

When, Where and for What Wildlife Species Will Contraception Be a Useful Management Approach?

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ABSTRACT: Despite the fact that many wildlife species have become overabundant both in North America and other parts of the world, the public is increasingly unwilling to manage wildlife populations with traditional techniques such as trapping or lethal methods. A growing segment of the public is urging the use of contraceptives to reduce populations of overabundant free-ranging wildlife. In spite of public pressure, the development and use of wildlife fertility control techniques has been slow to occur, partially because of the difficulty in developing efficient, cost-effective methods, and partially because of misconceptions about these potential techniques.

The regulatory authority for contraceptives has recently been moved from the Food and Drug Administration (FDA) to the Environmental Protection Agency (EPA); the extensive EPA registration process is both rigorous and costly. Only one wildlife contraceptive is currently registered and available: the National Wildlife Research Center (NWRC) worked to develop a product for reducing the hatchability of Canada goose eggs in cooperation with Innolytics, LLC, who holds the registration for OvoControl® G. Development is continuing for additional experimental products. Another product developed by the NWRC, the single-shot GonaCon™ Immunocontraceptive Vaccine is poised to begin the registration process. A third product, DiazaCon™, will be soon tested for field efficacy and should begin the registration process within the year. No single wildlife contraceptive technique would be applicable for use in all wildlife species and for all management situations for a particular species. Differences in animal physiology and behavior, as well as differences in the ecology of the damage, affect which contraceptives will be most effective. Therefore, contraceptives with different modes of action will need to be developed for different species and uses. Wildlife contraceptives will not replace other management tools and will probably have a limited use, primarily in urban/suburban areas. In most species, wildlife contraceptives will not rapidly reduce populations. Populations of short-lived species such as rodents could be rapidly reduced with contraceptives; however, in long-lived species such as deer and horses, it would take years to reduce populations with fertility control alone, and damage caused by those species will continue to occur. This manuscript will discuss what contraceptive techniques are being developed by the USDA Wildlife Services NWRC, and when, where, and for what species they may be applicable.

KEY WORDS: contraception, fertility control, immunocontraceptive, wildlife population control

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INTRODUCTION

For most of the last century, federal and state wildlife conservation agencies in the United States have focused on conserving or increasing populations of many species of wildlife. Although wildlife abundance is desirable in most cases, some populations may reach undesirably high levels and cause either ecological damage or human-wildlife conflicts. Conflicts can include damage to agricultural commodities through depredations of livestock, crops, or forest resources. Buildings and other structures and properties can be damaged by nesting, burrowing, feeding, or other wildlife activities. Overabundant wildlife also can cause human health and safety issues, including wildlife-aircraft strikes and deer-vehicle collisions. There is increasing concern about the potential for wildlife disease transmission to humans and livestock (e.g., Lyme disease, tuberculosis, brucellosis, pseudorabies, West Nile virus, chronic wasting disease, avian influenza). Many of the problems associated with overabundant wildlife occur in areas recently converted by suburban development or in parks or preserves. In many of these areas, regulation of some wildlife populations through conventional means, such as hunting, translocation, culling, or habitat modification, has not

been effective or feasible or is precluded because of human opposition. A growing interest in nonlethal methods for population control of nuisance or damaging wildlife species has fostered research in wildlife contraception. Because fertility control acts by reducing birth rates, rather than by increasing mortality rates, it is perceived by the public as being more humane and morally acceptable than conventional population control methods.

The changing cultural values and increasing urbanization of the United States are curtailing traditional wildlife management tools used to effectively manage conflicts between human and wildlife populations. Because of this trend, the USDA Wildlife Services National Wildlife Research Center (NWRC) began developing wildlife contraceptives in 1991. Since that time, NWRC scientists have steadily worked towards developing and registering contraceptive products that are practical to use, safe for the treated animal, and present little risk to humans, nontarget animals, and the environment. Wildlife contraceptives will not replace other management tools. Contraceptives will probably be used primarily in urban/suburban areas or areas where alternative wildlife management techniques, such as

hunting and trapping, cannot be employed. This manuscript describes the products being developed by the NWRC and discusses the biological, economic, and public policy factors that may affect their future use.

CONTRACEPTIVE PRODUCTS UNDER DEVELOPMENT FOR WILDLIFE

No single wildlife contraceptive technique would be applicable for use in all wildlife species or for all management situations. Differences in animal physiology and behavior, as well as differences in the ecology of the damage (type of damage done, access to target species, nontarget species in the area), affect which contraceptives will be most effective. Therefore, contraceptives with different modes of action and application methods will need to be developed for different species and uses.

This manuscript focuses only on contraceptive products for which research is being conducted at the Wildlife Services' National Wildlife Research Center. The regulatory authority for wildlife contraceptives has recently switched from the Food and Drug Administration (FDA) to the Environmental Protection Agency (EPA) (Eisemann *et al.* 2006). One fertility control agent for wildlife (OvoControl® G) was approved by the EPA in the fall of 2005. An injectable immunocontraceptive vaccine, Gonadotropin-Releasing Hormone (GnRH), and the orally delivered contraceptive DiazaCon™ are being tested prior to being submitted for registration by the EPA. Another injectable immunocontraceptive vaccine, Porcine Zona Pellucida (PZP), may be considered for registration at a later date.

Avian Contraceptives

Interfering with egg laying or the hatchability of the egg can reduce reproductive capacity in birds. Egg addling by shaking or oiling the eggs in the nest is effective at reducing egg hatchability (Pochop *et al.* 1998). The EPA allows egg oiling with corn oil under a Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) 25b exemption for natural products, and egg oiling is currently being used to reduce reproduction in Canada geese (*Branta canadensis*) and gulls (*Larus* spp.). However, this method is labor intensive and probably useful only in small areas.

Nicarbazin

Nicarbazin (NCZ) is an anticoccidial drug routinely used in the poultry industry to prevent coccidiosis in broiler chickens (*Gallus domesticus*). When fed to laying hens, nicarbazin either reduces egg hatchability or causes cessation of egg laying (Jones *et al.* 1990, Hughes *et al.* 1991). Exploiting this side effect, the National Wildlife Research Center (in cooperation with Innolytics, LLC) began extensive research on NCZ as a potential contraceptive for Canada geese in the late 1990s (Bynum *et al.* 2005). An initial study in coturnix quail verified that NCZ caused reduction in hatchability. Comparative studies in chickens, mallards, and Canada geese showed that a higher dose of NCZ would be required in geese than in the other species to achieve a reduction in hatchability of eggs. Studies in both penned and wild

Canada geese identified a palatable bait, showed that reduction in hatchability was possible, and showed that the ideal dose rate allowed the female bird to lay eggs and sit on them, but prevented hatching. Nicarbazin (OvoControl® G) field studies have reduced the percentage of eggs hatching in a treated population by about 50% (Yoder *et al.* In Press, Bynum *et al.* 2007); this is probably an underestimate of efficacy because when consumed at high rates, geese do not even lay eggs. Advantages of NCZ are that it is specific to egg laying avian species, it is cleared from the body within 48 to 72 hours, and the infertility effect is reversible in the same time frame. A disadvantage of the compound is that it has to be fed at least every other day prior to and during egg laying. OvoControl® G 2500 ppm nicarbazin bait was registered with the EPA in fall 2005 as a reproductive inhibitor for managing urban resident Canada geese and is commercially available in the U.S. through Innolytics, LLC.

DiazaCon™

DiazaCon™ (Ornitrol) is a cholesterol mimic that has a chemical structure similar to cholesterol (Miller and Fagerstone 2000, Yoder *et al.* 2005). It inhibits formation of pregnenolone (the parent compound of all steroid hormones), preventing formation of testosterone, progesterone, and estradiol. DiazaCon™ persists in the body, so its reproductive inhibition effects can last up to several months. It was registered in the late 1960s by the EPA as the oral pigeon (*Columba livia*) reproductive inhibitor Ornitrol, but the registration was cancelled in 1993. Although the drug was effective in reducing egg laying and egg hatchability (Woulfe 1968), the pigeon is a year-around breeder, and long-term use of the compound became expensive. Also this product may have undesirable health effects on birds (Lofts *et al.* 1968) when given for a long period of time at high levels, because cholesterol is necessary for body functions in addition to production of reproductive hormones. However, when fed for shorter periods (e.g., to seasonal breeding species), health effects may not be a concern. In recent tests, Yoder *et al.* (2004) found DiazaCon™ effective in reducing egg laying and egg hatchability up to 4 months in coturnix quail (*Coturnix coturnix*) after feeding it for 12-14 days. This compound is currently being tested in a field effectiveness trial by the NWRC for monk parakeet (*Myiopsitta monachus*) management in Florida, where the birds cause power outages by nesting on power stations and power poles. DiazaCon™ is not species specific, and it potentially could be effective in mammalian as well as avian species. Among the advantages of DiazaCon™ is that it does not need to be fed on a daily basis; after several feedings it maintains its effectiveness for a few months. The disadvantage is that nontarget animals that eat multiple doses could be contracepted for a few months.

Immunocontraception Vaccines

The development of immunocontraceptive vaccines has been a high priority of the NWRC during the last decade. These vaccines use the animal's immune system to produce antibodies against gamete proteins, reproductive

hormones, and other proteins essential for reproduction. The antibodies interfere with the activity of the reproductive agents (Talwar and Gaur 1987) and the vaccines can be effective for 1 to 4 years or longer (Turner and Kirkpatrick 1991, Miller *et al.* 1999).

Zona Pellucida Vaccines

The zona pellucida (ZP) is a glycoprotein layer located on the outer surface of the mammalian egg. Antibodies to ZP result in infertility either by blocking sperm from penetrating the ZP layer or by interfering with egg maturation (Dunbar and Schwoebel 1988); consequently, a ZP immunocontraceptive vaccine is only effective in females. PZP has been used to produce immunocontraception in numerous species, including dogs (Mahi-Brown *et al.* 1985), baboons (Dunbar 1989), coyotes (*Canis latrans*; Miller 1995, DeLiberto *et al.* 1998), burros (*Equus asinus*; Turner *et al.* 1996), wild horses (*Equus caballus*; Kirkpatrick *et al.* 1990, Garrott *et al.* 1992, Killian *et al.* 2004), and white-tailed deer (*Odocoileus virginianus*; Turner *et al.* 1992, 1997, Miller 2002, Miller *et al.* 1999, 2001). PZP is not effective in cats (*Felis catus*; Jewgenow *et al.* 2000) or rodents (Drell *et al.* 1984). Injecting with an initial and a booster dose of PZP vaccine has caused infertility in deer and horses for several years (Miller *et al.* 1999). Miller *et al.* (2000) conducted a long-term study on the effect of PZP on white-tailed deer that demonstrated an 89% reduction in fawning during the first 3 years (during which deer were given a boost if antibody titers dropped) and a 72% reduction over 7 years.

The porcine zona pellucida (PZP) vaccine includes both the PZP protein from the pig ovary and an adjuvant (an additive to increase the immune response). A vaccine (SpayVac[®]) recently developed by ImmunoVaccine Technologies (Halifax, Nova Scotia) and injected with AdjuVac[™] (an adjuvant developed at the NWRC) as a single-shot has been effective in white-tailed deer for at least 5 years in some animals. The single-shot is a major breakthrough because animals only need to be injected one time to achieve multiple years of infertility.

The advantages of PZP are that, because PZP is a protein broken down in the gastrointestinal tract when consumed, it does not enter the food chain. Also, its effects are normally reversible when the antibody level declines. It is not species specific and is effective in reducing fertility in most female mammals tested. Disadvantages are that PZP must be applied as an injection. Also, the PZP vaccine results in multi-estrus in female deer, which could result in late season births if antibody titers drop below a critical threshold.

Gonadotropin Releasing Hormone (GnRH)

Gonadotrophin Releasing Hormone (GnRH) immunocontraceptive vaccine inhibits the reproductive activity of both sexes by causing development of antibodies blocking GnRH. The antibodies reduce the circulating level of biologically active GnRH, thereby reducing the release of other reproductive hormones, causing atrophy of the gonads (Miller *et al.* 1997). Therefore, a GnRH immunocontraceptive vaccine is effective in both sexes. Both avian and mammalian GnRH have been identified

(Sad *et al.* 1993, Meloen *et al.* 1994). GnRH contraceptive vaccines have been evaluated as immunocastration agents in pets (Ladd *et al.* 1994), cattle (Robertson 1982, Adams and Adams 1992), horses (Rabb *et al.* 1990), sheep (Schanbacher 1982), and swine (Meloen *et al.* 1994). Miller *et al.* (1997) immunized Norway rats (*Rattus norvegicus*) with GnRH and created 100% infertility in both males and females. Miller *et al.* (2000) completed a long-term study on the effect of GnRH on white-tailed deer that demonstrated an 88% reduction in fawning during the first 2 years and a 74% reduction over 5 years (deer were injected with GnRH yearly for the first 2 years). The NWRC GnRH immunocontraceptive vaccine has been shown to be effective in cervids, cats, dogs (*Canis familiaris*), domestic and feral pigs (*Sus scrofa*), bison (*Bison bison*), and wild horses.

GnRH is not species or sex specific, and mammalian GnRH is effective in reducing fertility in most mammals, including rodents. The contraceptive effects of a single shot vaccine last 1 to 2 years without boosting and are reversible over time as antibody levels decline, although multiple injections may cause permanent sterility (Molenaar *et al.* 1993). GnRH affects social behavior by reducing the sexual activity of both sexes. It is presently available only in injectable form but a single-shot vaccine (GonaCon[™]) has recently been developed by the NWRC that contains the GnRH protein and a new adjuvant (AdjuVac[™]) developed by the NWRC. The NWRC is currently conducting two field effectiveness studies with white-tailed deer. Results will be submitted to the EPA, along with other data requirements, to obtain a registration for use of GonaCon[™] in managing cervid populations in areas where other management techniques, such as hunting, cannot be used or are socially unacceptable. A registration for GonaCon[™] could be granted to APHIS as early as fall 2007.

Several studies have compared the contraceptive and behavioral effects of PZP and GnRH immunocontraceptive vaccines on white-tailed deer (Killian and Miller 2000, Miller and Killian 2000, and Curtis *et al.* 2001). All studies found that PZP-treated females had a prolonged breeding season and repeatedly returned to estrus. Curtis *et al.* (2002) compared the contraceptive effects of PZP and GnRH in a 3-year study with white-tailed deer at the Seneca Army Depot, New York. One year after vaccination with both a prime and a boost, 28% of the PZP-treated females produced 0.10-0.11 fawns per female and 29% of the GnRH-treated females produced 0.13-0.22 fawns per female. This is compared to control females that produced 1.22-1.38 fawns per female. GnRH-treated females had fewer observed estrous cycles (0.06) then did either the control (0.22) or PZP-treated females (0.36). In a separate study, the average number of breeding days each year for the control does was 45, whereas some PZP-treated does continued breeding for more than 150 days (Killian and Miller 2000). The average number of breeding days for the GnRH-treated does was comparable to that observed for the control group.

Miller and Killian (2000) found that PZP-treated deer returned to estrus up to 7 times, and the PZP contraceptive effect lasted slightly longer than that of the

GnRH vaccine. In both vaccines, the contraceptive effect was reversible and directly related to the antibody titer. GnRH-immunized bucks had no interest in sexual activity when paired with control females. Depending on the immunization schedule, antlers of GnRH-treated bucks either dropped early or remained in velvet.

BIOLOGICAL AND ECONOMICAL FEASIBILITY OF CONTRACEPTIVES

Whether fertility control is biologically feasible or economically advantageous when compared to lethal control for a particular species and population depends on a number of parameters (Curtis *et al.* 1997, Nielsen *et al.* 1997), including whether the population is “open” or “closed”, population numbers, sex ratios, age structure, and estimated rate of increase and mortality of the concerned species. A number of researchers have produced various models to assess the effectiveness of fertility control. Dolbeer (1998) used population models to compare the relative efficiency (i.e., % decline in population size relative to number of animals sterilized or removed) of reproductive control and lethal control in managing wildlife populations. He predicted relative efficiencies of lethal and reproductive control for various wildlife species based on adult survival rate and age at which animals reproduce. He found that for species in which females reproduce their first year and where few adults survive, reproductive control may be an effective control technique. When females first reproduce at 2 or more years and adult survival rates are high, lethal control would be more efficient than reproductive control in reducing populations (Dolbeer 1998).

In general, this predicts that reproductive control will be most effective in managing smaller wildlife species, such as rats (*Rattus* spp.) and cowbirds (*Moluthrus ater*), with high reproductive rates (i.e., reproducing at early age, large litter or clutch size) and low survival rates. Knipling and McGuire’s (1972) theoretical model demonstrated that if 70% of rats could be sterilized for 3 generations (1 year), the entire population would be eliminated. Conversely, reproductive control will be less efficient than lethal control in managing populations for larger species such as deer (*Odocoileus* spp.), coyotes, Canada geese, and gulls that do not typically reproduce until 2-4 years of age and have smaller litter or clutch sizes than most rodents and small birds.

A population model for Canada geese shows that a combination of removal and contraception may prove to be more effective than contraception alone. Canada geese have become a significant problem in many urban areas. During the 1960s, Canada geese were introduced into many urban areas in the U.S. to augment migratory populations that were thought to be in decline. From 1966 to 2001, Canada goose populations in these areas experienced a high rate of growth (Sauer *et al.* 2005), and nonmigratory populations have become frequent because of year-round food sources and lack of predators (Forbes 1993, Ankney 1996, Gosser and Conover 1999). Urban geese can contaminate water supplies and cause over-fertilization of lakes (Conover and Chasko 1985, Fairaizl 1992, Ettl 1993). In most urban areas, neither hunting nor translocation are allowed; egg oiling and addling can be

effective in reducing number of goslings produced, but it is frequently difficult to find goose nests. Contraception by an oral compound such as NCZ (OvoControl® G) may provide an alternative to maintaining goose populations at levels acceptable to the general public. Yoder *et al.* (In Press) modeled population growth based on a 50% reduction in eggs hatched and estimated that without culling, a population of 140 birds would increase to about 3,400 geese within 10 years without contraception versus a population of about 1,200 geese with contraception. Yoder *et al.* (In Press) therefore recommended that culling programs be implemented once every 3 years and contraception be used yearly to maintain populations at a given size.

In deer species, most of which have a low reproductive rate and a life span from 10 to 12 years, fertility control alone will probably not be effective in reducing the population. Male contraception is considered inefficient and impractical (Warren 2000, Killian *et al.* 2005). With an estimated annual mortality rate of 20% for road kills and other losses, a deer herd where females were treated only with contraceptives would remain at a high population level for several years after initiation of a contraception program. From a practical standpoint, it would be better to reduce the deer herd to a desired number by some other management technique, then apply fertility control to stabilize herd growth (Nielsen *et al.* 1997). The proportion of deer that would have to be treated with fertility control agents would depend on average reproductive rates and the female age structure of the herd.

Several biologists have modeled contraception use and generally agree that managing large free-ranging populations of ungulates with a contraceptive that is only effective for one year is impractical (Garrott 1991, 1995; McCullough 1996; Curtis *et al.* 1998; Warren *et al.* 1992, Warren 2000). Hobbs’ (2003) models showed that treating 75% of female fallow deer (*Dama dama*) every 4 years with a contraceptive that was only effective for one year actually allowed a population to increase. R. Barrett’s model (NPS 2004) calculated that up to 99% of fallow deer does had to be treated on a yearly basis with a contraceptive effective for one year to reduce the population rapidly, and the last doe would not die of old age for about 30 years. With the advent of single-shot immunocontraceptives whose effects last for multiple years, managing ungulate populations with contraception will be more feasible. Modeling shows that maintaining deer populations at a desired level can be accomplished with long-lasting contraceptives (lasting 4 years), but reducing populations will be difficult without some lethal control. For example, to reduce fallow deer numbers within 15 years from 860 to 350 at Point Reyes National Seashore, about 75% of does would require initial contraceptive treatment, and 75% of their female fawns would also require treatment, levels that would be very difficult to achieve (Hobbs 2003).

Hobbs (2003) modeled the use of a combination of culling and contraception to reduce herds of non-native axis (*Axis axis*) and fallow deer at the Point Reyes National Seashore and Golden Gate National Recreation Area lands administered by the National Park Service

(NPS 2004). Non-native deer displace and compete with tule elk (*Cervus nannodes*) and black-tailed deer (*Odocoileus columbianus*), potentially transmit disease to these native ungulates, and cause negative impacts to riparian habitat and to the native wildlife dependent on this habitat. Because The National Park Service is mandated to control exotic species “up to and including eradication” to return parks to their natural condition and preserve them for future generations, an Environmental Impact Statement (NPS 2004) examined alternatives for eradicating these non-native deer. Simulations by both R. Barrett (NPS 2004) and N. T. Hobbs (Hobbs 2003, NPS 2004) showed that attempting to eradicate the population using fertility control alone was futile. Even lifetime-effect sterilant treatment of 75% of all fertile females, along with treating missed females every 4 years, could not achieve eradication in 15 years (Hobbs 2003). Modeling showed that culling up to 250-300 deer per year would likely result in eradication of both axis and fallow deer by 2020, but the NPS determined that culling alone was not an acceptable method of management. Therefore, the preferred alternative (NPS 2004) was eradication of non-native deer by 2020 using a combination of lethal removal and long-acting contraceptives. Hobbs (2003) modeled a scenario in which a long-acting contraceptive was combined with lethal removal to extirpate the 860 non-native deer populations in the Seashore. When 25% of the fertile does were treated with a 4-year contraceptive, 567 would need to be culled and 129 treated with contraceptives over a 15-year span (653 would need to be culled during this time frame if no fertility control were used). If 75% of fertile does were treated with contraceptives, only 374 deer would require culling, but 917 would require contraceptive treatment.

Contraception has been proposed as a technique to decrease the spread and prevalence of wildlife diseases. Some recent models have predicted that a combination of culling and fertility control would be more effective than vaccination at suppressing rabies in situations involving a focal outbreak (Barlow 1996, Smith and Cheeseman 2002, Smith and Wilkinson 2003, Sterner and Smith 2006), without killing diseased animals. Smith and Wilkinson (2003) showed that culling would be most effective in eradicating fox rabies during a single campaign when fox densities were high, and that vaccination would be least effective. If the rabies vaccine contained a fertility control agent (V+F), then effectiveness would be intermediate between culling and vaccination (Figure 1) (Sterner and Smith 2006). The model in Figure 1 also shows that the effectiveness of vaccination declines as fox density increases, and vaccination plus contraception becomes more effective than vaccination alone. The difference between vaccination and vaccination plus contraception is the reduction of new susceptible young animals with the vaccination and contraception. The difference between culling and vaccination and contraception is the removal of infected animals.

Other researchers have proposed preventing pregnancy using a GnRH immunocontraceptive vaccine to decrease transmission of brucellosis in bison (Rhyan *et al.*

2002, Miller *et al.* 2004). The bacterial disease, caused by *Brucella abortus*, is transmitted among animals primarily through contact with infected aborted fetuses and placental material. Transmission of the disease is therefore dependent on the occurrence of pregnancy and exposure to abortion or calving in infected animals. Rhyan *et al.* (2002) suggested sterilization as a disease-management strategy that could be used in *Brucella*-infected bison to reduce the possibility of transmission to other animals; animals would be tested, treated with a disease vaccine, and contracepted. The temporary period of infertility in the female bison through use of a contraceptive vaccine may allow time for *Brucella* infection to clear and may prevent the need for culling of infected females. Limiting fertility of feral swine may also work to reduce transmission of diseases such as brucellosis and pseudorabies (Killian *et al.* 2006b).

In addition to being biologically feasible, infertility agents will need to be economically practical to use. Economic practicality involves costs for research, development, and registration of the contraceptive, as well as costs for treatment of wildlife, including labor and equipment. The cost of development and registration can be extensive. The length of time required to conduct the research to develop a new contraceptive is probably 5 to 10 years. For every 10 chemicals tested as potential contraceptives, experience at the NWRC suggests that only one will be effective. The registration process can also be expensive, with data requirements including product chemistry, toxicology, environmental fate and effects, residue chemistry, product performance, and worker protection studies (Eisemann *et al.* 2006). Costs for registration can exceed \$1 million. The NWRC has or is entering into research partnerships with government and private organizations in the U.S., Great Britain, Australia, India, and New Zealand to provide increased personnel and research funding to assist in contraceptive development.

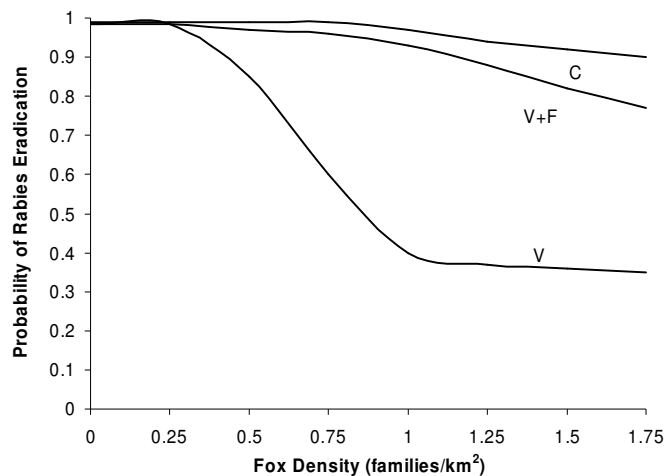


Figure 1. A simulated comparison of culling (C), vaccination (V), and vaccination plus fertility control (V+F) for a single campaign that affects 80% of the host population (Sterner and Smith 2006; redrawn from Smith and Wilkinson 2003).

Development of single-shot GnRH and PZP immunocontraception vaccines has made their use more economical and logistically feasible than when multiple shots of vaccines were required. It is estimated that the GnRH vaccine itself will be inexpensive. Therefore, the main cost of using GonaCon™ will be associated with the time and money required to capture and vaccinate deer if individual marking is desired. Costs to capture and inject deer have been estimated to be \$250 or more for each deer marked (Curtis *et al.* 1997). If marking individual deer is not required, costs for remote injection by dart gun would be less.

Oral delivery would be a practical, cost-effective means to deliver contraceptive vaccines to some populations of free-roaming animals (Miller 1997). However, oral delivery of vaccines is a difficult technology and no oral vaccines are currently available.

Chemical contraceptives such as DiazaCon™ and OvoControl® G can be delivered orally in baits but it can be difficult to get adequate bait consumption. OvoControl® G must be fed to Canada geese daily for the entire egg laying period. DiazaCon™ also must be fed to animals several times over a 10-day to 2-week period. To reduce populations, these compounds will have to be used over multiple years.

HEALTH AND SAFETY ISSUES

Wildlife contraceptives must be shown to be safe for: 1) target animals, 2) nontarget animals, and 3) humans. Fagerstone *et al.* (2002) summarized potential health effects of contraceptive agents. Additional health data to target animals have been recently gathered for the immunocontraceptive vaccines PZP and GnRH. Long-term studies involving PZP and GnRH on white-tailed deer (Miller *et al.* 1999, 2000) showed no adverse effects on the animals' health.

GnRH vaccine treatments of white-tailed deer led to reduced plasma progesterone concentrations, altered estrus behavior, contraception, and reduced fawning rates (Miller *et al.* 2000), all of which were expected. Infertility lasted up to 2 years without a booster injection and necropsies of recently vaccinated deer showed normal ovaries. To further evaluate toxicity and safety of the GnRH contraceptive vaccine, a 20-week study was conducted with white-tailed deer where does were given either a single injection of saline, a single injection of GonaCon™ or 3 injections of GonaCon™ at 2-week intervals per dose. Blood samples were taken at intervals during the study and all deer were euthanized and evaluated at necropsy at 20 weeks. Aside from granulomata formation at the injection site, there were no significant contraindications or toxic effects associated with GonaCon™ (Killian *et al.* 2006a).

Data on health and behavioral effects related to PZP (Fagerstone *et al.* 2002) are available from limited field applications (Turner *et al.* 1997, Warren *et al.* 1997, McShea *et al.* 1997), and from long-term studies (Miller *et al.* 1999, 2001). A 9-year study of PZP-injected deer at Pennsylvania State University showed deer vaccinated 2 or more times returned to fertility within 4 to 7 years after vaccinations ceased (Miller *et al.* 2000). A long-term blood chemistry survey study on PZP-immunized deer

found no statistically significant health changes in vaccinated deer (Miller *et al.* 2001). However, the PZP vaccine increased the number of times does came into estrus, prolonging the breeding season and potentially resulting in late summer or autumn births (Killian and Miller 2000, Miller and Killian 2000).

Nicarbazine has been used by the poultry industry in numerous countries for 45 years. It has no effects in mammal species and is safe for both target and nontarget bird species, even when administered at much higher doses than needed to cause the contraceptive effect (WS 2004). DiazaCon™, as a cholesterol inhibitor, could potentially cause health effects in either target or nontarget species if fed for extended periods (Sachs and Wolfmann 1965). However, when fed only a few times over a 2-week period to stop reproduction in seasonal breeding species, no adverse effects would be anticipated.

In addition to being safe for target animals, contraceptives should not cause adverse effects on nontarget animals. None of the contraceptives discussed previously are species specific, so the delivery systems must limit exposure to nontarget species. Delivery by hand injection or darting, such as with GnRH or PZP vaccines, requires direct contact with animals and will not affect nontarget species. Oral bait delivery systems allow treatment of larger, free-roaming populations at lower cost, but there is increased risk of unintentional treatment of nontarget species. Therefore, the delivery system for contraceptive baits should be designed to exclude most nontargets. For example, OvoControl® G bait was designed to be palatable to geese but too large for smaller nontarget species. Baiting occurs in the morning to maximize consumption by geese and minimize the amount of bait remaining on the ground. In addition, geese nest earlier in the season than most other urban species that would consume bait, reducing the chance of nontarget reproductive effects. In some instances, low levels of reproductive effects on nontarget species may be an acceptable risk, much as a low level of nontarget risk is inherent in use of most pesticides.

Contraceptives used on huntable species of wildlife pose an additional safety consideration—safety to humans who may consume them. This risk is addressed by regulatory requirements for registration of pesticides. For compounds that accumulate in body tissue and could have secondary effects, such as some of the steroid contraceptives, FDA or EPA approval would not be granted for use in food animals such as deer and Canada geese without adequate data on chemical withdrawal times. The compounds being considered by APHIS for registration have low risk to humans or other secondary consumers. Immunocontraceptive vaccines contain proteins; these proteins and the antibodies they produce are broken down to harmless amino acids in the digestive tract. Nicarbazine is already authorized by the FDA for use in broiler chickens, so OvoControl® G used in Canada geese does not pose a risk to humans. The other compound being tested in birds, DiazaCon™, was initially designed to be given to humans to lower serum cholesterol levels, and therefore should present minimal hazard for human consumption at levels that would be potentially present in animal tissues.

Most of the infertility agents being developed have temporary effects. However, there is a large variation in the length of time that they are effective. OvoControl® G must be fed almost daily because it does not remain in the body. DiazaCon™ must be fed several times over a 1- to 2-week period and effects may last for a few months. The two immunocontraceptive vaccines (PZP and GnRH) are both reversible, but after a longer period of time. Depending on the species, the PZP vaccine can be effective for 1-4 years before antibody titers decline and the contraceptive effect wears off, whereas the GnRH vaccine is normally effective for 1-3 years. If given a boost, animals can sometimes become permanently infertile.

PUBLIC ATTITUDES TOWARDS WILDLIFE FERTILITY CONTROL AGENTS

Traditionally, hunting and trapping have been the primary management tools for controlling overabundant wildlife. Many wildlife agencies and biologists have been reluctant to acknowledge the potential applicability of fertility control for managing wildlife populations (Warren 1995), in part because fertility control has been publicized as a replacement for sport hunting. Sanborn *et al.* (1994) conducted a survey of 134 state, regional, and national agencies and organizations in the United States, and they found that only 9% of state wildlife agencies had an established policy on wildlife contraception, compared to 39% of 54% of environmental and animal activist groups. However, managers and the public are seeking alternative means to manage wildlife in the urban-suburban environment and in city, county, state, and federal park lands where regulated public hunting or trapping are not permitted by law or are impractical. Use of contraceptives increasingly is being advocated, and wildlife management agencies are being asked by the public to consider the costs and benefits of use of contraception for managing wildlife populations.

The American Association of Wildlife Veterinarians (AAWV) stated in a 1993 resolution that fertility control may be an acceptable means of population regulation in free-ranging wild animals if the following conditions are met: 1) the compound does not affect the health of target species and humans; 2) a risk assessment is completed delineating potential effects on nontarget species; 3) the application is limited to site-specific, well-defined subpopulations or populations; 4) the application does not alter the gene pool of the species; 5) short- and long-term effects on population dynamics, including age structure and behavioral effects, are evaluated through modeling and monitoring; 6) the program is evaluated by regulatory and wildlife management agencies before use, with full public participation; and 7) costs of the fertility control program are borne by the organizations or public that benefit from the program. The position of the AAWV reflects most of the concerns of both wildlife managers and the general public regarding use of contraception to manage wildlife populations. These requirements for a contraceptive agent are similar to those desired by the Rocky Mountain National Park Service (NPS 2006) for potential management of elk (*Cervus canadensis*) populations; these include: 1) at least 85% effective with

a single dose, 2) appropriate approvals and certifications, 3) safe for treated animals, 4) no recognizable behavioral effects, and 5) safe for non-target animals.

In 2004, the Science and Research Liaison for the International Association of Fish and Wildlife Agencies (IAFWA) queried state wildlife agency chiefs for their position on potential use of immunocontraceptive vaccines. The following question was asked: "Would your agency use an immunosterilant vaccine for ungulate management if such a product was commercially available (as a veterinary product)?" Responses were categorized as "yes", "maybe", "probably not", or "no". Responses were obtained from 46 states and the District of Columbia. Seventeen state agencies (34% of respondents) answered "yes" or "maybe", while 31 state agencies (61% of respondents) answered "no" or "probably not" (Russ Mason, IAFWA, 2004 pers. commun.). Responses differed among regions; wildlife agencies belonging to the Northeast Association of Fish and Wildlife Resource Agencies were evenly split, with 46% answering "yes" or "maybe" and 54% answering "no" or "probably not". In the Southeast, 40% responded "yes" or "maybe", and 54% responding "no" or "probably not" (7% could not respond). The Midwest and West were the least inclined to use contraception, probably in part because they do not face the urban deer pressure found in eastern states. In the Midwest, 26% of states said "yes" or "maybe", and 67% said "no" or "probably not" (7% could not respond). In the West, 32% said "yes" or "maybe" and 68% "no" or "probably not". The main reason given for wanting to use immunocontraceptives was "unhunting populations", while the main reason for not wanting to use immunocontraceptives was a preference for traditional management techniques (hunting). Most states indicated that they would not implement this management tool themselves using departmental resources and personnel. Instead, they might license other entities to perform the work at their own expense, and only after careful scrutiny by agency personnel.

In most wildlife damage situations, the traditional methods of population reduction such as trapping and hunting will be preferable to use of contraceptives because of the cost and difficulty of using contraceptives, especially if animals need to be handled. In addition, the species most commonly tested to date have been primarily long-lived species such as deer and horses, which are least suited for population reduction through use of fertility control because the treated animals live for a long time and continue to cause damage. From the perspective of population dynamics, infertility agents are best suited for management of short-lived, highly fecund wildlife populations such as rodents and small birds. However, many rodent species breed year-round, so oral contraceptives would have to be fed periodically during the year to reduce reproductive rates. Seasonal breeding species such as prairie dogs and ground squirrels may be good candidates for contraceptives.

This finding conflicts with the growing public desire for nonlethal methods such as reproductive control to solve human-wildlife conflicts. Despite the high cost and sometimes questionable feasibility of present contraceptive programs, more and more communities are opting to

fund reproductive control of wildlife populations such as deer. Wildlife management agencies are increasingly being asked to consider the views of the public, as the public is demanding a voice in wildlife management, even to the point of filing lawsuits and passing local and state referendums (e.g., Proposition 4 in California). The public views contraception as a positive alternative to other management tools, and managers are increasingly being asked to become active partners with the public in developing practical applications for this technology (Fagerstone *et al.* 2002). The challenge for wildlife managers for many species will be to integrate potentially valuable contraceptive technologies with more conventional methods of wildlife population management.

REGULATION OF WILDLIFE CONTRACEPTIVES

A recent agreement between the FDA and the EPA changed the regulatory authority of animal contraceptives (Eisemann 2006). Reproductive inhibitors for use in wildlife and feral animals will now be regulated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Contraceptives used for livestock, companion animals, and in zoos will be considered veterinary drugs and will be regulated by the Center for Veterinary Medicine (CVM) of the FDA under Section 512 of the Federal Food Drug and Cosmetic Act (FFDCA). OvoControl® G was recently registered by Innolytics, LLC, working cooperatively with the NWRC, for reducing the hatchability of Canada goose eggs. A data package for the single-shot GonaCon™ Immunocontraceptive Vaccine will be submitted to the EPA in fall of 2006 to begin the registration process. This product could potentially be registered within a year of the submission date. A third product, DiazaCon™, is being tested in the field efficacy, and may begin the registration process within the year.

In addition to the EPA regulatory permits for use of the contraceptive, managers need to have a variety of other information/data at their disposal prior to implementation of any wildlife contraception program. If the contraceptive project is conducted on federal lands, uses federal funds, or is conducted by federal employees, the National Environmental Policy Act (NEPA) requires that the action be evaluated for potential adverse impacts on humans and the natural environment. When the project involves bird species protected under the Migratory Bird Treaty Act, the U.S. Fish and Wildlife Service (FWS) must be contacted prior to use of a contraceptive agent. If potential exists for a threatened or endangered species to be exposed to the agent, a consultation with the FWS may be required by the Endangered Species Act. Activities involving resident wildlife (i.e., those protected by state laws) are regulated by the respective state agencies and require appropriate authorizations. Additionally, other local laws and regulations often place further restrictions on management activities.

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