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Wildlife Fertility Control

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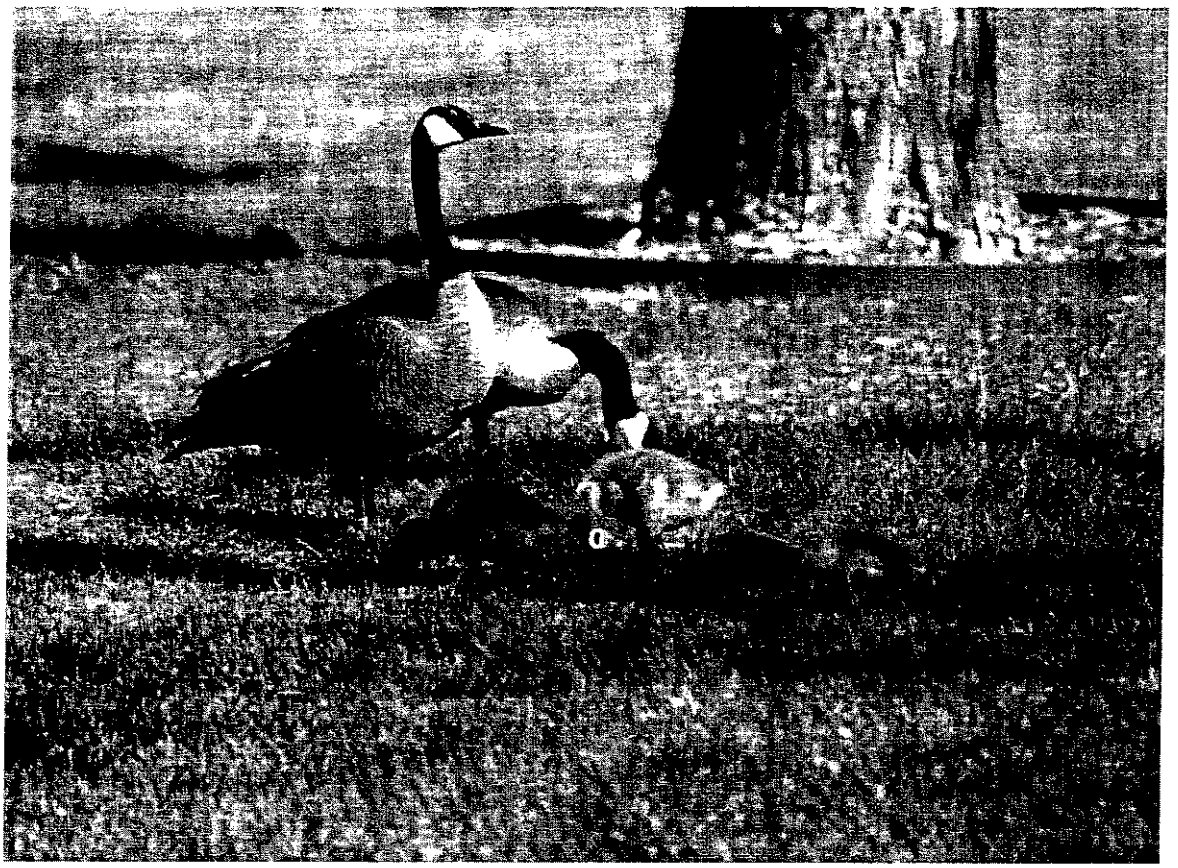
Abstract:
Huge flights of Canada geese turn off local park visitors with their messy, smelly "business cards." The superabundant white-tailed deer we love to watch also can do a number on your car at night and host the ticks that carry Lyme Disease. Blackbirds and gulls and coyotes and other critters bring their own problems when their numbers get out of hand.

Most such problems reach their highest profile in urban/suburban areas where traditional animal-control techniques such as hunting and trapping are frowned upon or illegal. More and more people are calling for wildlife managers to use "fertility control"–-but is that concept really feasible on populations of free-ranging wildlife? The definitive answers–in the form of the latest science–are contained in a new Technical Review titled Wildlife Fertility Control. The 29-page Review notes that in the past, fertility control has been far less successful than observers had hoped, but thanks to new findings about animal reproductive systems, the technology is advancing rapidly and is being tested on several species on a small scale. Hurdles include the need to develop and commercialize effective vaccines or baits, cost-effective delivery systems, and public-agency acceptance of the technique.

The new publication states that "birth control" will undoubtedly play a role in the science of wildlife management in the future. Managers face two major challenges: integrating contraceptive tactics with more conventional ways of managing critter numbers, and giving the public accurate information about the feasibility of using fertility control vs. lethal methods to reduce populations of deer and other long-lived species.

Wildlife Fertility Control



THE WILDLIFE SOCIETY
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WILDLIFE FERTILITY CONTROL

The Wildlife Society

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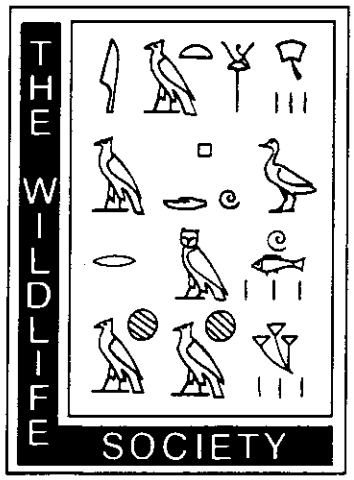

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Foreword

Presidents of The Wildlife Society occasionally appoint ad hoc committees to study and report on selected conservation issues. The reports ordinarily appear in 2 related series called either Technical Review (formerly "White Paper") or Position Statement. The review papers present technical information and the views of the appointed committee members, but not necessarily the views of their employers. Position statements are based on the review papers, and the preliminary versions ordinarily are published in *The Wildlifer* for comment by Society members. Following the comment period, revision, and Council's approval, the statements are published as official positions of The Wildlife Society.

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Cover photo by Kathleen Fagerstone.

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EXECUTIVE SUMMARY

A number of wildlife species have become overabundant either locally or regionally in North America, including white-tailed deer (*Odocoileus virginianus*), Canada geese (*Branta canadensis*), coyotes (*Canis latrans*), various blackbird (Icterinae and *Sturnus vulgaris*) and gull (*Larus*) species, and double crested cormorants (*Phalacrocorax auritus*). These and other overabundant species cause a myriad of conflicts with humans, ranging from minor nuisance problems to serious habitat and crop destruction, spread of disease, and collisions with vehicles and aircraft. Traditional population management techniques for overabundant wildlife such as hunting and trapping increasingly are restricted or infeasible in parks and suburban areas. Thus, wildlife managers and administrators are being urged by a growing segment of the public to apply wildlife fertility control to manage populations of overabundant free-ranging wildlife.

Wildlife fertility control has been less successful than hoped in the past, partly due to failure to understand reproductive strategies of targeted species. With an increasing research focus on contraceptive development, and more knowledge of animal reproductive systems and behaviors, fertility control as a technology is rapidly advancing. Wildlife fertility control is currently being tested in several species on a small scale and will undoubtedly hold a place as a wildlife management technique in the future. Major hurdles still include development of cost-effective delivery systems for effective products, public and natural resource agency acceptance of fertility control as a wildlife management practice, and commercialization of vaccines or baits. There are currently no contraceptive products available for commercial use. Investigational New Animal Drug (INAD) files have been established for several fertility control products. This allows for interstate transport of the investigational drug for use in studies to support the drug's approval. For a New Animal Drug to be approved, a drug sponsor must provide evidence of safety and substantial evidence of effectiveness in the target species. Environmental, human food, user safety, chemistry, and manufacturing issues must also be adequately addressed. Because contraceptive products for wildlife use will be a minor market, and the cost of obtaining authorization for their use by the FDA will be high, drug manufacturers will be reluctant to develop products on their own. Therefore, natural resource agencies may need to be involved in product development. Product development is a nontraditional role for wildlife management agencies, but one that will be required if contraceptive products are to be used in anything other than a research context.

Wildlife agencies and biologists have been reluctant to acknowledge the potential applicability of fertility control for managing wildlife populations, in part because the techniques available have been publicized as a replacement for sport hunting. In reality, it is doubtful if the cost or efficiency of delivery for contraceptive techniques would allow their use on free-ranging game populations outside of urban areas where hunting is typically prohibited anyway. The current techniques often have proved uneconomical or infeasible for practical implementation even in small, localized populations of game species such as deer. Furthermore, the species for which contraceptives primarily have been tested (long-lived species such as deer and horses) are those least suited for population reduction through use of fertility control. 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.

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 willing to view fertility control as an alternative to other management tools for nongame species and for game species in areas where hunting is already restricted. Public forums discussing the advantages and disadvantages of various management techniques will be more important in the future. The challenges for wildlife managers will be (1) to integrate potentially valuable contraceptive technologies with more conventional methods of wildlife population management and (2) to provide the public with accurate information about the length of time required for fertility control to reduce populations of long-lived species such as deer relative to lethal control.

INTRODUCTION

Wild animals are valuable natural resources and vital components of a healthy ecosystem. Wildlife provides economic, recreational and aesthetic benefits, and to many people, the knowledge that wildlife exists is a positive benefit in itself. The rich wildlife resources in the United States are an important part of our heritage. For the last 70 or more years, wildlife conservation agencies have focused on conserving and even increasing populations of many species of wildlife in the United States. In many cases, such as for the white-tailed deer and the Canada goose, these conservation efforts have been extremely successful, to the point where these species are locally overabundant.

Although wildlife abundance is desirable in most cases, some populations may reach undesirably high levels and

cause either ecological damage or human–wildlife conflicts. If these populations are allowed to increase unregulated, they may adversely affect the overall health of the population or of other species sharing the ecosystem or may result in an unacceptable degree of environmental degradation. These populations also may result in an unacceptable level of human–animal conflict. 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. Damage can be relatively minor or can be severe enough to affect the livelihood of producers or property owners. Overabundant wildlife also can cause human health and safety issues; wildlife aircraft strikes and deer–vehicle collisions have increased at alarming rates. There is increasing concern about the potential for wildlife disease transmission to humans and livestock (e.g., Lyme disease, tuberculosis, pseudorabies, West Nile virus, chronic wasting disease). 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 presence.

The general public has a positive attitude toward wildlife that can only be sustained if managers are able to minimize the negative impacts of overabundant wildlife. Prevention of the many and varied types of wildlife damage that occur in the United States involves an integrated pest management approach by federal, state and private landowners. The need for wildlife management is increasing as people continue to encroach upon natural habitats and human–wildlife conflicts become more frequent. At the same time, the public is becoming intolerant of perceived inhumane means of control. 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.

There are a number of complex technical, biological, economic and legal issues that will need to be addressed before infertility agents can be used widely in field situations. Some of these issues deal with the technology itself. If contraception is to become a successful wildlife management tool, the vaccines or infertility compounds will first need to be effective in inducing infertility. The most important fundamental for success in inducing infertility in a particular species is development of an understanding of the reproductive behavior and physiology of that species and the use of that knowledge to select the most suitable infertility agent. Examples of the reproductive behaviors that need to be considered are (1) is the species a seasonal or year-round breeder?, (2) is it monogamous or polygamous?, (3) is it monestrus or multiestrus?, and (4) does it need a specific vegetation, temperature, or landscape to be successful in reproduction? Each of these factors may impact the effectiveness of a particular infertility agent. Infertility agents also will have to be safe for the animals being treated, for nontarget animals, and for the human population and the environment. They will need to be cost effective relative to other methods of population management, meaning that they must be easily deliverable to large numbers of free-ranging animals in the target populations. Legally, they must be authorized through a regulatory agency such as the Food and Drug Administration (FDA), and they must be used according to the statutes and regulations set forth by federal and state agencies. In addition, they need to be socially acceptable for that particular use.

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.
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.

The purpose of this technical review is to summarize past wildlife contraception efforts, discuss the current state of research and where the research is headed, and examine the feasibility of field use for contraceptives. Specifically, can

the techniques proposed be used safely, economically, and within legal state and federal mandates? Many contentious issues have been raised regarding use of infertility agents for managing wildlife populations (Bomford 1990). The following sections will address each of these issues, followed by a review of the current status of wildlife fertility control products. A list of acronyms is provided in Table 1.

BIOLOGICAL FEASIBILITY

The use of infertility agents to control populations of wild animals may offer an alternative to the use of population reduction by increasing mortality. However, whether fertility control is biologically feasible for a particular species and population depends on a number of parameters (Curtis et al. 1997*a*, 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. Also required is an estimate of the number of animals in the population that will require treatment and for how long.

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. The predicted relative efficiencies of lethal and reproductive control for various wildlife species (Table 2) can be generalized based on adult survival rate (ASR) and age at which animals reproduce. For species in which females first reproduce at 1 and 2 years, lethal control will be more efficient than reproductive control in reducing populations when the ASR is greater than about 0.56 and 0.23, respectively. For species in which females first reproduce at 3 years, lethal control always will be more efficient than reproductive control in reducing populations. In general, this means that reproductive control will be most effective in managing smaller wildlife species such as black rats (*Rattus rattus*), brown-headed cowbirds (*Molothus ater*) and red-billed quelea (*Quelea quelea*) with high reproductive rates (i.e., reproducing at early age, large litter or clutch size) and low survival rates. Knipling and McGuire (1972) developed a theoretical model demonstrating that if 70% of male and female rats could be sterilized for three generations (1 year) the entire population would be eliminated.

Conversely, reproductive control will be much less efficient than lethal control in managing populations for larger species such as deer (*Odocoileus* spp.), coyotes (*Canis latrans*), Canada geese (*Branta canadensis*), and gulls (*Larus* spp.) that do not typically reproduce until 2–4 years of age and have smaller litter or clutch sizes than most rodents and small birds. These population simulations (Dolbeer 1998) demonstrated that for many wildlife species in need of population management, such as deer and Canada geese, lethal control will be more efficient than reproductive control in reducing population levels. For example, in white-tailed deer, 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. With an estimated annual mortality rate of 20% for roadkill and other losses, a deer herd 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.

Curtis et al. (1998) used 4 years (1993–96) of culling data from the Irondequoit, New York deer herd to study the biological feasibility of contraceptive applications. The age and sex structure of the population was simulated using an automated program for reconstructing deer populations (Moen et al. 1986). The program established an initial breeding population of the size necessary to support human-related mortality (i.e., culling, deer–vehicle collisions), and natural deer mortality with a biologically reasonable sex and age structure. Simulated annual reproduction and losses contributed to changes in the sex and age structure in successive years. This simulation produced an initial preculling population size of 905 deer in 1993, and fall deer populations in subsequent years of 852, 702, and 457 deer for 1994–96, respectively (Curtis et al. 1998). Next, the number of females culled each year was divided by the weighted mean reproductive rate for the population to determine the number of females that would have to be treated with fertility control agents to remove their potential fawns from the population; the number of females to be treated was twice the number culled because of the male:female fawn sex ratio. The total was divided by 0.89 to account for the 89% efficacy observed for contraceptive vaccines delivered via dart gun. The proportion of female deer in the simulated population that required treatment in any given year varied from 29–100% (Curtis et al. 1998). This wide variation was directly related to the number of female deer culled in relation to changing deer numbers and shifts in the population age and sex structure over time. In 1 year, more females in the simulated herd required treatment with contraceptives than were actually available. This example raises concerns about the biological feasibility of wildlife fertility control in long-lived species when agents are delivered via dart rifle.

From the perspective of population dynamics, efforts for developing infertility agents to manage wildlife populations should focus on those species for which the concept is most likely to be successful, such as rodents and small birds. This finding conflicts with the growing public desire for nonlethal methods such as reproductive control to solve human–wildlife conflicts in larger, long-lived species. Furthermore, if infertility agents are developed and used on long-lived species such as deer and geese, biologists need to be honest with the public about the inefficiencies of this approach and the length of time required for such strategies to reduce populations relative to lethal control.

PUBLIC ATTITUDES TOWARD WILDLIFE FERTILITY CONTROL AGENTS

Changes in sociopolitical values have resulted in more of the public wanting to be included in wildlife management decisions today than at any other time since the advent of applied wildlife management in North America (Curtis and Richmond 1992, Curtis et al. 1997). Citizens want to participate in setting objectives for management and in approving the methods for accomplishing those objectives. The decision-making process is no longer just a decision made by the manager. Today's decision must bring together all concerned parties—federal, state, private citizens, and special interest groups. Whether we call this process "stakeholder groups," "citizen task forces," "committee action groups," or "human dimensions," it is a break from the traditional way of managing wildlife. Wildlife management agencies are now working within a new paradigm for management that strives to integrate the biological and human dimensions of wildlife management for improved decision making (Decker et al. 1992). This contemporary paradigm recognizes that decision making occurs in an environment with sociocultural, economic, physical, legal, and administrative aspects, as well as biological components (Decker et al. 1992, Slate et al., 1992). Agencies recognize that people representing a variety of views are legitimate stakeholders in management, and the public is demanding to have their concerns addressed—one of which is that managers seek nonlethal means for the management of wildlife. Nowhere is this more evident than in the area of wildlife contraception as a potential management tool. Gill (1993) stated that "given the nature and potential polarity of the wildlife contraception issue, wildlife agencies will have to behave proactively by projecting themselves into their future." Kania and Conover (1991) emphasized that wildlife agencies should respond to these societal changes rather than resist them, thus enhancing the value of the wildlife resource for all people. In fact Schmidt (1992) argued that natural resource management decisions, previously thought to be defined by science and economics, are now driven by human values.

The purpose of this discussion is to describe public involvement in wildlife management decisions with particular reference to wildlife fertility control. Because few studies have focused on identification and explanation of people's beliefs and attitudes toward wildlife fertility control, the public involvement aspects are reviewed in detail.

Public Involvement Strategies for Making Wildlife Management Decisions

Sanborn et al. (1994) conducted a survey of 134 state, regional, and national agencies and organizations in the United States, and determined that most lacked a policy relating to contraception in wildlife management. Only 9% of state wildlife agencies had an established policy, compared to 39% of 54 environmental and animal activist groups. Sanborn et al. (1994) also indicated that the first step in gaining public acceptance of wildlife fertility control is to convince the public that this is a viable wildlife management tool. None of the groups surveyed indicated that wildlife fertility control was a practical management option at that time.

Beliefs and values that influence the acceptability of wildlife fertility control should be considered early in the research and development process, before too much time and money are invested in approaches that may later prove to be morally or ethically unacceptable. For example, Turner et al. (1992) noted that female white-tailed deer treated with a porcine zona pellucida (PZP) vaccine continued to exhibit estrous cycles after not becoming pregnant. These changes in deer reproductive biology, and their potential to change behavior and energetics, could raise ethical and management questions, and may influence stakeholders' perceptions of this contraceptive technique. Stakeholders must understand the full range of effects that different contraceptive methods may have on wildlife populations before making decisions to accept or reject their use.

People's beliefs and attitudes about wildlife are formed, exist, and change in a context of broader attitudes and values concerning several domains of their lives. Wildlife-associated attitudes and values also are related to other major world views, such as appropriate human interaction with the environment, religious beliefs, beliefs about safety and security of family and community, and beliefs about individual freedom of choice in dealing with problems (i.e., those caused by wildlife). Based on studies by the Human Dimensions Research Unit in the Department of Natural Resources at Cornell University, a Wildlife Attitudes and

Values Scale (Purdy and Decker 1989) was developed and applied in over a dozen situations. This work identified the existence of three broad dimensions of public attitudes toward wildlife: wildlife use, wildlife preservation, and wildlife damage/nuisance tolerance. The attitudes and beliefs toward wildlife damage/nuisance tolerance vary widely. Thresholds exist for tolerance of wildlife-caused problems depending upon economic or health and safety risks. For example, some people will incur high levels of economic losses from wildlife before they find the tradeoff tips toward damage abatement or lethal control. However, when the perceived risk of health and safety problems associated with wildlife (e.g., rabies, Lyme disease, motor vehicle accidents, etc.) reach even modest levels, tolerance of wildlife causing the risk is reduced markedly (Stout et al. 1993). It is likely that people will change their attitudes toward fertility control if perceived risks of economic loss, or health and safety impacts, exceed tolerance thresholds.

Increasingly the wildlife management profession is finding that public-involvement techniques are helpful in reaching community consensus on controversial wildlife management issues (McAninch and Parker 1991, McMullin and Nielsen 1991, Nelson 1992, Curtis et al. 1993, Stout et al. 1993). If conceived carefully and implemented effectively, citizen participation strategies present educational opportunities, improve the agency image as being responsive to stakeholder needs, and lead to more acceptable decisions and actions to solve management problems (Stout et al. 1993). Several models have been used to involve citizens in wildlife management decisions (McAninch and Parker 1991, Curtis et al. 1993), and these may be adapted to fit other situations. In a New York deer contraceptive study, the work of citizen task forces was greatly enhanced by the availability of systematically collected human-dimensions data gathered from the community at large and from members of specific stakeholder groups. Evaluation of participants involved with ongoing task forces can improve communication and is invaluable for effectively managing the process (Stout et al. 1992).

Involving communities in wildlife management decisions has led to the evolution of comanagement (Schusler 1999), which was defined by the World Conservation Congress in 1996 as "A partnership in which governmental agencies, local communities and resource users, nongovernmental organizations, and other stakeholders share, as appropriate to each context, the authority and responsibility for the management of a specific territory or set of resources." Proponents of comanagement believe it is more appropriate, efficient, and equitable than more conventional government control. An example of a comanagement approach is deer contraception research in the Town of Irondequoit, NY, where funding and political support were provided by the New York State Department of Environmental Conservation (through a direct, line-item appropriation from the New York State Legislature) as well as by the local community.

Identifying Public Acceptance of Wildlife Fertility Control

Wildlife managers considering the use of contraception for resolving wildlife problems need knowledge of the specific attitudes held by stakeholders in a given management situation. Currently, insufficient research is available that describes public attitudes toward wildlife fertility control. The Town of Irondequoit was selected as the site for an in-depth study because of a long-standing deer-management controversy surrounding Durand Eastman Park and implementation of a public involvement process for setting deer management objectives (Curtis et al. 1993). In addition, the NY Department of Environmental Conservation and the College of Environmental Science and Forestry at State University of New York are conducting an experimental field application of fertility control vaccines in this community (Nielsen et al. 1997).

To learn about public attitudes toward deer management alternatives in Irondequoit, a mail survey of property owners was conducted (Lauber and Knuth 1998). The survey included several questions concerning contraceptive management of a locally overabundant deer herd. The questionnaire was sent to 1,494 Irondequoit residents, and 890 useable responses were received. The community was divided on the preferred approaches for managing the deer herd. About 27% of respondents supported contraception, 24% supported lethal control (e.g., bait and shoot), 18% wanted trap and transfer of deer, and 13% supported other nonlethal approaches (Lauber and Knuth 1998). Compared to respondents who favored lethal control, people who supported deer contraception placed a higher emphasis on humaneness, protecting other wildlife and pets, minimizing violence, and choosing politically acceptable methods. Contraception supporters perceived this technique to be more effective and reliable, faster, less expensive, more humane, and more widely supported in the community than residents who supported other deer management methods. For respondents who opposed contraception, maximizing hunting opportunity and speed in reducing the size of the deer herd were more important considerations. Respondents who supported lethal control also wanted to minimize management costs (Curtis et al. 1997). Respondents who were interested in increasing deer-hunting opportunities and reducing economic costs generally were opposed to contraception.

Community support for any deer management action, lethal or nonlethal, will require significant public education (Stout

et al. 1997), and it may be necessary to build consent for management among several stakeholder groups with divergent viewpoints (Curtis and Hauber 1997). Addressing the social conflicts associated with overabundant wildlife may be much more difficult than managing the biological aspects of population management.

POLICY AND THE DECISION-MAKING PROCESS

Federal/State Agency Management

Hunting and trapping traditionally have been the primary management tools for controlling populations of many species of wildlife. During the past 20 years, changes in wildlife distributions and density have increased the frequency of human–wildlife interactions 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. As a result, managers are seeking alternative means to manage wildlife, and use of contraceptives increasingly is being advocated as a wildlife management tool.

What Information Is Needed Prior to Wildlife Contraception?

Prior to implementation of any wildlife contraception program, managers need to have a considerable amount of information/data at their disposal to aid in the decision process. A paramount piece of information required is the legal status of a species and site. In general it is the state and federal agencies that have primary responsibility for the management of wildlife. Each branch of the federal government and each state and local government has a unique set of statutes and regulations (Guynn 1997) that may be applicable and that managers must be aware of prior to implementing a wildlife contraceptive program. These include the FDA regulatory requirements and permits for use of the contraceptive; field use of a contraceptive must occur under an Investigational New Animal Drug (INAD) permit or a New Animal Drug (NAD) authorization. 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. Depending on the scope of the contraceptive project, the project may require an Environmental Assessment or an Environmental Impact Statement or can be "categorically excluded" (actions do not have a significant effect on the quality of the human environment and do not require an Environmental Assessment of an Environmental Impact Statement). 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 an antifertility agent. If potential exists for an 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. There also are state-specific environmental policy/protection laws and regulations, state laws relating to the conditions and use of drugs and/or vaccines, and other state wildlife and public health requirements. Additionally, other local laws and regulations often place further restrictions on management activities.

Wildlife management in the United States and the methods used for management of wildlife and of certain nonwildlife species (i.e., wild horses [*Equus caballus*], feral burros [*Equus asinus*], and bison [*Bison bison*]) are largely dependent on the management goals and objectives of the agency with delegated legal management authority. The goals and objectives of management may vary among states and among federal agencies. To further confuse the issue, management authority and the responsibility for implementing management actions may vary, with one or more bureaus, departments, or agencies having responsibility within each state or the federal government. The question of land ownership adds even greater confusion; lands can be owned by cities, counties, states, federal agencies or private citizens. In the case of game farms, there also is a question of whether or not certain wildlife is publicly or privately owned.

Therefore the first question to be asked before a contraception program is implemented is "Who has the authority over this group of animals?" Once that is established, the specific goals and management objectives of the contraceptive program must be clearly defined and articulated, i.e., why are we doing this and what is it that we want to achieve? Caughley and Sinclair (1994) suggest answering the following questions: Where do we want to go? Can we get there? Will we know when we have arrived? How do we get there? What disadvantages or penalties accrue? What benefits are gained? Will the benefits exceed the penalties?

Tools Available to Aid in the Decision Process

As stated above, management policies, goals and objectives differ from agency to agency. Generally, agency policies are couched in broad terms that provide little more that a general guide for managers. Goals provide ideal ends or effects and give direction and purpose; they provide limits to the range of potential objectives. Objectives are statements

of specific conditions to be achieved. In considering what goals or objectives are appropriate, managers must consider social, political, biological and economic factors. Although consensus on agency management policies, goals, and objectives may not be possible, consent may be obtainable (Curtis and Hauber 1997). We recommend that as an aid in the decision process managers prepare an objective—action matrix in which possible objectives are ranked against feasible actions to determine how each action is likely to meet each objective (Norton 1988). Managers can then assess whether or not an objective can be met by each action of a particular management problem. Another matrix that managers may use to aid in the decision-making process is one examining possible management actions against criteria of feasibility (Bomford 1988). These matrixes will assist managers in determining whether the use of wildlife contraceptives as a management or research action is technically and biologically feasible, and socially, politically, and economically acceptable. If feasible and acceptable, can all the legal, regulatory, and permit requirements be met, and can the goals and objectives of the agency be met?

Managers could consider using a decision and alternative key (Coffey and Johnston 1997) developed using an integrated pest management (IPM) approach for managing white-tailed deer. The IPM alternative management approach uses problem-solving based on identified or suspected ecological, economic, sociological, and political consequences. The process starts with clearly defined goals and objectives for management and a decision key provides a guide for managers to ensure that specific and necessary actions are completed. A "No" answer to any question precludes going to the next step until the previous step or action is completed. Once the decision key has been completed, managers proceed to the alternative key, which provides for a selected list of alternatives ranging from those that have the least ecological, economic, sociological, and political impacts to those that are the most difficult to implement. In most cases wildlife contraceptive problems may be resolved by combining alternatives or components of alternatives and by cooperating with other federal, state, and local agencies, and the private sector.

REGULATION OF WILDLIFE CONTRACEPTION DRUGS

An unapproved new animal drug is unsafe within the meaning of Section 512 of the Federal Food Drug and Cosmetic Act (FFDCA). It is illegal to transport unapproved drugs in interstate commerce. Therefore, it will be necessary to gain approval of wildlife contraception drugs intended to curtail population growth of "nuisance" wildlife. Veterinary drugs are approved by the Center for Veterinary Medicine of the Food and Drug Administration (CVM/FDA). As defined by the FFDCA, drugs are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and...articles (other than food) intended to affect the structure or any function of the body of man or other animals...." Veterinary biological products, which are "for use in the diagnosis, treatment, or prevention of diseases in animals," on the other hand, are licensed by the Biotechnology, Biologics and Environmental Protection of the Center for Veterinary Biologics of the Animal and Plant Health Inspection Service (APHIS) of U. S. Department of Agriculture (USDA) under the Virus, Serum, Toxin Act (1913). Pregnancy is not considered a disease; therefore, development of products, including vaccines, for this indication falls outside of USDA jurisdiction. Likewise, regulation of animal drugs falls outside jurisdiction of the Environmental Protection Agency (EPA). EPA is responsible for regulating pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Regulations regarding the investigational use of new animal drugs are set forth in 21 Code of Federal Regulations (CFR) 511 and the regulations describing the new animal drug application are set forth in 21 CFR 514. The process begins with the establishment of an Investigational New Animal Drug (INAD) exemption. This allows for the interstate transport of an unapproved new animal drug for use in safety and effectiveness studies conducted to support the drug's approval. To support a new animal drug approval, a drug sponsor must provide substantial evidence of a drug's effectiveness through adequate and well controlled studies. The safety of the drug in the target species also must be proven. In addition, the drug must be manufactured under Good Manufacturing Practices of FDA to assure its identity, strength, quality, and purity from batch to batch. Environmental, human food, and user safety issues also must be addressed. Finally, a suitable label is produced and a Freedom of Information Summary (required by FDA) written. The new animal drug approval process can take several years depending on the quality of the information submitted to support the drug's approval, the time needed to generate that information, and the status of the manufacturing facility employed to manufacture the drug.

CVM/FDA recognizes that novel approaches to the approval of wildlife contraceptives may be necessary because of public ownership of wildlife, intrinsic value of such animals to society, and the difficulty in collecting data under less than ideal conditions. However, the current standards for approval of wildlife drugs, including contraceptives, are identical to those for other new animal drugs. As noted

above, drugs approved for wildlife contraception must be labeled according to FDA regulations and policies. These drugs will most likely bear an "Rx" or prescription legend, thereby limiting use by or under the direction of a licensed veterinarian for several reasons. These include the special training that may be necessary to ensure the humane treatment of the animals (i.e., knowledge of darting, trapping, and other capture methods) and the possible danger to the person administering the product if it is not handled properly. Furthermore, the "Rx" status may limit the adverse impact on the environment and will provide controls to minimize the potential for inappropriate usage. CVM may consider allowing those involved in the practice of wildlife management to use the drugs also. All new animal drugs are monitored postapproval for the occurrence of adverse events. Appropriate labeling changes are made, if necessary.

Anyone can sponsor a drug approval package. However, sponsors are generally pharmaceutical firms because of the monetary resources needed to conduct safety and effectiveness studies and to maintain acceptable chemistry and manufacturing standards. Nevertheless, multiple organizations may work together in drug development to meet FDA requirements. There are currently no fertility control agents for wildlife that have received approval by FDA and that are commercially available in the U.S.

ECONOMICAL PRACTICALITY

In addition to being biologically feasible for reducing populations of the target species, infertility agents will need to be economically practical to use. The economic practicality involves development and authorization of the contraceptive drug, as well as assessment of all costs of treatment, including personnel, equipment, contraceptive vaccines, and other equipment and supplies.

Product Development

The cost of obtaining authorization by the FDA can be very high for use of new infertility drugs such as contraceptive vaccines. A survey developed by the Animal Health Institute (Mark Wood, Animal Health Institute, personal communication) indicated that companies average 11 years and spend an average of $22 million to develop and bring a new animal drug to market. The cost and time of development are less (about $2 million and 4.5 years) for new veterinary biologicals, but still are high. These high costs may prevent the majority of infertility agents from being developed commercially, because profits are not large (87% of all animal drugs have individual sales of less than $1 million a year), and wildlife are only a minor portion of the animal drug market. Infertility agents targeting potential food species, such as deer and geese, will potentially cost more to register than those targeting nonfood species because of concerns for human safety. A company interested in developing a wildlife infertility agent must compare the developmental costs to the eventual monetary returns. The more radical the product (e.g., a recombinant bacteria delivering a contraceptive vaccine) the higher the cost for registering the product. Research is increasingly focusing on products already licensed by USDA or FDA for other purposes. An infertility agent that has already passed FDA scrutiny for its proposed use (such as a commercial agricultural product) will cost less to develop as an approved product for contraceptive use. Examples include Lutalyse®, which is an FDA-approved drug for synchronizing estrus and terminating pregnancy in several species of animals used for human food, but which also is a potential fertility control agent for white-tailed deer (DeNicola et al. 1997*b*), and nicarbazin, an FDA-approved drug for the control of coccidiosis in broiler chickens, but which is being tested as a fertility control agent for pest species of birds.

There are currently no fertility control agents for wildlife that have received approval by FDA and are commercially available in the U.S. Several agencies and organizations currently hold INAD exemptions allowing interstate transport of the unapproved drugs for use in studies to support the safety and efficacy of those drugs. For example, research is being conducted by the USDA under INAD exemption numbers for Gonadotropin-Releasing Hormone (GnRH) and Porcine Zona Pellucida (PZP) immunocontraceptive vaccines, for the cholesterol inhibitor DiazaCon, and for the avian reproductive inhibitor, nicarbazin. All are classified as investigational drugs.

Cost of Implementing Fertility Control Programs

Immunocontraceptive Vaccines

Although infertility agents may show effectiveness in laboratory or pen situations, economical methods of manufacturing and delivering the agent to the animals are needed before they will be widely used. A potential hurdle in the development of a zona pellucida contraceptive vaccine is the difficulty in purifying sufficient quantities of the protein, making the cost of the vaccine high (about $50 per dose); large scale production could potentially be achieved through recombinant DNA technology and genetic engineering. Also, use of currently available immunocontraceptive vaccines is costly, because they require both an initial dose and a subsequent booster dose to achieve adequate contraceptive effect, and annual booster inoculations may be required. Presently the vaccines are injectable only by hand or by a biobullet or dart gun. These remote delivery systems have certain advantages (Kreeger 1997): (1) they target specific animals; (2) they can

administer a dose on a body weight basis; and (3) they can deliver solid, semisolid, or liquid formulations. However, they also have inherent disadvantages: treatment cost is high; personnel must locate and approach target animals; they can be used only on large animals; and they are complex, noisy and require experienced personnel to employ.

The current vaccines also use Freund's adjuvant; because of concerns by FDA about the safety of this adjuvant, huntable animals must be eartagged with a "Do Not Consume" notice. Turner et al. (1997) found that a 2-injection protocol presented logistical and economic problems for use in feral horses because of the need to keep horses gathered together for 3–4 weeks to give a second injection. They estimated that a single injection with the current PZP vaccine would be effective in only about 20–28% of the vaccinated horses in the first year. After a booster in subsequent years they estimated that efficacy should increase to about 90%. Curtis et al. (1998) also demonstrated that the 2-shot paradigm of vaccinating deer (and ear tagging as required by the FDA for current products) is too labor intensive and costly to be a practical solution for reducing deer populations. During the field study of PZP and GnRH vaccines in New York State, 183 deer were captured and tagged at an average cost of $136/deer for fuel and equipment, and 11.2 hrs/deer for labor, which totaled about $250 for each deer marked (Curtis et al. 1998). Capture and marking accounted for about 28% of the estimated program costs. Costs to administer contraceptive vaccines to a herd of about 300 deer were approximately $80,000 per year.

A single-shot, dart or biobullet-delivered vaccine is needed to make immunocontraception programs economically and logistically feasible. Research currently being conducted cooperatively by the National Wildlife Research Center of APHIS and Pennsylvania State University has demonstrated that a single-shot PZP vaccine mixed with a newly developed adjuvant and delivered to deer by dart or biobullet may effectively cause infertility in deer, possibly for multiple years. The new adjuvant also may eliminate the requirement that vaccinated deer be ear-tagged, making immunocontraception using PZP a feasible approach for some sites. Brown et al. (1997*a*) tested a single shot PZP vaccine called SpayVac on gray seals (*Halicoerus grypus*) and suggested the single-shot vaccine may be effective for multiple years.

Even with capture and tagging costs removed, however, funding for labor and vaccine expenses in the New York deer study still totaled more than $180,000 over 4 years. According to the Cornell simulation, more than 400 female deer would require multiple vaccine treatments to match the effects of culling. A field study conducted to determine the actual feasibility of using contraceptive vaccines to regulate numbers of free-ranging deer (Nielsen et al. 1997, Rudolph et al. 2000) in Irondequoit, indicated that, at least for deer, it will be extremely expensive to treat enough individuals to regulate population growth as long as fertility control agents need to be delivered by dart-gun to individual animals. And if the problem associated with the deer herd is serious, a contraceptive program may not reduce that problem quickly enough, as all the adult deer are still present. As indicated above, it may be preferable to cull a herd to a goal population size, then dart a portion of the remaining females with contraceptive vaccines to inhibit or slow herd growth (Nielsen et al. 1997). If a community decides to use contraceptive vaccines to control deer numbers, it needs to realize this requires a long-term commitment of funding and personnel and careful planning to ensure that the fiscal and human resources are available to support the work over the long term.

Oral Delivery of Immunocontraceptive Vaccines

There are 2 facets to drug delivery that present challenges to wildlife managers—getting the agent into the animal, and controlling its release to maximize efficacy. The methods of delivery may need to be as varied as the species targeted, because no single technology will be able to satisfy all the concerns of efficacy, economics, and animal and human safety. A practical and cost-effective means to deliver a vaccine to some populations of free-roaming animals is by oral delivery (Miller 1997*a*). However, oral delivery is a difficult technology to develop and would increase the USDA and FDA regulatory involvement because it is a new and unproven technology. There also would be a need to prove that oral vaccines are safe in the environment and that they will not adversely affect nontarget species. Although there is a great need in third world countries for human oral vaccines because of the lack of physicians to administer injectables, little money is currently being spent by drug companies on oral vaccine research. Because much of the technology wildlife researchers use comes from human infertility studies, it is not expected that oral immunocontraceptive vaccines will be available soon.

The ideal oral delivery system will need the ability to (1) survive the acidic stomach, (2) be taken up into the bloodstream from the intestines, and (3) cause a strong immune response (Mestecky and McGee 1989, McGhee et al. 1992, Walker 1994). Live microorganisms such as attenuated (noninfective) forms of *Mycobacterium bovis* , *Vibrio cholerae*, some strains of *Salmonella*, and *E. coli* have some of these properties (Attridge et al. 1997) and could be coupled to contraceptive vaccines. In a live viral vector, inserted DNA would synthesize the vaccine protein

as the virus multiplied in the host animal, thereby vaccinating the host animal. In a bacterial vector, a recombinant bacteria genetically rendered harmless could deliver an immunocontraceptive protein. Attenuated *Bacillus calmette guerin* (BCG) bacterium (which is widely used as an oral tuberculosis vaccine in its nonrecombinant form) and double gene-deleted *Salmonella typhi* bacillus are considered safe, are economical to produce, and are used in human vaccine delivery applications. However, there have been few field uses of recombinant bacterial and viral vectors. Oral vaccination of wildlife is currently being used in the U.S. to halt the spread of rabies in wildlife populations in Texas and in the northeastern states using a vaccinia virus genetically engineered to deliver a rabies vaccine. And Miller et al. (1999*a*) demonstrated the laboratory feasibility of oral vaccination using the BCG bacterium. There is considerable reluctance in the U.S. to use a live vector to deliver a contraceptive vaccine; thus, little research is being conducted in this area.

In contrast to U.S. researchers, scientists in Australia and New Zealand are looking at self-sustaining infectious biological vectors such as genetically modified myxoma viruses (Tyndale-Biscoe 1997), bacteria, or nematodes to spread contraceptive vaccines. This approach has raised widespread concern from the public and from other countries because of the difficulty in containing the infectious vector, a difficulty underscored by the recent spread of rabbit calicivirus from an island quarantine area to the Australian mainland. There are a number of issues regarding the international consequences of introducing an agent designed for a species that is a pest in one country but a desirable species in another. A recent development in Australia raises an additional concern about genetically manipulated infectious vectors (Nowak 2001). As part of a study aimed at creating a contraceptive vaccine, researchers from Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) and the Australian National University inserted into a mousepox virus a gene that creates large amounts of interleukin 4 (IL-4), a molecule that occurs naturally in the body. The mousepox virus provided the oral delivery system for the vaccine and the gene for IL-4 was added to boost antibody production. Surprisingly, the modified virus totally suppressed the immune response to the mousepox virus. Although mousepox normally causes only mild symptoms, with the added IL-4 gene it became lethal; the engineered virus also appeared unnaturally resistant to attempts to vaccinate the mice.

Because of the concerns of releasing bacterial and viral material into the environment, APHIS/USDA is researching inserting contraceptive vaccines into baker's yeast, and other scientists are researching the use of genetically engineered plants as vectors (Arntzen et al. 1994, Greenhouse et al. 1999). Although both of these technologies are in the initial research phase, they have the potential to provide a safe vaccine delivery system. These technologies could theoretically be used to grow the vaccine in the laboratory; the vaccine then could to be delivered as an expressed contraceptive protein or in oral form.

The use of encapsulation may potentially provide acceptable oral delivery of vaccines by protecting the protein vaccine from the harsh environment of the stomach. Synthesized vectors, such as biodegradable microspheres (slow release antigen-delivery systems), and liposomes (spherical, artificial lipid membranes), can theoretically protect the vaccines and deliver them to the mucosal immune cells. Researchers (Alving et al. 1986, Holmgren et al. 1993, Hornquist et al. 1994) have synthesized liposomes (lipid membranes) that incorporate bacterial receptors that promote binding to the intestinal epithelial cells. Contraceptive vaccines can potentially be delivered to the bloodstream while encapsulated in these liposomes. Miller and Fagerstone (2000) tested an adhesive liposome containing a GnRH immunocontraceptive as an oral vaccine in wild Norway rats. They achieved an inconsistent oral response, with 50% percent of the rats showing antibody titers and a significant reduction in serum testosterone, but the other 50% showing no antibody titer.

Oral Delivery of Chemical Contraceptives

Chemical contraceptives such as steroids and nicarbazin can be delivered orally in a bait. The problem with this method of delivery is getting adequate bait acceptance. An example of the difficulty in developing an adequate delivery system for wildlife is the development of nicarbazin for infertility control for Canada geese. Canada geese are monogamous and territorial during the breeding and nesting season, making this species vulnerable to induced infertility (Kennelly and Converse 1997). When fed on a regular basis, nicarbazin reduces hatchability of eggs. In many areas, urban geese are accustomed to being fed, so it was assumed that development of a nicarbazin bait to be fed regularly during the breeding season would be relatively easy. However, the nicarbazin has an astringent taste that geese find aversive, so its taste must be masked to achieve adequate consumption. Also, geese during the nesting period go from group feeding to individual feeding around nests and from grains to green grasses, so it is difficult to get a product to them consistently and in sufficient amounts. A controlled-release system such as a grit treated with nicarbazin may be required to deliver a product to this species, which would further increase the difficulty and cost of developing an effective contraceptive product.

HEALTH AND SAFETY ISSUES

Health Effects on Target Animals

One of the issues faced by policy makers when making decisions on whether infertility agents are a reasonable approach for wildlife population control will be effects of contraceptives on the health of the target species (Guynn 1997). Effects on the target species include not only the physiological effect of the contraceptive on individuals, but also how the treated individuals affect the dynamics of the population. These data are difficult to obtain because wildlife do not lend themselves to intensive study as individuals or as populations. Nevertheless, studies will need to be conducted to define potential benefits and adverse effects.

One issue of concern to wildlife managers is the reversibility of infertility agents. There is considerable disagreement among scientists regarding the advisability of reversibility, depending on the species targeted and the intended population effect. In some cases, such as with invasive species (nonnative exotics), an irreversible contraceptive is desirable. In other cases where yearly management strategies may be important, a short-term effect may be preferred. In many cases it would be an advantage if the contraceptive effect lasted several years but was then reversible to decrease risk of nontarget hazards and to increase management options.

Most of the infertility agents discussed in this technical review are reversible. However, there is a large variation in the length of time that they are effective. Most of the steroid compounds need to be continuously fed to be effective—discontinuing feeding causes rapid reversibility. Other oral compounds (nicarbazin and DiazaCon) being studied as contraceptive agents must be fed frequently and do not have long-lasting effects. Therefore, developing methods to deliver these compounds efficiently to animals will be critical. Fortunately, many of the overabundant species that wildlife managers are concerned about are seasonal breeders in which these short lasting compounds may be useful. The two immunocontraceptive vaccines (PZP and GnRH) are both reversible, but after a longer period of time. The PZP vaccine can be effective for 1–4 years before the contraceptive effect wears off, whereas the GnRH vaccine is effective only for 1–2 years.

The picture of how contraceptives affect overall animal physiology is far from complete. Data are needed from controlled studies of wildlife that have been treated with contraceptives to better understand how these agents may affect reproductive behavior, reproductive status, animal health and interactions among herd members. Observations should be made on individuals for periods of several years to better understand both the short and long-term physiological and behavioral responses that may occur as a result of contraceptive treatment.

A number of adverse effects have been postulated for the use of chemical contraception and immunocontraception on the behavioral and physiological responses of wildlife (Table 3). These include potentially adverse effects on individuals, as well as adverse affects on populations, such as changes in the social hierarchy among males and females, feeding behavior, energy expenditure, local shifts in population, and increases or decreases in animal movement. What should be emphasized about many of the potentially adverse effects listed in the table is the word *potential*. For many of the effects, we lack sufficient data from controlled studies involving the wildlife species being treated with contraceptives. Often inferences are made from case studies of one or two animals, or from one species to another. In only a few studies have the potentially adverse effects been observed and their incidence quantified. Health data on treated individuals are available for some compounds and some species (Table 3) but are not widely available for all infertility agents. Nettles (1997) provided a comprehensive review of possible adverse health effects of infertility agents. The steroidal compounds showed potentially harmful effects on pregnant females, inhibition of parturition or dystocia, changes in ovarian function, impaired lactation, impairment of fertility of offspring, changes in secondary sex characteristics, and late abortions. However, a problem with assessing the information currently available is that it is often contradictory. For example, early reports using diethylstilbestrol (DES) for contraception have been associated with the potentially adverse affects listed in Table 3 under chemical sterilants as reviewed by Nettles (1997). However, many subsequent studies using DES and other contraceptive steroids administered via slow release subcutaneous implants or biobullets have found these to be effective without adverse effects (as reviewed by Kesler 1997 and Warren et al. 1997).

Two of the few compounds for which health data are currently being gathered are the immunocontraceptive products PZP and GnRH. In two long-term immunocontraceptive studies involving PZP and GnRH on white-tailed deer (Miller et al. 1999*b*, Miller et al. 2000), animals were observed for reproductive behavior, animal health, interactions among individuals, hormonal status, antibody titers and other blood parameters, body measurements, and early pregnancy determination by ultrasound and later confirmation with fawning rates. These intensive studies of treated animals and controls have enabled a fairly complete picture of the physiological and behavioral response of the individual treatment.

GnRH immunocontraceptive treatments of white-tailed deer led to reduced progesterone concentrations, altered estrus behavior, contraception, failure to maintain pregnancy following conception, and reduced fawning rates (Miller et al. 2000). Infertility lasted up to 2 years without a booster injection. GnRH immunized bucks demonstrated no sexual activity when paired with control females. Depending on the immunization schedule, antlers either dropped early or remained in velvet. Necropsies of recently vaccinated deer showed that ovaries looked normal, although the GnRH vaccine did not block folliculogenesis in all ovaries as expected (F. Quimby and P. D. Curtis; Cornell Univ., personal communication).

Numerous studies have been conducted on use of PZP (Turner et al. 1996, 1997; McShea et al. 1997; Warren et al. 1997; Miller et al. 1999*b*, 2000). Collectively, these studies have included detailed evaluations of long-term effectiveness and health effects on individuals of this treatment (Miller et al. 1999*b*, 2001), as well as quantitative data from limited field applications (Turner et al. 1997, Warren et al. 1997, McShea et al. 1997). A 9-year study of PZP-injected deer at Pennsylvania State University showed vaccinated deer 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). Over a 4-year period, the health of control and treated deer were compared using measurements of body weight, serum cholesterol, and blood serum chemistry profiles. Although weights of treated deer were slightly less than control deer (probably because of early pregnancy of controls), no significant differences were found, suggesting that the health of the PZP-treated deer was not affected by long-term immunocontraceptive treatment (Miller et al. 2001). Necropsies on 15 deer vaccinated with PZP during a 2-year study at Seneca Army Depot, New York, are in progress; for deer recently injected with PZP (P. D. Curtis and F. Quimby; Cornell University, personal communication), some abnormalities were associated with the ovaries and uterus, including mild inflammation, swelling and localized degeneration of ovarian tissues. Nettles (1997) in his health effects review, also cited potential ovarian damage in horses, rodents, and rabbits. However, the fact that the PZP infertility is reversible implies that ovarian damage is reversible as well.

Other health data on PZP will be required prior to regulatory approval and widespread use of the product. The Food and Drug Administration requires that standardized Target Animal Safety and Drug Tolerance studies (Guideline 33 of the FDA Target Animal Safety Guidelines for New Animal Drugs) be conducted using the final drug formulation and method of administration to determine potential health problems for target species. For a Target Animal Safety Study, female deer would need to be injected with 3 times the standard dose of PZP for 3 consecutive days, followed through the fawning season, and then necropsied to determine any toxic effect of high multiple doses. For a Drug Tolerance Test, female deer would be injected one time with 10 times the standard dose of PZP, followed through the fawning season, and then necropsied to determine any toxic effect of the very high dose.

Another expectation of many wildlife managers is that, in addition to being safe for treated individuals, contraceptives should induce infertility without affecting social behavior. As reproduction itself is a "social behavior," this is a difficult request and may be impossible or unnecessary in some situations. Behavioral responses to infertility agents are variable. Contragestion (interference with early pregnancy) vaccines and some steroidal compounds cause disruption of implantation, pregnancy, or estrous cycles. Immuno-contraception vaccines GnRH and PZP both result in some behavioral changes (Garrott 1995). The PZP vaccine can affect social behavior in some species by increasing the number of times a mare or doe comes into estrus (estrus was occasionally extended into February for white-tailed deer), thereby prolonging the breeding season and potentially resulting in late summer or autumn births. Care must be taken with this product to ensure that the contraceptive activity lasts throughout the breeding season to avoid young being born when environmental conditions are unsuitable for offspring survival. On the other hand, PZP-induced infertility could have minimal behavioral effects on a species such as the coyote, which is a monestrous animal. The GnRH vaccine causes total reduction of sexual function in both males and females, which could be either a desirable or undesirable effect in deer, but in coyotes could potentially have the effect of reducing the pair bond between the coyote pair. It should be recognized that multiple cycles, failure to maintain implantation of the fertilized egg, and females sitting on eggs that never hatch are all variations found naturally and in most cases may not be of concern.

The infertility vaccine using human chorionic gonadotropin (βhCG) currently being tested in India is a good example of a vaccine with little effect on social or sexual behavior. The vaccine prevents progesterone production and subsequent implantation of the egg in the uterine wall (Talwar and Gaur 1987). If similar tropic hormones can be identified in wildlife, they could provide species specific vaccines with few behavioral effects.

In addition to the physiological and behavioral effects of contraceptives on individuals, potentially adverse impacts of

their use on wildlife populations also have been an area of concern (Nettles 1997). Controlled studies, although essential for establishing the physiological and behavioral responses to contraceptive agents, also may be of value for predicting how populations of treated animals may respond and for developing risk assessments for the contraceptives used. Even the best human and veterinary drugs are known to have some adverse effects in a small percentage of the population. Without knowing the incidence of the adverse effects in a wildlife population treated with contraceptives, it is not possible to assess whether the adverse effect is significant or a reasonable trade-off for the benefits derived from the contraceptive's use.

Table 3 may be misleading, because it leaves the impression that adverse effects arise from contraceptive use without considering that the adverse impacts may be offset by beneficial effects. For example, increased energy expenditure is cited as a potentially adverse effect in populations treated with some contraceptives such as PZP, because female deer repeatedly show estrus (Turner et al. 1996, 1997; McShea et al. 1997; Miller et al. 1999*b*). Although increased activity of females in estrus is well documented, energy expenditure for this activity could be offset by the reduced expenditure of energy of not being pregnant. In terms of survival, it is the net energy expenditure of the treated animal that is important, not isolated increases or decreases. However, these data generally are not available because assessing net energy expenditure for individuals presents a difficult challenge under controlled conditions, let alone in a free-roaming population treated with contraceptives. For example, if female deer were treated with the GnRH immuno-contraceptive, one would predict their energy expenditure would be less because females would not be pursued by males and would not invest energy in pregnancy or lactation. However, untreated bucks could potentially expend more energy in pursuit of females outside of the range of the target population. If both males and females were treated in the target population with the GnRH immunocontraceptive, one would predict little if any expenditure of energy for sexual activity or gestation and a net decrease in energy expenditures compared to nontreated populations. The problem with theoretical energy expenditure assessments is that data are often not available to define how much positive or negative influence each of the known and unknown factors contribute to the outcome of the energy expenditure equation.

Contraceptives often are described as affecting the social hierarchy of an animal population (Table 3), but the social change may not be truly adverse. For example, although the social hierarchy of populations treated with the GnRH immunocontraceptives may differ from that of untreated populations during the breeding season, it may not differ from that during the nonbreeding season. Table 3 also includes vasectomy (Kennelly and Converse 1997) and hunting as approaches that have been used to limit population growth to illustrate that they too have potential adverse effects. If males are vasectomized, social hierarchy may be maintained, but repeated estrous cycles and extended breeding seasons would be predicted for females that fail to conceive. Therefore, an increase in energy expenditure would be expected for the populations. Hunting is the conventional method of population control for game species of wildlife, which may have adverse effects similar to population control with contraceptives. Although adverse effects on individuals are minimal if death occurs quickly, animals that are injured, but successfully avoid the hunter, may subsequently die from the injury or infection. Culling males or females from a wildlife population will likely change the social hierarchy and the potential genetic pool. The social reshuffling that takes place also may result in increased energy expenditure.

Regardless of the method considered for population control, there is clearly some difficulty in assessing the true impact of each of these potentially adverse effects on animal populations and nontarget species. Although some of the hypotheses regarding adverse effects may be reasonable, most have not been tested experimentally on the species in question, and in most instances observations have not been made under field conditions to support or refute their validity. Moreover, without detailed observations it is not possible to know how many potentially interacting factors within an animal population will be affected by a perturbation. It is likely that the validity of the health and population concerns will become apparent only by actual testing of contraceptives under semi–free-ranging field conditions that will enable data to be gathered for analysis and modeling (Bomford and O'Brien 1997).

The management of wildlife overpopulation through use of contraceptives is a goal that has achieved some success, particularly in populations limited in number and geographically isolated. However, for large free-roaming populations the challenge to find an ideal contraceptive that will render the target species reversibly infertile without some effects on social hierarchy or aspects of individual or population biology may not be achievable. Policy makers will likely be faced with the fact that some changes that occur in response to a contraceptive treatment will be adverse, but are less so than the consequences of overpopulation of the target species.

Risks to Nontarget Animals

Ideally, all infertility techniques would be species specific. However, this goal is proving difficult to attain. Steroids are common to many species; additionally, some of the steroid contraceptives accumulate in body tissue and could have secondary effects on predators. The current immunocontraceptive vaccines have only limited specificity. The GnRH molecule is present in both birds and mammals; however, avian and mammalian GnRH are different, providing some specificity between classes. Much of species specificity in normal mammalian reproduction is related to sperm binding to the zona pellucida, yet immunizing against porcine zona pellucida (PZP) results in infertility across most mammalian species other than cats (Jewgenow 2000) and rodents. Rodent zona pellucida is unique among mammals; therefore PZP is not effective as a contraceptive in rodents (Miller et al. 1997*b*), and rodent zona pellucida contraceptives should not affect other nontarget mammals. The bird contraceptives nicarbazin and conjugated linoleic acid act on the egg and would not affect mammals.

In the absence of species specificity, one needs to be concerned about effects on nontarget species (Guynn 1997). When contraceptives are used for population control, the potential threat to nontarget species is dependent largely on the method used to administer the contraceptive to the target species (Table 3). Effective delivery of contraceptives to the target species may prove to be as difficult as developing an effective contraceptive. Delivery mechanisms such as injection, darting, or implanting require direct contact with animals, and are practical only in targeting specific populations of limited numbers. If properly implemented, there is virtually no chance of nontarget species receiving the treatment. In contrast, although the use of oral bait delivery systems offers a way to treat larger, free-roaming populations at lower cost (Asa 1997), the risk of unintentional treatment of nontarget species increases significantly. Therefore, if an oral contraceptive delivery system is not designed to be limited to the target species, then nontarget species could become infertile as well. For example, a decade of research toward development of a prototype delivery device for oral raccoon rabies vaccination (Rupprecht et al. 1987) in the eastern U.S. resulted in a fishmeal polymer bait readily consumed by raccoons, yet a high percentage of other carnivores and some rodents also consumed baits (Rupprecht et al. 1992). When vaccinating against disease, consumption of vaccine baits by nontarget species presents few problems. However, contraception should be limited to the target species and thus the delivery system for contraceptive baits should be designed to exclude nontargets. To illustrate, if one wanted to orally cause infertility in female white-tailed deer, an elevated bait station could be designed to exclude nontarget species and allow a doe to put its head between the bars, but exclude the rack of a buck. In some instances, low levels of effects on nontarget species may be an acceptable risk, much as a low level of nontarget risk is inherent in use of most pesticides.

The use of infectious biological vectors to deliver contraceptive vaccines also could affect nontarget species if the infectious organism was not specific to the host species (Tyndale-Biscoe 1997). The risks associated with dissemination of a biological vector to unintended target populations and nontarget species may be too great at this time to warrant serious consideration for wildlife contraception. However, this approach is under active consideration in Australia for control of feral rabbit populations (Holland 1999).

Risks to Humans

Contraceptives used on huntable species of wildlife pose an additional safety consideration—safety to humans who may consume them. This risk is minimized by regulatory requirements of approval for drugs. Before granting an INAD application, the FDA examines the potential for human health risk and requires adequate data precluding risk prior to allowing human consumption. For compounds that accumulate in body tissue and could have secondary effects, such as some of the steroid contraceptives, approval would not be granted for use to cause infertility in food animals such as deer and Canada geese without adequate data on chemical withdrawal times. Immunocontraception vaccines provide few risks for consumptive use of dosed wildlife; an animal that has been vaccinated contains antibodies that prevent reproduction in addition to millions of other antibodies, all of which are harmless to the organism that digests them—like any other proteinaceous food consisting of amino acids. The FDA is more concerned about the Freund's adjuvant currently used with immunocontraceptive vaccines than they are about the protein vaccine. An adjuvant is a compound added to the vaccine to increase the immune response. For contraceptive vaccines to be successful, long lasting titers to the contraceptive antigen must be achieved. To achieve these high titers, the most immunogenic contraceptive protein must be combined with the best possible adjuvant. Previously, the only adjuvants that have provided high and long lasting immunocontraceptive responses have been Freund's Complete adjuvant (FCA) and a modified FCA produced by Calbiochem. Both adjuvants contain mycobacteria; the waxy coat of the mycobacteria activates the phagocytic cells to ingest the mycobacteria and present the immunocontraceptive antigen to the immune system. The presence of mineral oil, an indigestible compound, further promotes the antigen response by slowing the degradation of the vaccine. These qualities make FCA extremely effective.

The FDA has objected to the use of FCA for three reasons. First, the FDA has had concerns for false-positive TB skin tests in deer treated with contraceptive vaccines containing FCA (*M. tuberculosis*). Second, FDA expressed concern about the potential carcinogenicity of FCA as it relates to the human food safety of edible products derived from treated animals. Third, FDA was concerned about the presence of granulomatous lesions caused by FCA at the injection site. Based on the latter two concerns, FDA has required that food animals, such as deer, that are treated with FCA or modified FCA be marked with a tag prohibiting human consumption. APHIS/USDA has recently developed a new adjuvant that appears to be as effective as FCA while having few of the negative side effects. APHIS is requesting that the FDA allow the new adjuvant to be used in immunocontraceptive vaccines without the requirement that animals be marked with a tag prohibiting human consumption.

Two of the three infertility agents being researched for birds (nicarbazin and CLA) are authorized by the FDA for use in broiler chickens and also should have low risk. The third compound potentially proposed for 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.

REVIEW OF CURRENT TECHNOLOGY FOR WILDLIFE CONTRACEPTION

Steroids/Hormones

Chemical contraception through the use of synthetic steroids, estrogens, and progestins was investigated widely during the 1960's and 1970's in many species, such as coyotes (Balser 1964; Brusman et al. 1968), pigeons (*Columba livia*, Woulfe 1970), red-winged blackbirds (*Agelaius phoeniceus*, Guarino and Schafer 1973), rats (Garrison and Johns 1975), coturnix quail (*Coturnix coturnix*, Schafer et al. 1977), and deer (Matschke 1977*a*, 1977*b*, 1980; Roughton 1979). More recently, androgens have also been tested for use in male rodents and wolves (Asa 1997). These steroid hormones act by interfering with ovulation or implantation of the egg in females and by impairing spermatogenesis in males.

Diethylstilbestrol (DES) is a synthetic estrogen that showed some success in reducing fertility in female coyotes and foxes (*Vulpes vulpes*) (Balser 1964, Linhart and Enders 1964, Linhart et al. 1968); it was considered to be of limited value, however, because its use required precise timing of administration in relation to the breeding cycle. DES had variable effects in voles, interrupting early pregnancy or causing sterility or delayed sexual maturity of female offspring when fed late in pregnancy or during lactation (German 1980). DES curtailed all reproduction of prairie dogs (*Cynomys ludovicianus*) when fed during the peak breeding period (Garrett and Franklin 1983). Oral doses of DES successfully interrupted pregnancy in white-tailed deer (Matschke 1977*a*), but the does rebred and showed poor acceptance of subsequent baits, leading to poor efficacy. Because it accumulates in body tissue, DES presented hazards to predators consuming treated animals and was never registered with the EPA. Mestranol is another orally active estrogen tested for rodent, rabbit, and bird control. The half life of mestranol is less than 6 hours, so retention in food chains is not a problem (Sturtevant 1970, 1971), but it has caused bait shyness. Mestranol was somewhat successful in reducing fertility in birds when force-fed in a grit or sprayed on eggs.

One of the more promising uses of steroids for contraception in wildlife has been the delivery of norgestomet (a potent progesterone approved by FDA for use in cattle for estrus synchronization, Darling 1993) to black-tailed deer (*Odocoileus hemionus*) using a biobullet (Jacobsen et al. 1995). The 10 treated does failed to exhibit estrous behavior and 2 treated bucks exhibited no sexual behavior for 1 year. Additional studies with white-tailed deer (DeNicola et al. 1997*a*) confirmed the contraceptive effect of the implant.

Agents that cause the failure of the fertilized egg to implant in the uterine wall, or agents that interfere with the maintenance of early pregnancy, are called contragestive agents. Given later on in gestation, the technology could be considered abortifacient. Progesterone is the main hormone involved in maintaining pregnancy. Progesterone antagonists, which can be given orally, compete for progesterone binding sites but do not induce the biological activity needed to maintain pregnancy. These antagonists may prove valuable as orally delivered contraceptives or contragestive agents. Progesterone antagonists (which are difficult for the body to degrade and excrete) can be fed monthly as contraceptives or once in early pregnancy to interrupt pregnancy. They act by causing a sufficient disruption in the uterine lining to prevent implantation (Gao and Short 1994). The controversial RU486 (mifepristone) was evaluated for effectiveness as a contragestive agent in coyotes (DeLiberto et al. 1998) without success.

Lutalyse®, produced by Upjohn (prostaglandin $PGF_{2\alpha}$), is routinely used in feedlot cattle during the first 100 days of gestation and will cause abortion within 35 days of injection. DeNicola et al. (1997*b*) and Waddell et al. (2001) reduced

fertility in white-tailed deer by injecting Lutalyse. Depending on the gestational time of administration, the technology could be considered either contragestive or abortifacient. Lutalyse is available only in an injectable form. Several other synthetic progestins (which prevent ovulation in female mammals and inhibit testicular activity in males) have been identified as having potential as wildlife infertility agents. Levonorgestrel (norgestrel) is the active component of the Norplant® implant approved for human use as a contraceptive implant by FDA (McCauley and Geller 1992); it has been used in zoos but was not effective in deer (Plotka and Seal 1989, White et al. 1994). Norethindron acetate is used in combination with ethynylestradiol as an oral contraceptive in humans but has not been effective in suppressing estrus in heifers (Kesler 1997). Megestrol acetate is marketed in Europe as Ovarid® (Kirkpatrick 1989) and in the U.S. as Megace® and Ovaban® and is sometimes used as a contraceptive in domestic dogs and cats. It showed only weak effects on feral cats (McDonald 1980) and no effect on white-tailed deer (Matschke 1977*b*). Medroxyprogesterone acetate (Provera®) has been used in zoos. Melengestrol acetate (MGA) is the steroidal compound most widely tested in wildlife and is approved by FDA for use in cattle as a daily administration (Zimbelman and Smith 1966) for suppression or synchronization of estrus, increased weight gain, and improved feed efficiency (Bennett 1993). It inhibited reproduction in white-tailed deer when ingested daily (Roughton 1979) or implanted (Bell and Peterle 1975, Plotka and Seal 1989). MGA implants have been used by zoos for about 20 years, but recent findings of uterine pathology in felids have raised concerns about its use (Kazensky et al. 1998).

Some steroid hormone preparations target males rather than females (Asa 1997). Bisdiamine is a compound that selectively interferes with spermatogenesis but not testosterone production. When administered in ground meat daily to gray wolves it suppressed spermatogenesis without affecting mating behavior. Indenopyridine also blocks sperm production; it has been tested only in rodents. Alpha-chlorohydrin (Epibloc®), a male chemosterilant, was approved by the EPA for use as a rat control agent in 1982 (Bowerman and Brooks 1971, Ericsson 1982, Andrews and Belknap 1983), but is no longer marketed. At low doses it caused temporary sterilization, with time to recovery of fertilization dependent on dose. A single high dose caused permanent sterility but showed toxic effects. In addition, rats have a promiscuous mating system, so targeting only males offered little promise as a population control technique.

Despite more than four decades of effort, research has yet to develop and implement an effective wildlife damage management program based on the use of steroid hormones to inhibit reproduction in overabundant animals (Kennelly and Converse 1997). Steroids have the advantage that they can be fed orally or implanted, and they have been shown to be effective for some species. However, none of these steroids has proven practical as a wildlife management tool for various reasons. Orally, they are effective for only a short period and need repetitive applications, making them costly and impractical in most field situations. Although MGA is effective as an implant for several seasons (Matschke 1980), the large implant requires capturing animals and performing minor surgery. Some of the steroids, such as DES, persist in tissue and in the food chain, making them unsatisfactory from an environmental point of view. They can also have deleterious health effects on treated animals and potentially on predators that eat treated animals (discussed earlier under health effects).

Natural Plant Compounds

The livestock industry has been concerned for some time about naturally occurring plant compounds that can result in lowered reproductive rates in domestic herds (James et al. 1994). Phytoestrogens naturally occur in over 300 plant species (Shemesh and Shore 1994). A constant source of estrogen interferes with normal estrous cycles in most animals, and phytoestrogens exert many of the same effects as estrogen, even though their chemical structure is quite different. Another source of reproductive loss in cattle is endophyte-infected tall fescue. Ergot peptide alkaloids produced by the endophyte are suggested as the primary cause of the reduced reproduction (Porter and Thompson 1991). Vasoconstrictive effects and neurohormonal imbalances are thought to be the principal mechanisms for the reproductive losses (Browning et al. 1998). Bromocriptine (cabergoline) is a derivative of the alkaloid ergot family that acts as an enzyme inhibitor of prolactin. The lactation-blocking effects have been tested on kangaroos (Tyndale-Biscoe et al. 1990) by injection into lactating females. Bromocriptine is currently being tested in coyotes by the NWRC. Plant estrogens and toxins show some promise in causing infertility in overabundant animals, but much more research on them will be necessary.

Avian Contraceptives

Two compounds have been tested in the past for sterilizing male red-winged blackbirds: triethylenemelamine (TEM) and ThioTEPA (Davis 1961, Vandenbergh and Davis 1962, Guarino and Schafer 1973, Potvin et al. 1982). Both chemicals caused some reduction in hatching rates, but studies did not show an overall population reduction.

Interfering with egg laying or the hatchability of the egg appears to be the best approach to reducing reproductive

capacity in birds. Egg addling, including shaking, freezing puncturing, or oiling the eggs in the nest, effectively reduces egg hatchability (Pochop et al. 1998). Egg oiling with corn oil is allowed by the EPA under a (FIFRA) 25b exemption for natural products, and is being used to reduce reproduction in Canada geese (and gulls. However, this method is labor intensive and probably useful only in small-scale operations.

Ornitrol (DiazaCon) is a cholesterol mimic that has a similar chemical structure as cholesterol (Miller and Fagerstone 2000). DiazaCon has two possible modes of action; it may inhibit the formation of cholesterol, or it may inhibit side chain cleavage of cholesterol. In both cases, formation of pregnenolone (the parent compound of all steroid hormones) is reduced, preventing formation of testosterone and progesterone. DiazaCon persists in the body because the side chain cannot be cleaved, preventing it from being excreted like cholesterol, so its reproductive inhibition effects can last up to several months. As Ornitrol, it was registered in the late 1960's with the EPA as an oral pigeon reproductive inhibitor, 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 usage of the compound became expensive. Also this product had undesirable health effects on the birds (Lofts et al. 1968), because cholesterol is necessary for body functions in addition to production of reproductive hormones. Ornitrol also showed some success in reducing fertility in red-winged blackbirds (Fringer and Granett 1970, Lacombe et al. 1987). The compound needs to be applied over several days before breeding occurs. In recent tests, Yoder (2000) found the compound effective in reducing egg laying and egg hatchability up to 4 months in coturnix quail after feeding it for 10 days. This compound (renamed DiazaCon) is authorized for experimental use in field situations by APHIS under an INAD application through the FDA. It may prove useful in controlling the reproduction of seasonal breeding species such as the Canada goose when fed just prior to breeding in the spring. During the summer, DiazaCon would be cleared from the system, allowing animals to be hunted in the fall and to breed normally the next season. DiazaCon is not species specific, and potentially could be effective in mammalian as well as avian species.

Nicarbazin (NCZ) was developed in the 1950's as a compound that controlled coccidiosis (an avian disease) and improved weight gain and feed efficiency in broiler chickens. If accidentally fed to breeder or layer hens, NCZ causes reduction in hatchability and egg laying, apparently due to increased vitelline membrane permeability, which destroys the conditions necessary for viable development of the embryo (Jones et al. 1990). Fertilization is not affected by Nicarbazin (Hughes et al. 1991). Nicarbazin has several potential advantages as an antifertility agent. Although not species specific, it is specific to egg layers, the compound is cleared from the body within about 48 hours, and the infertility effect is reversible. Nicarbazin is FDA-approved for the control of coccidiosis in broiler chickens through Koffolk, Inc.; therefore, many required safety and toxicity studies have been completed. A disadvantage of the compound is that it has to be fed for several days prior to egg laying; thus delivery would be a problem in the field. Also, formulations or delivery methods would have to be developed to limit ingestion by nontarget bird species. Nicarbazin is currently being successfully tested on Canada geese in penned and field situations by the NWRC under an FDA INAD. The ideal dose rate would allow the female to lay eggs and sit on them, but prevent hatching, which is a relatively common occurrence in nature.

Conjugated Linoleic Acid (CLA) also is being tested for its potential to reduce avian reproduction. CLA is used as a feed additive to increase weight gain and feed efficiency in broiler chickens (Chin et al. 1994). Chickens with low grade infections produce prostaglandin, which stimulates a fever and muscle catabolism, resulting in weight loss of up to 10%. CLA prevents the synthesis of prostaglandin and subsequent weight loss after infections (Miller et al. 1994). CLA is sold in health food stores as an antioxidant and promoted to reduce the loss of muscle in the elderly that results from low grade infections (Pariza 1993). When fed to laying chickens, CLA reduces hatchability by causing solidification of the yolk at refrigerator temperatures (Cooney 1995). In theory, when the clutch is being laid in the spring, the bird does not incubate the nest until the clutch is complete. As the temperature drops during the night the yolk of unincubated eggs from CLA-fed birds solidifies, interfering with the hatchability of the eggs. CLA is specific to avian species and its infertility effect is reversible. It needs to be fed for 10 or more days. A limited field trial with Canada geese was ineffective (S. Craven, University of Wisconsin, personal communication), but with further research the compound could have utility in cold climates.

Immunocontraceptive Vaccines

Much of the recent infertility research has centered around immunocontraceptive vaccines. The principle behind the vaccines involves using the animal's immune system to produce antibodies against gamete proteins, reproductive hormones, and other proteins essential for reproduction. These antibodies interfere with the normal physiological activity of the reproductive agents (Talwar and Gaur 1987). This approach is a natural process in the sense that

antibodies induced in the target animal interfere with reproduction without the need for constant or repetitive treatment with synthetic compounds; initial treatments can be effective for 1 to 4 years (Turner and Kirkpatrick 1991, Miller et al. 1999*b*).

Reproduction can be blocked at many sites in the reproductive process using vaccines. A vaccine can affect both sexes by blocking GnRH and preventing the release of essential reproductive hormones. A vaccine can selectively affect females by barring sperm penetration of the zona pellucida. Embryo development can potentially be hindered by preventing implantation and development of the fertilized egg via antibodies to human chorionic gonadotrophin (hCG) or to similar tropic hormones in other species. Sperm proteins also can be targeted by vaccines. Most use of immuno-contraceptives has been applied to white-tailed deer (Garrott 1995) and feral horses (Turner and Kirkpatrick 1991); however, this technology could also be applied to other wildlife species such as rodents, pest species of birds, coyotes, and foxes (Miller et al. 1998) if suitable delivery systems are developed.

Zona Pellucida

Reproduction in female mammals can be prevented by antibodies that bar sperm penetration of the zona pellucida of an ovulated egg by binding either to the zona pellucida or to the sperm. Zona pellucida is an acellular glycoprotein layer located between the oocyte and the granulosa cells on the outer surface of the egg. Antibodies to this glycoprotein layer result in infertility either by blocking the sperm from binding to and penetrating the zona pellucida layer or by interference with oocyte maturation, leading to the death of the developing oocyte (Dunbar and Schwoebel 1988). The zona pellucida vaccine in use today comes from the pig ovary—Porcine Zona Pellucida (PZP). PZP vaccine has been used to produce immunocontraception in numerous species, including dogs (Mahi-Brown et al. 1985), baboons (Dunbar 1989), coyotes (Miller 1995, Deliberto et al. 1998), and burros (*Equus asinus*, Turner et al. 1996). Most research has been on wild horses (Kirkpatrick et al. 1990, Garrott et al. 1992) and white-tailed deer (Turner et al. 1992, 1996, Miller et al. 1999*b*).

The contraceptive effect is titer dependent. Injecting with an initial and a booster dose of PZP vaccine is effective in causing infertility in deer and horses for several years. Miller et al. (1999*b*) achieved 89% reduction in fawning during 2 years of active immunization and 76% reduction in fawning over the 7-year study. A 2-year study by Cornell University and the NWRC, conducted at the Seneca Army Depot, demonstrated that the same contraceptive effect can be achieved in deer by using darts to administer an initial and a booster vaccination.

As an injected protein broken down in the body, PZP does not enter the food chain. Also, its effects are reversible after short-term use. Disadvantages are that PZP is not species specific and is effective in reducing fertility in most mammals tested other than rodents (Miller et al. 1997*b*) and cats (Jewgenow et al. 2000), which have very different zona pellucida antigenic determinants. Because of the similarity of effects for most mammal species, care must be taken in the delivery system to provide the vaccine only to the target animal. The PZP vaccine induces multiestrus in female deer and feral horses, which could result in late season births if antibody titers drop below a critical threshold.

Gonadotropin Releasing Hormone (GnRH)

Another active area of research (Jones 1983, Griffin 1992) is use of GnRH immunocontraceptive vaccine to inhibit the reproductive activity of both sexes by causing development of antibodies blocking GnRH. Antibodies to GnRH reduce the circulating level of biologically active GnRH, thereby reducing the subsequent release of gonadotropic hormones, leading to atrophy of the gonads and concomitant infertility of both sexes (Miller et al. 1997*b*). GnRH as a contraceptive vaccine has been researched in domestic farm animals for over 10 years, but little research has been done on wildlife species. Two forms of GnRH (avian and mammalian) 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*b*) immunized Norway rats with GnRH and created 100% infertility in both males and females. Miller et al. (2000) recently completed a long-term study on the effect of GnRH on white-tailed deer that demonstrated an 86% reduction in fawning during active immunization and a 74% reduction over 5 years.

GnRH is not species specific, although the presence of different avian and mammalian forms of GnRH would reduce the number of susceptible nontarget species. Mammalian GnRH is effective in reducing fertility in most mammals, including rodents. Its contraceptive effects last 1 to 2 years without boosting and are reversible. GnRH affects social behavior by reducing the sexual activity of both sexes. It is presently available only in injectable form and, like PZP, requires an initial and a booster injection. GnRH treatment may be a useful technique where sexual activity itself creates human–wildlife conflicts. In deer, where fall sexual activity has been associated with increased deer–vehicle collisions, GnRH could potentially reduce damage by reducing deer movement related to sexual activity. In cases where tame male deer have been fed in a park setting, GnRH also could reduce danger of aggressive

behavior to humans during the fall rut. However, for some species reducing sexual behavior may not be advantageous; for example GnRH could potentially reduce pair bonds in animals like coyotes (DeLiberto et al. 1998).

Sperm Antibodies

Sperm vaccines are promising because they can potentially disrupt fertility in females as well as in males. Sperm head glycoproteins that bind to zona pellucida have been identified. If these glycoproteins are used as vaccines, antibodies are produced in the female and are available to bind to sperm present in the oviduct, preventing conception by blocking the sperm from binding to the zona pellucida surrounding the egg. Sperm protein immunocontraception is being investigated for contraception in the red fox and the rabbit in Australia (Tyndale-Biscoe 1991, Morell 1993, Bradley 1997).

Chorionic Gonadotropin

Human chorionic gonadotropin, which is produced by the implanting embryo in humans, induces the corpus luteum on the ovary to continue production of the hormone progesterone required for the maintenance of pregnancy. Antibodies to hCG reduce the activity of this hormone, interfering with the maintenance of the uterine lining, and thereby preclude successful implantation of the fertilized egg, which sloughs off and is reabsorbed (Stevens 1992). An hCG vaccine would induce infertility with little effect on the social and sexual behavior of the species involved. Contraception clinical trials are underway at the National Institute of New Delhi testing effectiveness of a hCG vaccine on fertile women (Talwar et al. 1994). Primates and horses are the only two mammals known to use CG (chorionic gonadotropin) as a key tropic reproductive hormone. It is possible that feral horse numbers, which have become a problem on Bureau of Land Management (BLM) lands, could be reduced by fertility reduction through inducing antibodies to CG. Many species use other tropic hormones to maintain the implanted embryo, and all are probably involved with controlling the common gestational hormone progesterone. Because of apparent differences among species in tropic hormones, vaccines against these hormones may provide the best possibility of species specificity if these hormones can be identified.

Contraception Without Steroids or Immunological Methods

Gonadotropin Releasing Hormone (GnRH) Agonist

Gonadotropin releasing hormone is an endogenous decapeptide neurohormone with an obligatory role in reproduction. This hormone is synthesized and secreted in the hypothalamus of the brain and selectively stimulates the pituitary gonadotroph cells to release 2 important reproductive hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). These latter 2 hormones control proper functioning of the ovaries in the female and the testes in the male. The structure of GnRH has been determined (Matsuo et al. 1971) and numerous superactive analogs of the hormone (agonists) have been synthesized (Vale et al. 1976). The GnRH agonist analogs most commonly used to clinically suppress the pituitary-gonadal axis include leuprolide, buserelin, nafarelin, and histrelin. These analogues are 15 to 200 times more active than naturally occurring GnRH (Conn and Crowley 1991).

Pituitary gonadotrophs can be made unresponsive to GnRH by administering an agonist of GnRH in a continuous manner. Prolonged, continuous infusion of a GnRH agonist, especially at high concentrations, results in desensitization and suppression of gonadotropin secretion and loss of gonadal function (Clayton et al. 1979). However, when administration of the GnRH agonist is discontinued, fertility returns. The practicality of this approach is therefore dependent on the development of a long-acting, slow-release formulation that can be delivered remotely. Recently, a practical mode of delivery using subcutaneous or intermuscular implants has overcome the need for constant mechanical infusion of the agonist. Slow release formulations of GnRH agonist are now commercially available and have been shown to be effective in suppressing gonadal function for up to 6 months in some species. Continuous treatment with a GnRH agonist will inhibit ovulation in females of several species (Nett et al. 1981, Adams and Adams 1986, Khalid et al. 1989), including dogs (Vickery et al. 1989), cattle (Herschler and Vickery 1981), sheep (McNeilly and Fraser 1987), horses (Montovan et al. 1990), and stumptailed monkeys (Fraser 1983). Similar studies for wild ungulates are more limited. Continuous, subcutaneous infusion of Histrelin™ via osmotic minipump inhibited LH secretion and ovulation in female white-tailed deer for 14 days (Becker and Katz 1995). Leuprolide administered as a subdermal matrix implant was effective in suppressing LH secretion and pregnancy for one breeding season in captive mule deer (*Odocoileus hemionus*) and elk (*Cervus elaphus*, Baker et al. 2000). No negative behavioral or physiological side effects were reported in these investigations.

Gonadotropin Releasing Hormone (GnRH)—Toxin Conjugate

For most wild ungulate applications, a single dose, long-acting contraceptive offers the most promising technology for population management (Hobbs et al. 2000). A promising new nonsteroidal, nonimmunological approach to permanent contraception involves linking synthetic analogs of GnRH to cytotoxins. By coupling a superactive analog of GnRH to a cytotoxin, it is possible to specifically target that toxin to LH- and FSH-secreting cells in the anterior pituitary

gland. GnRH is responsible for secretion of LH and FSH in both males and females, and its structure is highly conserved across species. Therefore, a single GnRH-toxin conjugate has the potential to induce sterility in both sexes and numerous vertebrate species.

There are many natural cytotoxins available for conjugating to the GnRH molecule. Many toxins are composed of two subunits, a toxin subunit and a binding subunit. The binding subunit of most toxins interacts with a protein on the surface of cells. Once binding has occurred, the toxin is internalized via endocytosis, and the binding unit dissociates from the toxic subunit in lysosomes. The toxic subunit then crosses the lysosomal membrane and enters the cytoplasm of the cell. Within 24 hours a single toxin molecule can inactivate most (if not all) of the two million EF-2 molecules in a typical animal cell; when the cell is unable to make protein, it dies. To target the toxin to a specific cell type (rather than all cells) within the body, the binding subunit of the toxin can be removed and replaced by a molecule that will bind to only one cell type, in this case an analog of GnRH. This will target the toxin to gonadotropin-secreting cells in the anterior pituitary. This approach has several potential advantages over other methods of contraception: (1) a single treatment may permanently sterilize an animal; (2) the treatment should be effective in both males and females and in all vertebrate species; (3) the GnRH-toxin conjugate is metabolized from the body within 24 hours of treatment; (4) the proteinaceous nature of the GnRH-toxin conjugate eliminates the possibility of passage through the food chain; (5) the small volume required for effective contraception would facilitate microencapsulation and administration by syringe dart or biobullets.

At present, clinical trials are being conducted with dogs, cats, sheep, mule deer, and elk to evaluate the effectiveness of ribosome-inhibiting proteins extracted from plants as toxins for permanently deactivating pituitary gonadotroph cells. To date, no long-term investigations have been conducted to evaluate the effective duration of GnRH-toxin conjugate in suppressing gonadotroph function. Preliminary results in female mule deer indicate that GnRH-toxin conjugate will suppress LH secretion for up to 6 months (Baker et al. 1999). Safety studies have not been reported. Since there are GnRH receptors in other sites in the body, toxicity could be a potential problem with this technique.

SUMMARY

As we study the habits of most overabundant species, we generally find that they are adaptable to multiple and changing environments. That is why their populations increase in spite of a rapidly changing landscape. Wildlife contraceptive programs have been less successful than hoped in the past due to a lack of long-acting fertility control agents, as well as failure to understand mating strategies and related behavior patterns of species targeted for reproductive control. With an increasing research focus on contraceptive development, and knowledge of animal reproductive systems and behaviors, fertility control as a technology is advancing rapidly. Major hurdles still include development of cost-effective delivery systems for effective products, commercialization of vaccines or baits, and public acceptance of fertility control as a wildlife management practice.

Warren (1995), in a discussion of factors relevant to the practical and logistical implementation of contraceptives for controlling wildlife, correctly pointed out that contraceptive development requires a team approach involving laboratory scientists (e.g., immunologists, molecular biologists, reproductive physiologists) to develop the contraceptive techniques and wildlife biologists to develop delivery systems and methods to measure field efficacy and safety. Although laboratory scientists have made remarkable progress over the last 10 years in techniques development, the partnership with wildlife biologists and wildlife management agencies is just beginning.

There are currently no contraceptive products available for commercial use, and there are many barriers to overcome before commercial use will occur. Several products have been given an INAD number by the FDA allowing use under research protocols in laboratory studies, pen studies, and in limited field situations with small numbers of animals. But before contraceptives can be used by wildlife managers other than researchers, FDA will undoubtedly require that manufacturers of products obtain a NADA, which will require additional health and safety trials, efficacy trials, and final manufacturing methods. Because contraceptive products for wildlife use will be a minor market, and the cost of obtaining authorization for their use by the FDA will be high, drug manufacturers will be reluctant to develop products on their own. Researchers, wildlife managers, and management agencies will need to be involved in development of products along with the drug manufacturers. Development could occur by (1) focusing on products already licensed by FDA for other purposes, which will cost less to develop as an approved product for infertility use, (2) building partnerships with drug manufacturers to develop lucrative alternative uses such as animal production or pet neutering, or (3) providing direct funding and support for development. Product development is a nontraditional role for wildlife management agencies, but one that will be required if contraceptive products are to be used in anything other than a research context.

For any wildlife contraceptive product, there will be a number of health and behavior-related issues concerning use on target and nontarget species and effects on humans. First, infertility agents should have few adverse health effects on target animals. Second, they should not affect nontarget species adversely. Because technology is not currently available to make infertility agents species specific, delivery systems should be developed to limit effects on nontarget species. Third, treated food animals must be safe for human consumption. Products used on huntable species of wildlife could pose potential risks to humans who consume them. These risks are minimized by regulatory requirements of approval for drugs through the FDA. Fourth, infertility agents should result in little negative social effect on the target species, recognizing that because reproduction itself is a "social behavior," this is a difficult request and may be impossible or unnecessary in some situations. Fifth, for certain cases the infertility effect should be reversible. Most of the infertility agents discussed in this paper are reversible, but there is a large variation in the length of time that they are effective. Because much of the health and population information currently available is based on limited studies and conjecture, further controlled studies are needed to evaluate the physiological effects of specific contraceptives on individuals and populations of a target species. Results from these studies should provide reliable information for risk assessment so agencies involved with wildlife management are able to make informed decisions for policy implementation.

An additional hurdle to overcome before use of contraceptives is an accepted wildlife management practice is the attitude of wildlife management agencies. Many wildlife agencies and biologists have been reluctant to acknowledge the potential applicability of fertility control for managing wildlife populations (Warren 1995). In part, this is because the techniques available have been publicized as a replacement for sport hunting. In reality, it is doubtful if the cost of delivery for contraceptive techniques would allow their use on free-ranging game populations. The current techniques often have been uneconomical or infeasible for practical implementation even in small localized populations of game species such as deer. And the species for which contraceptives have been primarily tested (long-lived species such as deer and horses) are those that are least suited for population reduction through use of fertility control. 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.

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 forced 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. The public views contraceptives as a positive alternative to other management tools, and managers are increasingly being forced to become active partners with the public in developing practical applications for this technology. Public forums discussing the advantages and disadvantages of various management techniques will be more important in the future. The challenge for wildlife managers for many species will be to integrate potentially valuable contraceptive technologies with more conventional methods of wildlife population management. Furthermore, if infertility agents are developed and used on long-lived species such as deer and geese, biologists need to be honest with the public about the inefficiencies of this approach and the length of time required for such strategies to reduce populations relative to lethal control.

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TABLES

Table 1. List of Acronyms

Acronym	Compound Term
AAWV	American Association of Wildlife Veterinarians
APHIS/USDA	Animal and Plant Health Inspection Service/ U.S Department of Agriculture
ASR	adult survival rate
BCG	*Bacillus calmette guerin*
BLM	Bureau of Land Management
CFR	Code of Federal Regulations
CG	chorionic gonadotrophin
CLA	conjugated linoleic acid
CSIRO	Commonwealth Scientific and Industrial Research Organization
DES	diethylstilbestrol
EPA	Environmental Protection Agency
FCA	Freund's complete adjuvant
CVM/FDA	Center for Veterinary Medicine/Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FSH	follicle stimulating hormone
FWS	Fish and Wildlife Service
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotrophin
INAD	Investigational New Animal Drug
IPM	integrated pest management
LH	luteinizing hormone
MGA	melengestrol acetate
NADA	New Animal Drug Application
NCZ	nicarbazin
NEPA	National Environmental Policy Act
NWRC	National Wildlife Research Center
PZP	porcine zona pellucida
TEM	triethylenemelamine

Table 2. Estimated relative efficiency of reproductive and lethal control based on numbers remaining after 3 years from an initially stable population of 1,000 individuals in which reproductive or survival rate is reduced annually by 50% (using population models presented in Dolbeer 1998).

Species	Number remaining after 3 years			Relative efficiency[a] of lethal to reproductive control (RC/LC) after 3 years	
	Reproductive control (RC)	Lethal control (LC)			
		≥ Age 0[b]	≥ Age 1[c]	≥Age 0[b]	≥ Age 1[c]
Fruit bat (*Pteropus giganteus*)	731	125	191	5.8	3.8
Laughing gull (*Larus atricilla*)	720	125	180	5.8	4.0
Double crested cormorant	673	125	183	5.4	3.7
White-tailed deer	639	125	212	5.1	3.0
Beaver (*Castor canadensis*)	624	125	199	5.0	3.1
Canada goose	607	125	193	4.9	3.1
Coyote	486	125	264	3.9	1.8
Common grackle (*Quiscalus quiscala*)	460	125	349	3.7	1.7
Brown-headed cowbird	338	125	462	2.7	1.3
Red-billed quelea	368	125	421	2.9	0.7
Black rat	97[d] (406)[e]	307[c]	675[d]	0.3[c]	0.6[d]

[a] Efficiency ratios presented are specific to population status after 3 years and will increase during additional years of treatment.

[b] Survival reduced 50% for age classes ≥ 0.

[c] Survival reduced 50% for age classes ≥ 1.

[d] Survival and reproduction of adults (≥3 months old) reduced 3 times/year.

[e] Survival and reproduction of adults (≥3 months old) reduced 1 time/year.

Table 3. Potential adverse effects of antifertility agents. This list does not necessarily mean that these agents were successful or practical in causing infertility in the species tested.

Agent/Method	Species tested	Intended antifertility effect	Potential adverse effects		
			Individual	Population	Nontarget species
Synthetic Steroids [a]					
Estrogens					
Diethylstilbestrol (DES) [b]	*Coyotes, foxes, voles, prairie* dogs, white-tailed deer	*Disrupt/prevent* reproductive cycle, induce early abortion	Long-term disruption of ovarian function, impaired lactation, incomplete abortion, retained placenta, late abortion	Increased energy expenditure of males, disruption of social hierarchy	None or some as for target species
Methanol [c]	Rodents, rabbits, birds	Disrupt/prevent reproductive cycle	Long-term disruption of ovarian function	Increased energy expenditure of males, altered social hierarchy	None or some as for target species
Megestrol acetate (MGA) [d]	Domestic dogs, cats, feral cats, zoo felids, *white-tailed deer*	Disrupt/prevent *reproductive cycle*	Long-term disruption of reproductive cycle, *uterine pathology*	Increased energy expenditure of males, altered social hierarchy	None or some as for target species
Progestin					
Norgestomet [e]	Black-tailed deer, white-tailed deer	Disrupt/prevent reproductive cycle	Long-term disruption of ovarian function	Increased energy expenditure of males, altered social hierarchy	None or some as for target species
Androgens [f]	Male rodents, wolves	Inhibit sperm production	Long-term disruption of spermatogenesis and endogenous androgen production	Repeated cycling of females, increased energy ependiture	None or some as for target species
Steroid Antagonists					
RU 486 (mifepristone) [g]	Coyotes	Induce early abortion	Repeated cycles, late abortion, incomplete abortion, retained placenta	Increased energy expenditure of males, altered social hierarchy	None or same as for target species
Phytoestrogens (Ergots) [h]	Kangaroos	Impair lactation, disrupt reproductive cycle, induce abortion	Late abortion, incomplete abortion, retained placenta, fetal cannibalism	Increased energy expendirute of males, altered social hierarchy	None or same as for target species
Prostaglandin $F_{2\alpha}$ [i]	White-tailed deer	Induce early abortion	Late abortion, incomplete abortion, retained placenta	Increased energy expenditure of males altered social hierarchy	None or same as for target species
GnRH Antagonists [j]	White-tailed deer, mule deer, elk, African elephants	Suppression of pituitary gland hormones and gonadal hormones	In males, abnormal antler develoment, loss of masculinity	Increased feed consumption, disruption of social hierarchy	None or same as for target species, depending on delivery system
Immunocontraceptives					
PZP [k]	Burros, wild horses, domestic cats, dogs, deer, African elephants, pigs, rabbits, baboons, seals (grey, harp, hooded), bonnet monkeys (*Macaca radiata*), squirrel monkey	Disrupt egg production, block fertilization	Ovarian pathology, multiple infertile estrous cycles, increased energy expenditure, extended breeding season, late fawning	Increased energy expenditure, disruption of social hierarchy	None or same as for target species
Sperm Protein [l]	Red fox, rabbits	Disrupt sperm function, fertilization	Testicular autoimmunity, permanent if used in males, multiple cycles, extended season, late fawns if used in females	Increased energy expenditure	None or same as for target species
GnRH [m]	Deer, domestic livestock, pets	Inactivate native GnRH, prevent hormone and gamete production	In females, lesions of the hypothalamus, no reproductive behavior. In males, functional castration, loss of masculinity, abnormal antler development, possible permanent sterility	Decreased energy expenditure, disruption of social hierarchy, *increased feed consumption*	None or same as for target species
Immunocontraceptive/ Biological Vector [n]	Wild rabbits	Inactivate hormone or gamete proteins essential for reproduction	All of potential adverse affects of immunocontraceptives, potential lethal/harmful mutation of vector	Potential lethal/harmful mutationof vector, inability to limit to target subpopulation	Vector and associated effects may betransmitted to nontarget species

(*Continued*)

Table 3 (*continued*). Potential adverse effects of antifertility agents. This list does not necessarily mean that these agents were successful or practical in causing infertility in the species tested.

Agent/Method	Species tested	Intended antifertility effect	Potential adverse effects		
			Individual	Population	Nontarget species
Other Methods					
Vasectomy [o]	Wild horses, wolves, beaver	Sterility	Permanent sterility, female-multiple cycles, extended breeding season	Increased energy expenditure	None
Hunting		Limit reproduction by culling	Delayed death from injury, infection	Disruption of social hierarchy, increased energy expenditure	Death or injury from misidentification

[a] Nettles 1997, Warren et al. 1997, Kennelly and Converse 1997, Kesler 1997, Asa 1997.

[b] Balser 1964, Linhart and Enders 1964, Linhart et al. 1968, German 1980, Garrett and Franklin 1983, Matschke 1977.

[c] Sturtevant 1970, 1971

[d] Roughton 1979, Bell and Peterle 1975, Plotka and Seal 1989, Matschke 1980, Kazensky et al. 1998.

[e] Darling 1993, Jacobsen et al. 1995, DeNicola et al. 1997.

[f] Asa 1997.

[g] Deliberto et al. 1998.

[h] Tyndale-Biscoe et al. 1990.

[i] DeNicola et al. 1997*b*, Waddell et al. 2001.

[j] Becker and Katz 1997, Brown et al. 1993, Baker et al. 2000.

[k] Miller 1995, Miller et al. 1999, Warren et al. 1997, McShea et al. 1997, Muller et al. 1997, Turner et al. 1996, Brown et al. 1997*a*, 1997*b*.

[l] Simon and Alexander 1998, Bradley 1997.

[m] Miller et al. 2000, Brown et al. 1994.

[n] Tyndale-Biscoe 1997, Holland and Deliberto 1998, Brown et al. 1994.

[o] Kennelly and Converse 1997.