining APHIS includes 18 years environmental consulting experience specializing in human health risk assessments for environmental contaminants at Superfund, Resource Conservation and Recovery Act (RCRA), and state-regulated contaminated facilities.

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.

Writer: Thomas 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-one years of service in APHIS Wildlife Services including in CO and WY 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 from wildlife. Has worked with feral and wild horses, white-tailed deer, and other species.

Editors/Contributors for "Use of GonaCon™ in Wildlife Damage Management Risk Assessment":

Editor: Nikeeya Ali
Position: USDA-APHIS-WS, Operational Support Staff, Fort Collins, Colorado, 2017 Sumer Intern
Education: BS in Communications, South Carolina State University
Experience: Three years as a staff writer for The Collegian Newspaper, one year as Editor-in-Chief. Skilled in production, video editing.

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

Editor/Contributor: Jeanette O'Hare
Position: USDA-APHIS-Wildlife Services (WS), National Wildlife Research Center (NWRC), Registration manger, Fort Collins, CO
Education: B.S. Biology – College of Saint Mary; M.A. Biology – University of Nebraska - Omaha
Experience: Thirteen years of experience working for WS NWRC providing regulatory compliance support for the development of wildlife damage management tools. Prior experience before joining APHIS includes assessing the environmental fate of pesticides and providing the agency guidance on water quality issues at the state government level, and laboratory experience in the fields of pharmacology and toxicology, and immunology.

Editor: 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: Three years of experience with APHIS 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. Sixteen 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

USDA-APHIS Wildlife Services

Reviewer: Brett Dunlap

Position: USDA-APHIS-WS – State Director, Madison, TN

Education: BS Wildlife and Fisheries Sciences – Texas A&M University; MA Biology – Sam Houston State University

Experience: Special expertise in wildlife biology and wildlife damage management. Twenty-eight years of service in APHIS-Wildlife Services in TX, WA, CA, KY, and TN conducting and managing operational programs directed at managing a variety of mammalian and avian wildlife species associated with wildlife disease, invasive species, aquatic rodent, airport/airfield, livestock protection, agricultural resources, natural resources, and urban/industrial issues.

Reviewer: Douglas Eckery, PhD

Position: USDA-APHIS-WS National Wildlife Research Center, Researcher, Fort Collins, CO

Education: BS and MS Animal Science – Brigham Young University; PhD Physiology – Colorado State University

Experience: Special expertise in reproductive biology and development of tools for fertility control of overabundant wildlife species. Current species of interest include horses, feral swine, dogs, and macropod marsupials. Joined WS NWRC in 2013 as a research physiologist and leader of fertility control project. Oversees manufacture and product support for GonaCon Immunocontraceptive Vaccine. Prior experience includes 17 years in New Zealand leading basic and applied research focused on fertility control of the brushtail possum and other marsupials.

Reviewer: Kevin J. Sullivan

Position: USDA-APHIS-WS State Director - Maryland, Delaware and District of Columbia, Annapolis, MD

Education: BS and MS Wildlife Biology – West Virginia University and Mississippi State University

Experience: Special expertise in wildlife damage management. Extensive experience with white-tailed deer management in urban environments. Principle Investigator for the Pivotal Study for product registration of GonaCon Immunocontraceptive Vaccine (2005).

USDA-APHIS Veterinary Services

Reviewer: Albert Kane, DVM

Position: USDA-APHIS-VS Surveillance Preparedness and Response Services, Senior Staff Veterinarian and Epidemiologist, Fort Collins, CO

Education: BS Biology – Notre Dame, South Bend, IN; DVM - Virginia-Maryland Regional College Veterinary Medicine, Blacksburg, VA; MPVM & PhD - University California, Davis
Experience: Special expertise in veterinary medicine, wild equids, and horse roundups with the APHIS/Bureau of Land Management Horse and Burro Partnership. Have assisted with the use of GonaCon.

9.3 External Reviewers

U.S. Department of Interior- Geological Survey

Reviewer: James (Butch) Roelle
Position: USDI-U.S. Geological Survey (emeritus) Wildlife Biologist, Fort Collins, CO
Education: BS Biology – Yale University; MS Wildlife Ecology – University of Wisconsin; Ph.D. Wildlife Biology – Colorado State University
Experience: 40 years of experience as a wildlife biologist in various federal agencies. Special expertise in feral horse population dynamics and efficacy of immunocontraceptive vaccines.

9.4 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 GonaCon in Wildlife Damage Management" peer reviewed. WS worked with the Association of Fish and Wildlife Agencies to have experts review the documents.

9.4.1 Peer Reviewers' Agencies Selected by the Association of Fish and Wildlife Agencies

California Department of Fish and Wildlife
Montana Fish, Wildlife and Parks
Nevada Department of Wildlife
Ohio Division of Wildlife
Texas Parks and Wildlife Department

9.4.2 Comments

Comments regarding concerns with the risk assessment and a response:

1. **Comment:** It would be appropriate to evaluate the risks of the delivery methods, in this case dart gun, blow gun, jab stick, and syringe hand injection because they have the potential to cause physical trauma in the target animal, though probably low.

   Response: The difference in physical impacts as a result of the delivery method are discussed in Section 2.1 Chemical Description and Product Use. Additionally, these tools are analyzed in other risk assessments in more detail where appropriate

2. **Comment:** It is not clear in the document whether or not the two GonaCon products (USEPA Reg. No. 56228-40 and USEPA Reg. No. 56228-41) are identical?

   Response: Added that they have the same inert ingredients (99.68%), along with the 0.032% GnRH just following the labels.

3. **Comment:** What proportion of animals would be expected to develop injection site and lymph node reactions?

Response: Curtis et al. (2008) noted granulomas at the injection site of most white-tailed deer that were injected with GnRH. The risk assessment was updated to include this information in Section 4.2. It is not uncommon for vaccines to cause granulomas in many species including other wildlife, pets, and humans.

4. **Comment:** The recommended needle length is provided for GonaCon-Equine but not for GonaCon-Deer.

   Response: The risk assessment was updated to discuss the recommended needle length for GonaCon - Deer.

5. **Comment:** Birth control for wildlife population is very popular with the general public.

   Response: We agree.

6. **Comment:** Although the likelihood of exposure through ingestion of game animals is expected to be low based on the short half-life (less than 1 hour) of GnRH in the animal relative to the harvest date, it's worth keeping in mind that in some states, road-killed animals can be salvaged for consumption at any time of year. In such areas, should treated animals that could be consumed by humans be identified in some manner (e.g., ear tag).

   Response: The GonaCon-Deer label under the Use Restriction section states that all vaccinated deer must be tagged to identify vaccinated deer. The risks to the public from consuming GonaCon treated white-tailed deer is very low and the risk decrease further with the use or ear tags to identify vaccinated deer.

7. **Comment:** It seems it would be prudent, if at all possible, to record data such as route of administration, missed shots, how many darts were left in the field, how many darts failed to fire (how many animals were treated). Data such as number of times a dart wasn't recovered, number of accidental contact with GonaCon, etc. would be valuable to include.

   Response: Some of this type of data may be collected when WS is using GonaCon - Equine, GonaCon - Deer, or GonaCon - Prairie Dogs. Accidental exposures would be recorded and reported to USEPA under FIFRA 6(a)2 adverse effect reporting.

8. **Comment:** The document has no data to back up many of the risk claims, especially relating to personnel administering GonaCon, like other risk assessment documents such as "*The Use of Nets in Wildlife Damage Management*."

   Response: WS has not used GonaCon operationally for white-tailed deer and, therefore, does not have data related to use.

9. **Comment:** Some clarification on page 2 as to why hand-injection is the only option for white-tailed deer would be helpful to discern its risk differences over equine GonaCon.

   Response: Since the peer review of this risk assessment APHIS has received approval from USEPA to administer GonaCon - Deer using remote darting when administering the second dose. The risk assessment has been updated to reflect the most current use pattern for GonaCon - Deer.

10. **Comment:** Seems to be a discrepancy regarding word usage for locating/retrieving missed/fallen out darts. On page 3 in the fourth bullet point it says, "can make note of the location" leading one to believe it is an option to the applicator by using the word "can". But on page 6 it says, "label requires that applicators make every attempt to recover". Possibly noting internal policy related to this would also be beneficial as I assume it is covered in the Use of Immobilization Risk Assessment.

Response: The fourth bullet on page 3 was updated to reflect current label language. Applicators using remote darting when injecting GonaCon-Deer or GonaCon-Equine must make every attempt to recover lost or fallen darts. In situations that prevent searching for lost or fallen darts such as inclement weather or darkness, the labels state that applicators may note the location and continue searching later.

11. **Comment:** On page 3 it states, "labels specify that applicators are not to use these products near humans, domestic animals, or pets." It would then seem prudent to include some discussion on the use of GonaCon, especially related to white-tailed deer, in urban environments

    Response: This was a mistake and changed to read that the product is to be kept away from humans, domestic animals and pets, which primarily refers to storage and use. People involved in the use of the product, the applicators, also need to ensure that while they are using the product, others are not allowed access to the product. With the use of remote darts, applicators are to make every attempt to retrieve darts that miss the target. The risk assessment was updated to reflect current label language that states that all of the GonaCon products should be kept away from humans, domestic animals, or pets.

12. **Comment:** Section 2.4 notes, "With elk, no male precopulatory behavior…" Is this the same for white-tailed deer?

    Response: This type of behavior has not been noted in white-tailed deer in research.

13. **Comment:** In Sections 2.4, 4.1.2, and 6, it should be noted the potential for dart failure (ex. accidental discharge of a dart, dart body integrity failure, etc.) as a means for potential exposure.

    Response: The risk assessment exposure evaluation section was updated to include failed darts as a pathway of exposure.

14. **Comment:** Regarding human exposure, I didn't see any mention as to whether, both short-term or long-term, exposure to humans administering GonaCon can have any sterility effects on them. Might be helpful to mention that as a risk.

    Response: The human health exposure section was updated to address whether short- or long-term exposure can result in sterility effects. In general, the potential for exposure and subsequent risk is negligible under normal use. Exposure would only occur under accidental injection of GonaCon by an applicator during use.

Comments received not requiring a response.

1. **Comment:** I have reviewed the risk assessment and see no reason to discontinue or curtail its use in anyway.

2. **Comment:** I have reviewed the risk assessment and believe the methods described are adequate to achieve their purposes.

3. **Comment:** Overall this document is fairly well written regarding GonaCon.

Peer reviewers provided a few editorial comments on the manuscript. These were appreciated and incorporated into the final document.