National Park Service
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Natural Resource Stewardship and Science

Review of Ungulate Fertility Control in the National Park Service

Outcomes and Recommendations from an Internal Workshop - February 2012

Natural Resource Report NPS/NRSS/NRR—2015/1038

ON THE COVER
Free-ranging horses at Theodore Roosevelt National Park are part of an on-going fertility control study examining the safety, efficacy and feasibility of using a remotely delivered immunocontraceptive vaccine to decrease population growth rate and reduce the need to round-up horses periodically for sale or donation.
Photograph courtesy of Jenny Powers, NPS

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Executive Summary

Ungulate management in the National Park Service (NPS) has been a consistent and often controversial challenge since the inception of the Service in 1916. The objectives for ungulate management have ranged widely from protection, preservation, and restoration, to limiting adverse effects due to large numbers of native animals and elimination of exotic invasive ungulates. Fertility control may be a useful tool in achieving some of these objectives; however, altering reproduction is not without direct and indirect effects. In some situations, fertility control may be an alternative method to culling individuals within a population when low rates of natural mortality (e.g., predation, disease, starvation) do not allow the NPS to meet population management objectives. Although NPS Management Policy 4.4.2.1 (NPS 2006) allows the use of reproductive intervention as a population management technique, no Service-wide guidance yet exists to assist park managers in determining whether fertility control is an appropriate management tool. Public opinions and values toward wildlife management are evolving, and include an increasing desire to influence decisions made by agencies managing public trust resources. Debates about the humaneness and appeal of fertility control versus killing of wild animals arise from many different viewpoints, often vary by species, and are value-driven.

When making decisions regarding management of ungulates, the NPS completes a planning process that complies with the procedural requirements of the National Environmental Policy Act (NEPA). Through these planning efforts, it has become clear that NPS managers need accurate, consistent, and timely science-based information regarding technical aspects and policy implications related to wildlife fertility control to make knowledgeable decisions. Additionally, the NPS has not at a Service-wide level scrutinized in what situations and which circumstances fertility control may meet management objectives within the framework of the NPS mission.

Therefore, in February 2012, NPS managers representing park, regional, and Service-wide perspectives met and discussed the future utility and desirability of using fertility control as an ungulate management tool in NPS units. A review of the scientific literature and presentations by experts in the fields of fertility control technologies and wildlife population modeling as well as ethical considerations of natural resource management preceded and informed the discussion (see Appendices 1 and 4 of this report). Additionally, workshop members shared their own experiences with ungulate fertility control planning and implementation (Appendix 2). Common guiding themes surfaced during the workshop and from these basic criteria that were identified for the use of fertility control in ungulates within NPS units. First, while NPS policy strongly supports allowing natural processes to regulate ecosystems whenever possible, most NPS systems are substantially affected by anthropogenic changes; active management is within NPS policy and is often necessary to mitigate the effects of disruptions to ecological processes and ungulate population ecology. Second, fertility control methods may be useful and desirable tools under specific circumstances; most notably in small insular populations of habituated or at least easily accessible non-native ungulates. This is due to the significant logistical effort and resources required to implement a fertility control program (see Appendix 1.2) and the desire to avoid invasive reproductive manipulation of native species.

Fertility control may be more acceptable for non-native species. The consequences of altering the reproductive ecology of non-native species may be less disruptive to ecosystem function than creating the same disturbance in native species. For example, fertility control may be suitable for horses maintained as cultural resources or domestic cattle kept as demonstration herds than in native deer, elk, or bison populations which could be keystone species in ecosystem function. Alternately, if fertility control is considered in native species it is most appropriate for use in highly modified environments where effects of anthropogenic change are more acutely recognized than in areas with less human influence. In highly altered environments multiple human stressors including changed food sources and habitat availability, lack of predation, and habituation, among others, may have a more powerful influence on natural selection and ecosystem function than fertility control. Finally, fertility control may be a potential tool when other management options are prohibited by law or policy and the socio-political environment encourages its use. The NPS cares for wildlife resources in the public trust and must thoughtfully consider input from a wide range of stakeholders and use this information to make decisions within the context of the enabling legislation for the Service and individual units. Early and active engagement with neighboring state and federal management agencies and public stakeholders will be crucial for successful use of fertility control in ungulates.

In addition to identifying when ungulate fertility control could meet goals for the Service, participants discussed practical application of fertility control methods. There was agreement that any fertility control method used must meet the goals of a management plan. The NPS continues to be a park-centric management agency which values ecosystem conservation, with an emphasis on protecting population level processes, while often managing relatively small areas within larger landscapes. To assess whether or not fertility control methods meet individual park ungulate management objectives, participants believed the following criteria should be met:

- The park should have well-defined and explicit goals for managing ungulates and /or the processes that sustain them or that they affect.
- There should be sufficient information regarding population demographics and vital rates and species ecology to reasonably estimate or model success.
- There should be commitment to long-term monitoring and adaptive management.
- There should be sufficient empirical evidence to indicate a fertility control method/program will have minimal impact on native-species biology, ecology and related ecosystem conservation.
- Potential fertility control methods should: 1) minimize the need for repeat treatments (i.e., high efficacy and appropriate duration), 2) be safe for the individual animal (e.g., minimal negative health or behavioral effects), 3) be safe for humans or scavengers (e.g., no food chain concerns), 4) be regulated for use in a management context, and 5) be practical and feasible for use (e.g., relatively easy to deliver and cost effective).

The NPS continues to support science and research which further a more complete understanding of all of these criteria. Additionally, workshop conclusions suggest that future NPS direction on fertility control will recognize that, similar to most wildlife management tools, fertility control is not the "silver bullet" that many advocacy groups promote, and that biological as well as socio-political effects of their use can have both positive and negative outcomes. Despite these limitations, fertility control in NPS units may have appropriate applications when used to meet specific management objectives within a narrow range of situations.

Purpose

The purpose of this workshop was to explore how to best protect, maintain, or restore natural processes, in a context related to ungulate fertility control in the NPS. Certainly, human control of the reproductive capacity and associated physiological responses of an ungulate cannot be considered a natural process. However, it may be an important tool to balance the need to meet park management objectives, alter genetic contribution of individual animals within an isolated population, preserve ecosystem integrity and foster constructive social and political relationships. At this time there is no overarching guidance to assist NPS managers in considering ungulate fertility control. This has led to what may appear as inconsistent decision-making on the use of fertility control in ungulates in NPS units. While parks have unique circumstances driving ungulate management goals, they typically consider the same suite of tools to meet their management needs. The challenge for workshop participants was to discuss and help define under what circumstances ungulate fertility control complements NPS wildlife management tools.

This document relays key findings and discussions from an ungulate fertility control workshop held in Fort Collins, Colorado, February 23-24, 2012. Specific objectives of the workshop were, 1) to summarize the current science and ethics that surround the use of fertility control in ungulates by invited subject matter experts (Appendix 1); 2) to explore examples of how the NPS is using or may use fertility control in the future (Appendix 2); and finally 3) to consider the appropriateness of fertility control and its implications for the NPS (Appendix 3). In addition this report provides a summary of the major types of fertility control products and methods along with regulations associated with each (Appendix 4).

The findings and outcomes of the workshop reflect discussions of participants from across the Service informed by their own experiences as NPS employees and wildlife professionals as well as by workshop presentations by experts in the fields of wildlife fertility control, wildlife population modeling, and the ethics of natural resource management. The findings are not NPS policy but rather are deliberations of workshop participants on a NPS Service-wide approach to ungulate fertility control and the foundation from which policy may be developed and clarified. This report may serve as a framework to assist NPS managers when making decisions regarding fertility control as an ungulate management tool. The technical portions of this report may be updated as new scientific and regulatory information become available.

Background

Ungulate management by the National Park Service (NPS or Service) has been a consistent and often controversial challenge since the inception of the agency in 1916. The need for ungulate management ranges from species and habitat preservation to limiting adverse effects due to high concentrations of native species and limiting or eliminating exotic, particularly invasive, species. Fertility control may be a useful tool in achieving some of these objectives. However, altering reproduction is not without direct and indirect effects.

When making decisions regarding management of ungulates, the NPS completes a planning process that complies with the procedural requirements of the National Environmental Policy Act (NEPA). The NEPA process requires preparation of a Categorical Exclusion (CE), Environmental Assessment (EA), or Environmental Impact Statement (EIS), depending on whether an action has the potential to have significant impacts on the quality of the human environment. In most cases, the NPS is required to develop and consider a range of reasonable alternatives for managing ungulates as part of the NEPA process. In order to comply with NEPA and to make informed decisions, NPS managers need access to accurate, consistent, and timely information regarding the technical, economic, and policy implications of fertility control in free-ranging ungulates. Management Policy 4.4.2.1 (NPS 2006) broadly allows for "reproductive intervention" as a technique for meeting population goals, but does not address in which situations and what context fertility control methods might meet management objectives and constraints. At this time, interpretation of this policy is done through planning at the park level. Generally, more specific Service-wide recommendations and policy interpretation come in the form of Director's Memoranda, Director's Orders, or Reference Manuals. The findings presented here may serve as the beginning for development of these types of policy documents if needed.

The underlying mission of the NPS is guided by the Organic Act of August 25, 1916, which states: "…[The] purpose [of the NPS] is to conserve the scenery and the natural and historic objects and the wild life therein and to provide for the enjoyment of the same in such manner and by such means as will leave them unimpaired for the enjoyment of future generations" (54 USC §100101). The General Authorities Act of 1970 further clarified that "though distinctive in character, [Parks] are united through their inter-related purposes and resources into one national park system as cumulative expressions of a single national heritage; … these areas derive increased national dignity and recognition of their superb environmental quality through their inclusion jointly with each other in one national park system preserved and managed for the benefit and inspiration of all people of the United States…". Finally, the Redwoods Act as amended in 1978 further strengthened the assertion that all management would be consistent with the Organic Act and should be for "the common benefit of all the people of the United States" and that management "…shall not be exercised in derogation of the values and the purposes for which these various areas have been established, except as may have been or shall be directly and specifically provided by Congress."

Quite possibly one of the strongest underlying values the NPS embraces is the idea of "naturalness". As early as 1872, when Yellowstone was set aside by congress as the first national park, the enabling legislation speaks to retaining the natural condition of park resources including wildlife (16 U.S.C. § 21-22). Although initially the idea of having natural qualities (i.e., those existing in nature and not made or caused by people; Merriam Webster Dictionary) may appear to imply non-interference, active management is often necessary to address significant habitat and ecosystem changes resulting from human influence. Sometimes intervention is necessary to restore or mimic natural processes. The NPS Management Policies (NPS 2006) directs managers to "…understand, maintain, restore, and protect the inherent integrity of the natural resources, processes, systems, and values of the parks while providing meaningful and appropriate opportunities to enjoy them." Additionally, "the Service recognizes that natural processes and species are evolving and the Service will allow this evolution to continue minimally influenced by human actions." The "natural condition" is one that describes the condition of the resource "that would occur in the absence of human dominance over the landscape." Furthermore, "… in cases of uncertainty as to the impacts of activities on park natural resources, the protection of natural resources will predominate. The Service will reduce such uncertainty by facilitating and building a science-based understanding of park resources and the nature and extent of the impacts involved." Likewise, the "Service will not intervene in natural biological or physical processes, except when directed by Congress; in emergencies in which human life and property are at stake; to restore natural ecosystem functioning that has been disrupted by past or ongoing human activities; or when a park plan has identified the intervention as necessary to protect other park resources, human health and safety, or facilities. Any such intervention will be kept to the minimum necessary to achieve the stated management objectives." With these cautionary policies toward management the Service engages in active wildlife management on a regular basis (NPS 2014).

The state of fertility control science has reached a point where it may be possible to limit the size of some ungulate populations by inhibiting reproduction. Likewise, the regulation of fertility control products has progressed significantly in the past decade (Appendix 4 of this report describes available products, their efficacy, and regulatory issues). However, the availability of a potentially technically feasible tool does not necessarily mean that it is desirable to use in a management context. Identifying whether fertility control meets NPS objectives and desires for ungulate management begins through thoughtful discussion amongst NPS managers informed by relevant science. This was the primary objective of this workshop.

Key Findings

1. **Fertility control techniques should have a high likelihood of achieving biological and ecological management goals if they are considered for use in an NPS unit.**

   The NPS should be clear and consistent when expressing the values upon which the Service was created and how these influence management goals and methods. The NPS seeks to sustain or restore natural ecosystem processes when possible. Fertility control should not be considered unless it will assist in meeting these broad goals and will not have collateral impacts that conflict.

2. **As a public trust resource management agency the NPS should engage stakeholders with varying viewpoints on the use of fertility control, and make thoughtful decisions based on scientific results regarding its use, within the context of the mission and mandates of the Service.**

   Use of fertility control to decrease ungulate population growth rates, which may or may not lead to desired population size, is a complex issue because interested stakeholders have diverse values and often define "success" of a program differently than other interested parties or the NPS. There are no simple answers to resolve these issues. Differing viewpoints may be in conflict with NPS values though common desirable outcomes can often be identified. Important components in the decision-making process include engaging interested stakeholders and neighboring management agencies in problem-solving discussions, acknowledging that ungulates and their habitats are nearly always shared public trust resources, and considering the scientific evidence to inform whether fertility control is a technically, economically, and socially feasible tool.

3. **The NPS continues to select minimally invasive tools, whenever possible, to maintain or restore natural ecosystem function.**

   Tools that restore functions (e.g., reestablishing predator prey relationships) are preferable to those that modify natural ecosystem functions (e.g., altering reproduction). Management methods that require less handling, fewer applications and marks, and most closely mimic natural conditions are more desirable.

4. **The NPS has low tolerance for management actions when scientific uncertainty is prevalent or there is risk of harm to resources.**

   The NPS Advisory Board highlighted the *precautionary principle* in their recent recommendations for resource stewardship (NPS Advisory Board 2012) and encourages the NPS to continue to act with care with respect to changing natural resources and the environment. This caution is demonstrated by NPS planning processes and associated decisions. Fertility control may have implications for natural selection, social structure, reproductive behavior, immigration and emigration, timing of breeding, resource utilization and other aspects of ungulate life history characteristics (Gray et al., 2010). Managers will have to weigh benefits of fertility control (e.g., decreased population growth rate) against potential adverse effects on wildlife populations and the human environment (e.g., change in the reproductive ecology of the population).

Additionally, the NPS has a legal responsibility to use fertility control products as they are labeled for use and in accordance with laws and regulations. Regulations surrounding the use of fertility control products in free-ranging ungulate populations are complex (see Appendix 4). Actions of the NPS should be consistent with regulations pertaining to fertility control products for both management and research purposes.

5. **Natural resource management and specifically wildlife management are only a part of the broader NPS mission. Effective and efficient tools are needed to meet specific management objectives.**

   More than 80% of the units (~320) have ungulate management concerns and the single greatest concern is adverse effects of large numbers of ungulates on vegetation and habitat (NPS 2014). Logistics and cost-effectiveness are therefore important considerations for ungulate management. At this time, fertility control techniques, including immunocontraceptive vaccines, often require hand injection, marking or identification of animals, and repeated treatments to accommodate regulatory and biological limitations of the technologies. All of these qualities decrease the acceptability or feasibility of application. If fertility control techniques surmount these hurdles they are more likely to be considered a logistically feasible tool.

6. **Fertility control is least consistent with NPS values if applied to native species residing within lightly disturbed systems and is least feasible in relatively large or open populations.**

   Fertility control techniques are *least appropriate* in the following situations:

   - Native species: Fertility control has the potential for negative effects on species ecology (Gray et al., 2010). Potential effects include altering: natural selection pressures (Cooper and Larsen, 2006), timing of breeding and birthing (Heilmann et al., 1998; Nunez et al., 2010; Ransom et al., 2013), activity or movement patterns (McShea et al., 1997; Gilman et al., 2010), population age structure (Kirkpatrick and Turner, 2007), or underlying physiology (Powers et al., 2011; Curtis et al., 2007; Curtis et al., 2008). While research results investigating these collateral effects of fertility control are not always consistent, meta-analysis shows empirical evidence defining unintended side-effects is sparse (Gray et al., 2010). Short and long-term ecological effects of population level fertility control remain largely unknown.

   - Lightly disturbed ecosystems: The phrase ‘lightly disturbed’ represents situations where human activities are limited and are not a dominant force on the landscape. Lightly disturbed areas often represent high ecological integrity. Natural processes, or those most closely mimicking natural, are preferred per NPS Management Policy 4.4 (NPS 2006) particularly in areas with the highest ecological integrity and ecosystem resilience (NPS Advisory Board 2012).

   - Large or open populations: There is no empirical evidence that a population limiting fertility control program can be adequately applied in a large, free-ranging (i.e., not limited by fences

or natural barriers to movement) ungulate population. Capturing, treating, and marking sufficient numbers of animals may not only be expensive in large open populations, but could be ineffective depending on the response of animals to captures or treatments and changes in immigration or emigration (Hobbs et al., 2000; Porter et al., 2004; Merrill et al., 2006; Boulanger et al., 2012) and are often incompatible with NPS policy goals of naturalness and conserving natural processes. Additionally, open populations often cross jurisdictional boundaries increasing the need for inter-agency and land-owner coordination and cooperation toward mutual objectives.

7. **In contrast, fertility control is more consistent with NPS values when used in highly disturbed ecosystems, especially in closed, relatively small, populations or where inhibiting reproduction for a limited time period meets a defined management goal or solves a specific management conflict.**

   Fertility control is *more appropriate* in the following situations.

   - Highly disturbed ecosystems: In some areas, there may be disproportionately large influences from anthropogenic sources (i.e., where population drivers are more dependent on human actions than on natural processes [Holling and Meffe, 1996]) and the effects of fertility control on natural processes may be relatively minor in comparison.

   - Small, closed populations: Fertility control has the greatest likelihood of success at reducing or maintaining population numbers, using reasonable treatment efforts, when an ungulate population has little to no opportunity for an influx of new animals (i.e., it is effectively 'closed') (Hobbs et al., 2000; Porter et al., 2004; Merrill et al., 2006) and is relatively small (the definition of small depends in part on the species). These characteristics allow managers to more effectively locate, treat, mark and track individuals without an influx of new animals to dilute efforts.

   - Limited time periods: Fertility control used for discrete time periods to achieve specific management goals such as disease management or as a tool to induce repeated estrus (i.e., in Judas animal situations) may have application. Additional examples of limited special uses likely exist; however, research findings have yet to validate that fertility control can be effective in unique circumstances and still meet policy directives. Future consideration of fertility control for these purposes will require new evidence that supports management goals.

8. **Fertility control is most consistent with NPS values when used to manage non-native species or keep small populations of ungulates for demonstration or cultural purposes in situations conducive to intensive management (i.e., semi-captive on islands, behind fences, or otherwise limited to a small space).**

   Fertility control techniques are *most appropriate* in the following applications.

- Non-native species: Non-native species, and their effects on NPS resources, are generally inconsistent with NPS Management Policies 4.1.5, 4.4.4.2 (NPS 2006), unless the species is maintained for cultural or historical reasons, or is mandated by congress (section 4.4.4.1). In addition, because non-native species have not evolved in the current ecosystem (section 4.4.1.3) the system is not generally dependent upon these species for natural function. For these reasons, alterations to their life history, natural selection, or behavior may be more acceptable, as long as it does not affect the conservation of native wildlife species. Thus, there is a greater range of biological effects that are tolerable in non-native species.

- Intensive management: Treating individual animals by intensively manipulating and monitoring individual animal fertility and genetic contribution to a geographically limited population is only possible when individuals are uniquely identifiable and within a relatively confined space, allowing access to each individual on a repeatable basis. There are relatively few situations within the NPS that this is possible or desirable. One notable exception is uniquely identifiable feral horses maintained as a cultural resource within fenced parks or on islands, which can be located and treated on a regular basis (Kirkpatrick and Turner, 2008).

9. Site specific and applied research is an important piece of the NPS mission.

The NPS remains committed to using the best available science and adaptive management to maintain and restore natural and cultural resources within NPS units Management Policies 2.3.1.4, 8.11.2 (NPS 2006). To this end, it is important to support the development and implementation of research to rigorously evaluate fertility control agents in ungulates. However, the guidelines above should be considered before large-scale research programs are initiated. In addition, it is prudent to pursue research in a stepwise approach. Questions which inform how fertility control agents affect individual animal and population level outcomes, immigration and emigration patterns, natural selection pressures, resource utilization, behavioral ecology, disease transmission, ungulate physiology, and other aspects of natural life history of the species will be critical to inform management decisions.

> ***Adaptive management*** *- [is a decision process that] promotes flexible decision making that can be adjusted in the face of uncertainties as outcomes from management actions and other events become better understood. Careful monitoring of these outcomes both advances scientific understanding and helps adjust policies or operations as part of an iterative learning process. Adaptive management also recognizes the importance of natural variability in contributing to ecological resilience and productivity. It is not a 'trial and error' process, but rather emphasizes learning while doing. Adaptive management does not represent an end in itself, but rather a means to more effective decisions and enhanced benefits. Its true measure is in how well it helps meet environmental, social, and economic goals, increases scientific knowledge, and reduces tensions among stakeholders (Williams et al. 2009).*

Questions to Aid Decision Making

The following questions can assist parks in exploring whether or not fertility control may be a useful tool in their ungulate management program.

1. Are management goals well described (e.g., vegetation protection or restoration, ungulate population reduction or maintenance, desired population range, disease control, genetic management, etc.)?

    a. The more clearly goals and objectives are defined, the more likely technical questions can be answered regarding program success.

    b. Poorly defined or generally stated goals do not lend themselves well to predicting or measuring success of a fertility control program.

2. Is the target population a native wildlife species or a domestic/feral/non-native species?

    a. If the species is native, are there anticipated or potentially un-anticipated side-effects associated with fertility control that could alter the underlying ecology, biology, or natural selection of the species? If so, apply the precautionary principle and proceed with restraint.

    b. If non-native, managers can use fertility control with more intensity as effects on species biology and ecology are of less concern.

3. How significantly has the population been disturbed by anthropogenic forces? Has the resilience of the system been considerably altered? Is fertility control likely to significantly add to these effects?

    a. Highly disturbed. The potential side-effects of fertility control on the natural ecology of the population (e.g., changes in natural selection, altered lifespan, changes to population genetics) may be minimal when compared to other human-derived changes to the landscape and fertility control may be more appropriate.

    b. Lightly disturbed. If the population is relatively unfettered by human influence then fertility control, or any manipulative invasive management tool, should be approached with more caution.

    c. Clearly there are wide ranges in the types and intensity of disturbance (i.e., changes to vegetation species diversity and abundance, introduction of artificial food sources, influence to the density dependence of the population, non-native disease, loss of predators, hunting pressures inside/outside the park, etc.). Each park will have a different interpretation for their set of circumstances. Each disturbance need not be weighed equally. The intent is to acknowledge the acceptable range of variation (Unnasch et al., 2008) and resiliency of the ecosystem (Holling and Meffe, 1996) and

act with more caution in areas of high ecosystem integrity (NPS Advisory Board 2012).

4. Is the population open (e.g., functional ingress or egress) or closed (e.g., only births, deaths, and human-aided addition or removal affect the population size)?

    a. If the population is open to any significant degree, fertility control efforts are less likely to be effective at decreasing population size due to dilution of incoming animals and wasted effort of treatment effects on outgoing animals (Merrill et al., 2006; Porter et al., 2004). Pre-treatment data collection and modeling, program monitoring, and analysis followed by adaptive management will be needed for site specific examination of this question.

    b. Functionally closed populations, particularly those that are small, are more likely to be appropriate candidates for fertility control (Hobbs et al., 2000).

5. Is there sufficient baseline data (e.g., population demographic and vital rates) for the target population to forecast the likelihood of success of a fertility control program?

    a. Yes. Managers can develop or use an existing predictive management model. Overall, predictions from a model based on site-specific data and assumptions will allow for a more accurate understanding of how the population will respond. Continued data collection and adaptive management will be critical. This may include monitoring population size and demographics over many years, calculating growth rate, recruitment rate, survival rate and investigating stochastic events which affect population size. Estimating the uncertainty of model parameters is equally important, particularly when populations don't respond as predicted.

    b. No. To implement a management model, the park can either use event rates and inference from similar populations or can acquire site-specific information. Fertility control should be considered more cautiously without site-specific information.

    c. It is important to validate models based on empirical evidence (e.g., population demographic data collected during monitoring) and to question model assumptions to learn from adaptive management practices.

6. What is the timeline for meeting management objectives?

    a. If short (<5 years), fertility control alone is not likely to be a successful reduction strategy, but may be a useful maintenance strategy.

    b. If part of a long-term plan in which population reduction can be carried out over 5-20+ years, it is possible that population objectives could be met using only fertility control, assuming an appropriate agent is available and population characteristics (e.g., underlying birth rate, mortality rate, immigration and emigration rates, and access to animals) are conducive to success.

7. Are there other similar situations where the proposed fertility control method has had measurable success in achieving comparable long-term management goals?

    a. To date (2015) there are few examples of regulating population size of free-ranging animals. Notable exceptions are functionally closed herds of horses (Kirkpatrick and Turner, 2008) and small isolated sub-populations of deer (Rutberg and Naugle, 2008).

    b. If yes, were side-effects (e.g., behavior, time of birth, effects of multiple treatments) evaluated at a population level? Although published studies are not always in agreement on unintended side-effects, such as extending the breeding and birthing seasons (Ransom et al., 2013; Nunez et al., 2010; Kirkpatrick and Turner, 2003), at this time population level side-effects remain largely unknown (Gray et al., 2010).

    c. Are other ungulate population management or vegetation management actions being pursued, such as culling or fencing, in concert with fertility control to achieve long-term management goals (i.e., fertility control alone may not meet management objectives)?

8. What are the available resources for modeling, implementing, monitoring, and evaluating a fertility control program?

    a. Predictive modeling, fertility control application, annual monitoring of population size with sex and age ratios, and thoughtful adaptive management are crucial components for success of a fertility control program and require significant resources both on the ground and for data analysis. Planning for these expenses will assist with making decisions regarding total costs associated with a fertility control program.

    b. Updates to models should occur periodically as needed to adjust for changes in population demographic and vital rates.

9. Who are the interested stakeholders and how have they been involved in discussions? It may be important to spend significant time on pre-planning work to understand stakeholder views and concerns. This is the time to engage the state wildlife management agency, and the local, regional, and national publics. Professional consultation, facilitation, or research may be helpful to answer these questions.

    a. Are there shared management responsibilities with other wildlife management agencies or is the population completely confined within the NPS unit? If there are shared responsibilities (i.e., cross-boundary ungulate movement), engage other wildlife management jurisdictions and find out their views on fertility control.

b. Are there multiple stakeholder groups with conflicting values that are interested in the resource? If yes, are there components of potential actions that will unite or divide these groups? Can common ground be identified among all stakeholders?

10. What resources and expertise are available to engage stakeholders and perform social science research, outreach, interpretation, and communication with state wildlife agencies, stakeholder groups, and interested members of the public?

    a. Significant planning time, thought, and resources should be dedicated to public engagement.

    b. Professionals from the social sciences, communication, interpretation, and planning fields can assist with developing engagement strategies.

Recommendations

In summary, as the Service moves forward with the potential application of fertility control in NPS units we should:

1. Work to more effectively engage stakeholders and wildlife management partners regarding fertility control in ungulates. This engagement should illuminate common goals, alternate points of view, areas of true or perceived agreement and disagreement in both values and science.

2. Not propose fertility control as a population management action during planning processes unless it meets the criteria for "more appropriate" or "most appropriate" situations for using ungulate fertility control outlined in the *Key Findings* sections above.

3. Acknowledge that there are relatively few situations within the Service where current fertility control methods are likely to meet ungulate population management goals with reasonable certainty and reasonable cost while maintaining fidelity to NPS policies, mandates, and values. Notable exceptions include closed populations of non-native ungulate species which are maintained as cultural resources; functionally closed, very small populations of native species in highly disturbed areas; and well-designed research studies with specific objectives and timeframes. There is room for other potential limited uses in the future if research suggests fertility control will be an effective and efficient tool.

4. Distinguish the differences between application of fertility control methods in research and management settings. Management actions are intended to achieve a set of desired conditions and are generally based on well-established scientific findings or professional experience; whereas, the primary objective of research is to answer specific questions or gain a better understanding of the system when outcomes are unknown.

Appendix 1. Workshop Presentations

1.1 Dan Baker, PhD (Wildlife Biologist - specialty wildlife contraception)

This presentation provided a brief overview of wildlife fertility control methods; explaining how the most common ungulate fertility control products and methods work, advantages and disadvantages of each, their regulatory status, and ongoing research investigations associated with each. For a more complete description please see the fertility control methods overview section of this report (Appendix 4).

The vast majority of research in the field of wildlife fertility control has been devoted to captive species (often in zoos) or closed populations, clinical safety and efficacy studies, and small field experiments. Many agents have proven to be effective at the individual animal level but very little population level information is available particularly in free-ranging, open (non-delimited) populations of ungulates. The wildlife fertility control community needs to move to the next level and further test the most promising agents in large controlled captive experiments then move to population-level experiments before products are used for management.

Although we understand that all methods will have some drawbacks, it is necessary to define what would be considered an ideal method within the wildlife management profession. Historically, it has been suggested that an ideal fertility control method would meet the following criteria (Kirkpatrick and Turner, 1991):

- Highly effective
- Free from toxicity and harmful side-effects for the target animal
- Temporary, in order to preserve the reproductive capacity of the individual and genetic integrity of the population
- Inexpensive
- Have little impact on social interactions and behavior
- Be effective through remote delivery preferably with a single administration
- Be incapable of passing through the food-chain to predators, scavengers, or humans

There has been much discussion and disagreement regarding both appropriateness and agent suitability of these criteria, but these factors have generally remained relevant and provided direction for research within the field. Much of this information is required by regulatory agencies when evaluating the safety and efficacy of a particular agent or method. The NPS will have to consider whether these criteria are appropriate and adequate for park contexts or if other factors need to be addressed.

Reproduction is controlled by similar pathways in all mammals. In seasonal breeders, which include most ungulates, the reproductive phase is strongly influenced by photoperiod. Photosensitive cells

capture light signals which are transmitted from the retina to the pineal gland and signals change in the release of melatonin (Figure 1.1.1). This in turn alters the release of GnRH from the hypothalamus which stimulates the synthesis and secretion of two critical hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), both of which ultimately control gonad function in males and females. There are numerous places to intervene in the cascade to suppress reproductive function.

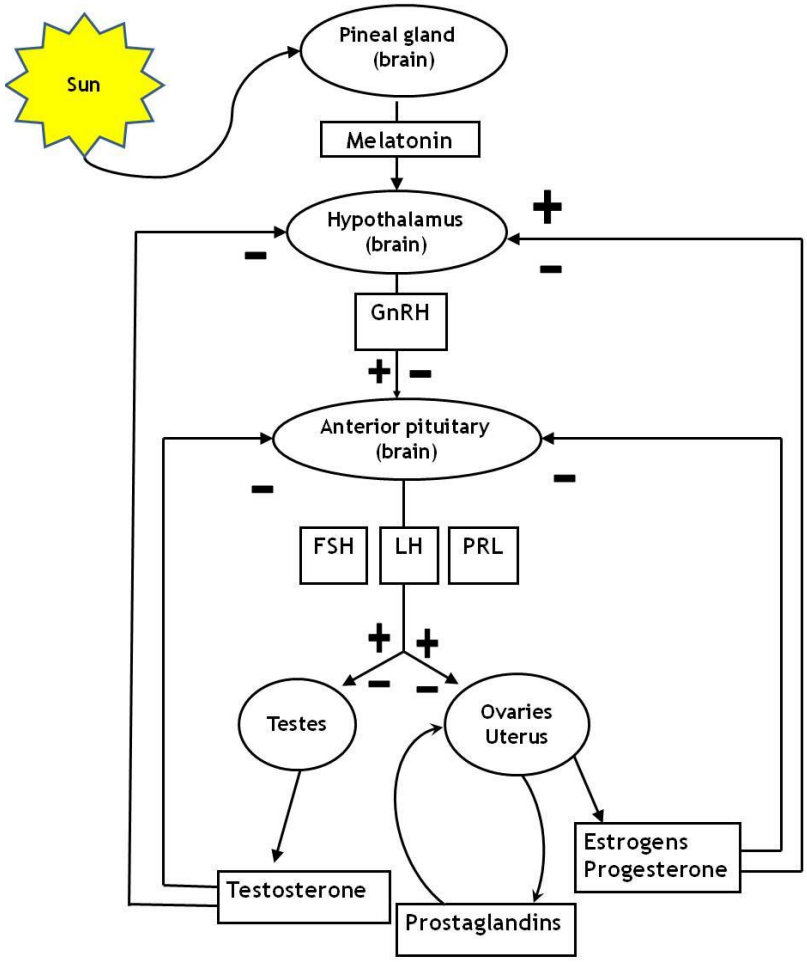

Figure1.1.1 Reproductive hormonal cascade (see Appendix 5 for definitions of terms); (+) indicates stimulation; (-) indicates inhibition. Organs are depicted in round shapes and hormones in square shapes.

There are 3 basic categories of fertility control methods: 1) Immunocontraceptive vaccines; 2) pharmaceuticals (includes hormone analogs); and 3) physical methods, including surgery and mechanical devices. At this time, the most likely products to be considered for use in ungulates within NPS units include: the GnRH vaccine (i.e., GonaCon, which induces antibodies specific to GnRH, and blocks the hormonal cascade that results in gamete and hormone production), and the pZP vaccine (i.e., Zonastat-H, which induces antibodies against the receptor that binds sperm on the oocyte, thereby blocking conception). Both are immunocontraceptives that have recently received regulatory approval for use in female white-tailed deer and feral horses (GonaCon) and feral horses

(Zonastat-H) respectively. For a more detailed review of fertility control methods see Appendix 4. Immunocontraceptive vaccines are at different points on the research, development, and regulation continuum for various ungulate species (Figure 1.1.2).

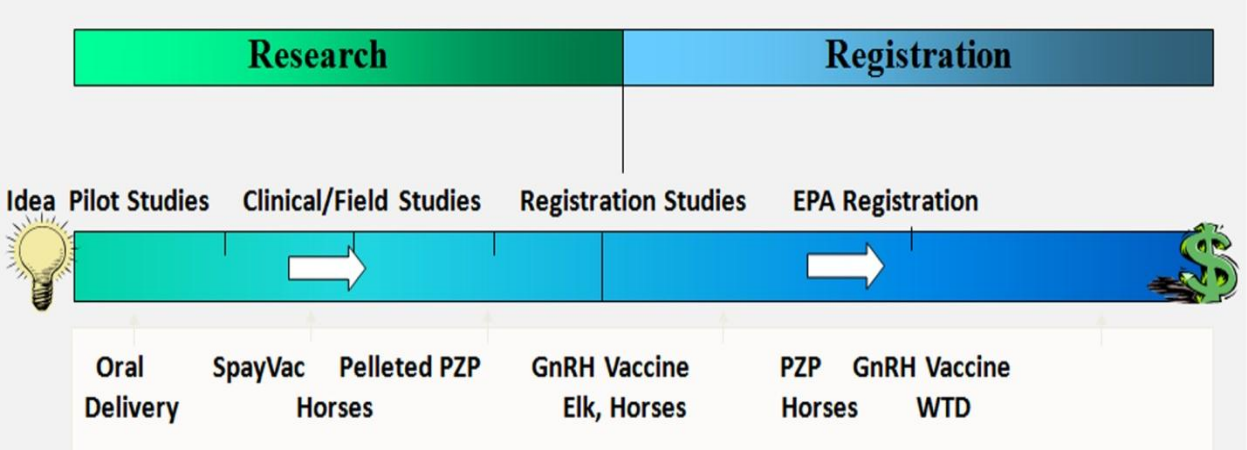

Figure 1.1.2 Research, development, and regulation continuum for current immunocontraceptive agents and some of the species in which they are being tested. WTD = white-tailed deer.

Regulation of wildlife contraceptive products can be confusing. Until 2006 the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) regulated all veterinary pharmaceuticals including products which prevent pregnancy in wildlife. The FDA required an Investigational New Animal Drug (INAD) application prior to testing the product. Many fertility control products such as the immunocontraceptives were used experimentally as INADs. Since 2006, responsibility for regulation of fertility control products for use in free-ranging wildlife has been transferred to the Environmental Protection Agency (EPA). The EPA regulates the use of pesticides. Fertility control products, specifically for use in free-ranging wildlife, are now considered pesticides. Prior to product registration with the EPA an experimental use permit (EUP) must be obtained to use the product for research purposes. Once testing is complete and the product is federally registered it must be specifically registered for use by state agencies which regulate the sale and use of pesticides within their borders. See Appendix 6 for labels associated with the two EPA registered ungulate fertility control products GonaCon and Zonastat-H.

1.2 N. Tom Hobbs, PhD (Wildlife Ecologist – specialty population modeling)

Fertility control in wildlife is not a new field of study; there have been publications since the 1970s on this topic. Most of these publications describe the effects of contraception at the individual level (i.e., the probability that an individual will successfully be contracepted with a particular method or the side effects of contraception). It is only relatively recently that there have been more publications, modeling as well as empirical studies, on the population level effects of wildlife contraception (Figure 1.2.1).

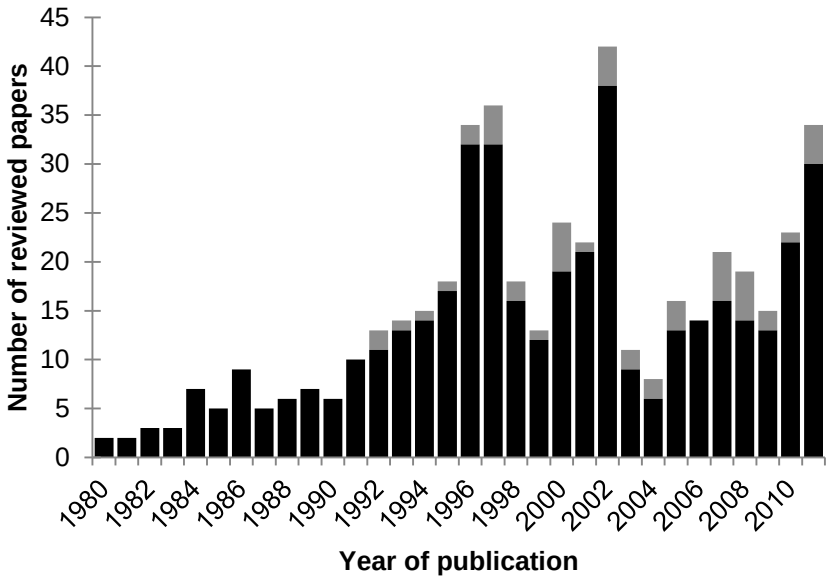

Figure 1.2.1 Trends in publication (*n* = 479 papers) for research on fertility control in wild and feral fauna from 1980 to 2011. Proportion of each bar in grey depicts investigations that included empirical or simulated population-level effects. Illustration from Ransom (2012).

Goal of Fertility Control

When ungulate numbers exceed management objectives, population reduction may be necessary. Underlying reasons for high animal densities and extent of the effects of these high density populations will influence how quickly the population may need to be reduced, which in turn may influence the management technique. It is possible one technique will be used to reduce the population and another technique used to maintain the population size at the new, lower level (Figure 1.2.2).

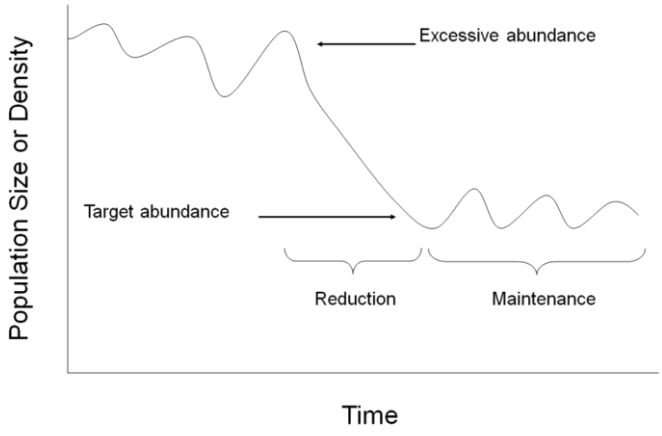

Figure 1.2.2 Schematic of the variations in population size and how management (reduction and maintenance) can theoretically reduce and stabilize the population. Illustration by N.T. Hobbs.

In order for fertility control to be a useful tool, the management goal(s) need to be well defined:

- Is the goal population reduction or maintenance or something else?
- How fast do objectives need to be achieved?
- Do modeling results suggest fertility control likely to be effective?
- What is the level of effort required? The logistics of treating a sufficient proportion of the population to significantly change the birth rate are not trivial. It is possible that fertility control could be feasible for maintenance but not for reduction, especially in long-lived species.

Because hunting or culling has traditionally been used for managing ungulate populations, it is important to compare fertility control to these methods.

- How does fertility control compare to hunting or culling in terms of efficacy (how well does it work) and efficiency (results per unit of cost/effort)?

NOTE: The following models have been made for **closed** populations. It is assumed that the entire recruitment of fertile females is achieved by births from females already in the population. Most of these results are from Hobbs et al. (2000).

Ungulates in North America are relatively long-lived, and have a relatively low fertility (1-2 offspring per female per year) (Stewart et al., 2005). Density dependence is generally demonstrated via reductions in recruitment (survival of young) as a population approaches the limits of their food base or ecological carrying capacity. Fertility control reduces the proportion of females with offspring and the population stabilizes when recruitment rate is the same as death rate. With these characteristics, fertility control will take an extended period to reduce population size. For example: if you have a species which produces 1 offspring per female per year; has an adult survival of 95%, and you can effectively treat **all** (100%) fertile females with a completely effective contraceptive agent (i.e., works 100% of the time), the time to reduce the population by 50% will be 14 years. Fertility control is never a short-term, quick fix answer to the problem of too many animals. However, it may be successful in holding populations steady once they are reduced, or reducing populations over an extended time period. It is possible to use a simple model to estimate how long it will take to reduce a population, if one assumes 100% efficacy after treating 100% of the female population. The only variable that needs to be substituted is survival probability. This provides the minimum time:

$$-\frac{\log(2)}{\log(\text{annual survival probability})}$$

For example, the situation of fertility control in a population of fallow deer in Point Reyes National Seashore (Figure 1.2.3).

- Ten fertile female deer (left panel)

- Treat 80% (8 of 10) of them with contraceptives (yellow)
- Fertile females comprise 20% of the population (green)
- Assume 100% efficacy of contraceptive
- Assume only half of the fertile females produce surviving offspring (recruitment rate 0.5)
- Assume only one offspring per pregnant female per year
- Assume 10% (1 of 10) mortality (upside down) in adult females
- Assume 50/50 male to female birth ratio

The following year (right panel), in spite of the effort necessary to treat 80% of the population, the population will still have 10 deer though has decreased the female population by 5% (if 50% of the offspring are male).

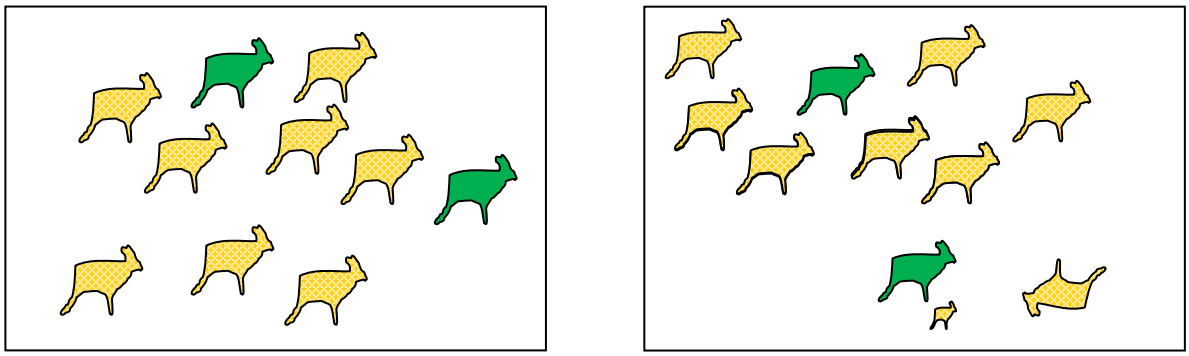

Figure 1.2.3 These figures illustrate the modeling of contraception efficacy in fallow deer at Point Reyes National Seashore. The left panel shows the population the year it is treated, the right panel the following year (after contraception, births and deaths) Illustration by N.T. Hobbs.

Models can also help predict how many females must be infertile in order to achieve the desired population goals. To calculate this, the number of new recruits must be estimated first:

$$\text{slope} = B$$
$$\text{recruits per female} = m - BN$$
$$\text{total recruits} = N(m - BN)$$

Figure 1.2.4 This graph shows linear density dependent recruitment for a closed population. m = maximum number of female recruits per female (per year), when all conditions for reproduction are optimal; N = female population size.

Then, by adding the equation from 1.2.4, the population is stabilized when the number of new recruits is equal to the number of deaths:

N (m – BN) = N (1 - S) = stable population

where number of deaths = N (1-S), and N is the population and S is the probability of surviving.

If we call P the proportion of breeding females that is affected by the management action, then the proportion of females that can breed (and recruit more females) is represented by 1 – P, and the total number of recruits in a managed population can be represented by the terms on the left:

$$N (m – BN) (1 – P) = N (1 - S)$$

In this equation, N represents the target population and P the number of females that need to be contracepted in order to reduce the number of recruits to the same number as deaths. The number of new recruits and the mortality rate for a population are often known or can be estimated. So it is possible to solve for P and determine the proportion of females that need to be rendered infertile. For example, in a population with a survival probability of 95% and a maximum recruitment of 0.6 females per female, 84% of the females must be infertile to maintain the population at half the biological carrying capacity.

"Small errors in infertility estimates can lead to large errors in achieved density. This is even more pronounced in smaller populations. Adaptive management is key."

The relationship between the proportion of the population that is infertile and the population size (in 1.2.5. it is represented as a proportion of carrying capacity) is not linear. This type of curve can lead to large errors in the population size when small errors are made in the proportion of infertile females, especially at the higher end (Figure 1.2.5).

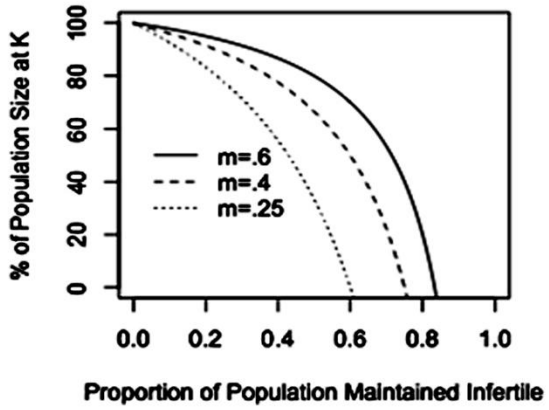

Figure 1.2.5 Population size as a proportion of the biological carrying capacity (K) against the proportion of the population maintained infertile in a closed population. The graph is plotted for three different maximum recruitment rates (m). The graphs assume a survival probability of 0.9.

For these models, the assumption has been that the number of recruits is in direct proportion to the number of animals in the population (Figure 1.2.4); however, for most large mammals the relationship between recruitment and density is not linear, and resembles more the dashed line in Figure 1.2.6.

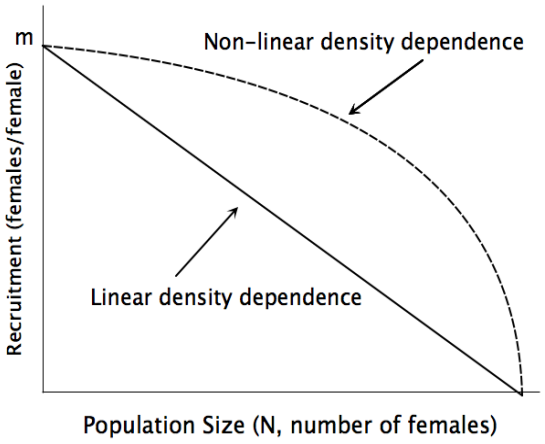

Figure 1.2.6 Density-dependent recruitment for a closed population. The solid line represents a simple relationship, where the recruitment is directly proportional to the number of animals in the population. The dashed line represents a more realistic density dependent recruitment.

If this non-linear relationship is used to calculate the effect of the proportion of infertile females on the population then the curves are even steeper (Figure 1.2.7).

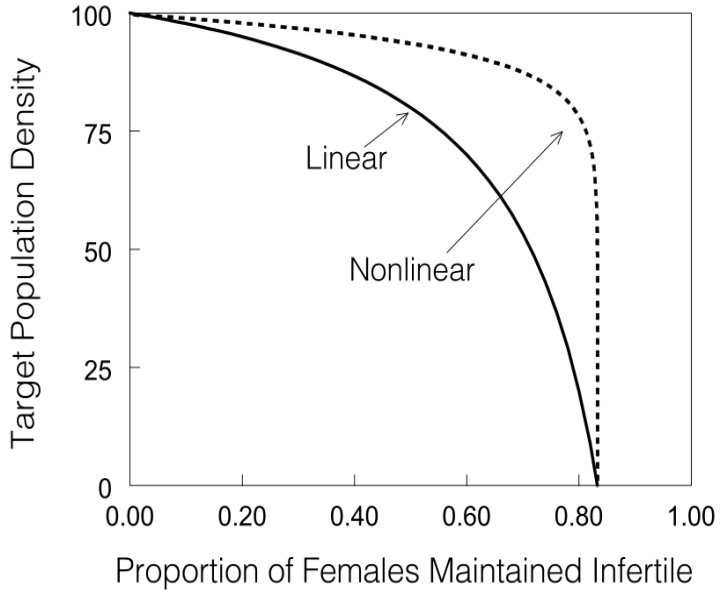

Figure 1.2.7 This graph is similar to Figure 1.2.5 and shows the effects of the proportion of infertile females on the population density (percent of carrying capacity K) in a closed population for a linear (solid line) density-dependent recruitment but also for a more realistic (dotted line) non-linear density dependent recruitment.

Figure 1.2.7 illustrates the importance of monitoring. The population tipping point is precipitous. It is paramount to monitor annually and examine predictive models annually to adjust management efforts. That is, to apply fertility control with adaptive management.

The duration of the contraceptive effect on fertility also has an effect on the number of individuals that need to be treated each year. Population density dependence effects may account for decreased treatment (either culling or fertility control) efforts with sterilized animals within the population. Non-reproductive animals compete for resources with fertile animals, thus suppressing the reproductive rate.

Culling or harvest is a technique traditionally used to decrease ungulate density. In many cases, it may be that this is the best option to achieve a rapid decrease of the population and then maintain the level through contraception or periodic culling. It is important to keep in mind that culling allows managers to distribute removals among different population age classes. Conversely, fertility control only decreases the number of births for a particular cohort of animals; therefore populations become progressively older with fertility control.

Adaptive management

Adaptive management was first developed by Carl Walters. He published his book "Adaptive Management of Renewable Resources" in 1986. This principle relies on a Bayesian forecasting model. The model is improved each management cycle by applying the technique for the duration of a forecasting cycle and then regularly updating it with information from a changing system (Figure 1.2.8).

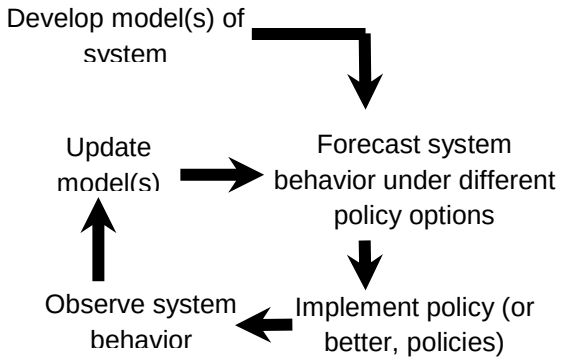

Figure 1.2.8 Model of adaptive management (Illustration by N.T. Hobbs, based on C.J. Walters)

Although a fertility control product may have high individual animal efficacy, there are many other factors that affect population size, including intrinsic birth and death rates, emigration and immigration rates; these are affected by forage production, habitat availability, and stochastic processes such as disease and weather-related mortality among others. If accurate estimates of these rates are available, it is possible to develop a predictive model that can forecast whether fertility control is capable of reducing or maintaining a population, the proportion of females that need to be treated with contraceptives, and the time it takes to achieve reduction or maintenance of a population.

However, when a population is continuously treated, vital rates such as immigration, emigration, and survival in addition to reproductive rates may change over time due in part to application of the fertility control agent. Therefore, updating the model and evaluating the effects of the management strategy on population parameters is important.

As biologists, we know that accurate estimates for many of these factors may not be feasible and models will need to use best estimate possible. As shown in Figures 1.2.5 and 1.2.7, small errors in fertility level estimates can lead to large errors in achieved density. This is even more pronounced in smaller, closed populations, emphasizing the need for adaptive management.

With models it is possible to forecast population sizes several years into the future (Figure 1.2.9), and determine whether they are likely to be consistent with objectives, choose the management option, and update the model and forecast as new information on the system is available.

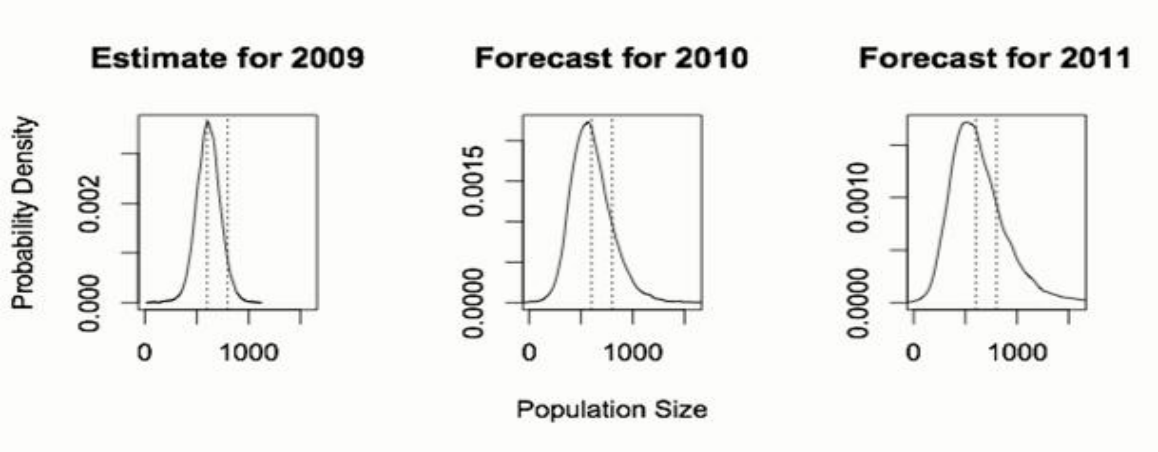

Figure 1.2.9 This is an example of how updating the information in a model can provide a different forecast in subsequent years (Illustration by N.T. Hobbs).

Conclusions

Fertility control alone is unlikely to be successful at reducing abundance of long lived species in open populations particularly where individuals are not individually identifiable. More than half the adult females will need to be maintained infertile to maintain population at levels well below carrying capacity and fertility control products with $\leq$ 1yr duration will not be useful for regulating large, free-ranging populations. Long duration fertility control agents show promise as an alternative to culling as a tool for maintaining population below biological carrying capacity if the population is closed or nearly closed (i.e., without significant immigration and emigration). However, successfully treated animals are fully withdrawn from the breeding pool particularly when reversal is prolonged.

1.3 Michael Nelson, PhD (Philosopher – specialty ethics of natural resource management)

The first two presentations discussed the advantages and limitations of ungulate fertility control as a management tool at the individual and population levels. This presentation explores the ethical concerns about using fertility control in wildlife. It is important to understand that a sensible ethical discussion of whether to use or not to use fertility control in wildlife needs to rest on sound facts, and then be built upon with reasons, premises, a conclusion, and finally an argument (a set of premises and the resulting conclusion).

During this discussion the problems of natural resource management will be framed as ethical problems. In order to address staff, intra-agency, inter-agency, and public concerns about ungulate fertility control, we need to make sure that the premises are true and that the conclusions follow rather than precede premises. When people speak they do not normally phrase things as a set of premises and a conclusion that follows, they simply say what is on their mind.

For example someone might say "We have a choice between killing excess numbers of ungulates and employing some form of fertility control. Wouldn't it be better to control their numbers through fertility control than by lethal control?"

The crux of this argument is the assumption that if fertility control is morally better than killing, then fertility control is acceptable. The person putting forth this argument has already made the value claim regarding what is better (fertility control is better than lethal control). There is also the underlying assumption that there are too many animals and they need to be controlled. Finally, there is an assumption that both fertility control and lethal control will adequately resolve the issue. The way this argument is presented implies that there are only two choices: fertility control or lethal methods, which may not be true. The assumptions involve both normative and factual claims. By dissecting such utterances we lay bare the things people are assuming and it makes it easier to address the full argument.

In fact, many natural resource arguments have this formula, where they end with a prescription (we ought to do or not do something):

Premise 1: Factual Claim – realm of science, this is the way the world is, or will be

Premise 2: Normative/Value Claim – this is what is of value, what should occur

Conclusion: This is what we ought to do (policy, action)

Often people judge a policy, action, or behavior, by the consequences of that policy, action, or behavior (i.e., consequentialism). Conservation is dominated by consequentialist utilitarian and pragmatic thinking. However, consequentialism is not the only way people think about moral questions. For example some people believe that our actions should follow the dictates of a divinity; it is not about the consequences but about God's dictates. Others similarly rationalize that we should follow dictates of nature (e.g., "do that which is natural"), others appeal to the inherent rights of

others (human or animal), yet others believe that our actions, either personal or as an institution, should reflect certain virtues (e.g., caring, humility, respectfulness).

One example of a moral question is that of whether genetic rescue is indicated for a highly inbred population of wolves on Isle Royale National Park. The project website posted the question and researchers analyzed the answers people gave for whether they were in favor or against genetic rescue in this population. This data was analyzed to obtain a better understanding of what motivates people to accept or reject a conservation policy (Gore et al., 2011). Most people invoked more than one moral theory (i.e., pluralists) to substantiate their point of view. One interesting aspect of this research was that the type of moral theory invoked to support the answer was similar between those who were in favor and those who opposed genetic rescue. That is, just because two people appeal to the same moral theory does not mean that they will arrive at the same answer. Although most of the people who appealed to natural law theory were opposed to intervention, not all were. The group that appealed to motives or virtues trended toward supporting genetic rescue. Many of the respondents used factual claims to endorse their decision. The authors evaluated the truth of those factual claims and found that "mistaken factual claims correlated with consequentialism, but did not correlate with motive approaches" (Gore et al., 2011). This means that factual outcomes influenced the decision when the consequences were more important to the person than the motives.

Much of natural resource management is driven by values, such as non-interference or natural regulation, utilitarianism, animal well-being, ecosystem health, and "wildness", and sometimes these values may conflict. There may be conflict within a value, for example when people appeal to "wildness" but have different perceptions and definitions for what this word means. The other type of conflict is between values, for example should we maximize for use of resources, welfare of animals or health of the population/ecosystem?

Common missteps people make in working through value based arguments are to ignore or prioritize some values (e.g., downgrade / ridicule those considered unimportant), insist only one value 'really' matters, or misrepresent the problem as a technical question rather than an ethical one. Tensions can be eased by acknowledging and understanding the many values expressed, clearly articulating the premises, and arriving at conclusions supported by both factual and normative premises. This will enable us to work towards solutions that infringe upon the least number of people's values and give respect to the full range of ideas. In summary, fertility control involves an ethical component to the decision making and, like the more technical elements of fertility control, the ethical dimension merits careful attention.

Conclusions

- Recognize factual and normative premises for what they are and avoid conclusions prior to building the argument.

- Fertility control is both a technical and ethical issue and both merit careful attention.

- We should not assume this is easy or doesn't require expertise: Assuming we're good at ethical analysis because we're good people is a lot like assuming we understand genetics because we're made of genes.
- We can make progress on thorny ethical value driven issues if we take them seriously and commit to rigorously and patiently working through them.
- Care should be taken to address the full range of values to engender stakeholder support.

Appendix 2. Park Experiences with Ungulate Fertility Control

Participants shared their experiences, which included field use of ungulate contraception, the decision to use fertility control when an appropriate product becomes available, or the decision to not use fertility control.

2.1 Assateague Island National Seashore, MD (ASIS; Carl Zimmerman)

The General Management Plan (GMP; 1982) for ASIS identifies the free-ranging horses found on the island as a "desirable feral species". In 1985 a Feral Pony Management Plan was developed to address on-going, negative effects of feral horses on other Park natural resources. In 1986 the Park partnered with Jay Kirkpatrick and John Turner to test the use of steroid contraceptives in the Assateague horse population. After disappointing results, the project transitioned to experimental field trials of a porcine zona pellucida (pZP) vaccine in 1988. Based upon six years of successful results, the park adopted use of pZP contraception as the primary tool for managing the horse population in 1994. Prior to the use of contraception, the population was growing at 10-15% per year. Stabilization of population growth was achieved relatively quickly; however, it took approximately 8 years (1994-2002) to see a decrease in the population size. Part of the reason for the slow decline in population size is that vaccinated females live longer because they are in better body condition, due to lack of pregnancy and lactation demands. There is now a new, older age-class in this population. The population has decreased steadily from a peak of 175 in 2001 to 114 in 2012. In 2009 a Finding of No Significant Impact (FONSI) was signed for an Environmental Assessment (EA) titled Managing the Feral Horses of ASIS. The preferred management alternative currently being implemented involves slowly reducing the population over a period of 5-8 years using fertility control (pZP immunocontraception) and supplemented, if necessary, with periodic additions to maintain genetic diversity and health of the population. The goal is to manage to a population size of approximately 80 - 100 horses, and the project is nearing its goal.

The park has made four conclusions about the use of pZP in ASIS. First, it is effective at the individual animal level; they have only observed one non-responder (a mare which became pregnant despite repeated vaccination). This fertility control technique could select for non-responders; however, at ASIS no offspring of the non-responder female have failed to respond to pZP immunocontraception. Second, the ability of pZP to control the horse population at ASIS has been determined to be feasible. In particular, given the small size of the horse population and the 9,000 acre park, it is possible to recognize and effectively treat individual animals because the vaccine can be delivered remotely and animals are identifiable by markings and accessible for treatment. Third, the technique is cost effective in achieving Park objectives (slowly decreasing the population); primary management costs include treatment (vaccine and staff time) and population monitoring (staff time). Fourth, the technique is reversible (i.e., temporary). Managers are able to select for genetic health and lineage composition of the herd, which may become important in a small, closed population where losing genetic variability could have a large impact. In this respect, reversible contraception has been more useful than culling. Finally, this approach is compatible with the horse management objective to not handle horses and keep them "wild". These characteristics allow the

Park to accomplish its mission: to minimize the negative effects of horses on the ecosystem while maintaining the horses as a cultural heritage herd.

There have been few observable side effects associated with vaccination. Visible injection site reactions have been noted in a few instances (< 5 out of 1,097 doses distributed). However, locomotion does not appear to have been affected by such reactions and longevity in treated horses has increased. The only non-responder female has foaled nine times and is apparently healthy.

Park managers at ASIS suggest fertility control can be a very effective component of a suite of management tools in an intensively managed, closed population of identifiable animals. The project treated over 85% of the female population during the first three years, and an average of 65% thereafter. Park managers have observed that mares receiving repeated yearly vaccination remain infertile for longer than one year. Additionally, as the population ages, more mares reach reproductive senescence. As a result, only 30 - 40% of mares currently need treatment in order to maintain a declining population.

2.2 Point Reyes National Seashore, CA (PORE; Natalie Gates)

This is a 90,000 acre park with two species of non-native deer (axis and fallow deer). In 2006, a Record of Decision (ROD) was signed at the conclusion of an Environmental Impact Statement (EIS) planning process which outlined the use of lethal removal and long-acting contraceptive techniques to eradicate these species. At the start of the non-native deer project there were an estimated 850 animals between the two species.

The implementation of fertility control was not new in the park at the start of the project. The park had previous experience using contraception in the Tule elk population (Shideler et al., 2002). In conjunction with the University of California-Davis, the park conducted a research project to investigate efficacy of pZP immunocontraception and fecal steroid monitoring techniques in elk. One of the main problems with treating elk consistently was animal accessibility and the ability to re-treat sufficient animals on a yearly basis. Additionally, the incidence of injection site abscesses in the Tule elk was high enough to be considered important.

After the elk experience, Park management decided that given the topography of the park and accessibility of animals, a vaccine that lasted only 10-12 months did not have sufficient duration to justify the effort to deliver the product. Park managers decided to only look at fertility control products that provided longer duration effects in future planning efforts. An agreement with the US Department of Agriculture (USDA)/ Animal and Plant Health Inspection Service (APHIS)/ Wildlife Services (WS)/ National Wildlife Research Center was made to test GonaCon (GnRH vaccine) on fallow deer as part of the eradication effort. Seventy female fallow deer were included in the study. Surgical sterilizations (laparoscopic tubal ligations) were also performed in three additional females. However, the major focus of program was lethal removal (culling) given the goal was to extirpate the deer. The vaccine trial was inconclusive. This was in part due to the rapid success of the lethal removal program.

Public concern influenced the decision making process because local and national animal rights groups have a strong presence in the area, and hunting is not part of the local culture.

2.3 Valley Forge National Historical Park, PA (VAFO; Kristina Heister)

In 2009, a ROD was signed and implementation of the Park's White-tailed Deer Management Plan/ EIS began. The preferred alternative combines the use of lethal and non-lethal methods to rapidly reduce the size of the deer population and then maintain it at a level that will promote biological diversity and natural processes such as tree regeneration. Sharp-shooting and capture/euthanasia are currently being used to quickly reduce the population from 1,300 to less than 200 deer. Then, if an appropriate reproductive control agent is developed, fertility control will be used to maintain the population at a reduced level. Minimum criteria for an acceptable fertility control agent at VAFO are: multiple-year efficacy (3-5 years with 85-100% efficacy); ability to remotely deliver the agent; an agent that leaves no residue in meat, which would prevent the meat from being used for human consumption (defined as having regulatory approval); agent has limited behavioral impact on the deer population; and the agent is reversible (i.e., temporary). These criteria assume that the agent poses no significant health risk to the deer.

The Park has a relatively closed deer population because intensively developed private and commercial land surrounds the boundary. Site-specific research documenting the average distance traveled by female deer from the park boundary was 401 feet, that deer have extremely small home range size (1/2 square mile), and the proportion of home range within the park boundary (>50%) supported this conclusion. Therefore, fertility control is more likely to be effective at a population level given treated animals aren't likely to leave the area and fewer untreated animals are likely to enter the population. Due to other uncontrollable factors that may affect survival (e.g., disease), permanent contraception may not allow for the population to recover if a large die-off occurs and results in a local population crash or extinction. In addition to the permanent nature of sterility being undesirable, surgical reproductive control was dismissed because this option would take a great deal of time per deer, and the number of deer that would need treatment makes it technically unfeasible as a standalone alternative. Finally, the mortality rate associated with the procedure (6%) (Mathews et al., 2005) may be greater than the acceptable level of mortality for the park (5%). Based on these reasons, surgical reproductive control was dismissed as a management option. The park also dismissed reversible (i.e., temporary) fertility control as the sole means of controlling a population because a rapid reduction in the population was required for resource protection. If fertility control is implemented and does not meet objectives, or a product is not identified which fit the criteria, the park will continue to use culling as a means to control the population.

Factors considered in the decision to adopt fertility control as part of the preferred alternative included the nature of the park boundary (generally open to neighboring people entering the park at multiple access points), park visitation (> 1 million annually), the nature of park visitors (80% local, recreation-based), characteristics of the deer population (closed population), use solely as a population maintenance tool, and the ability to achieve the plan objectives. Based on these factors and the fact that the completely lethal and combined lethal and non-lethal alternatives met the plan objectives equally well, action that removed firearms from the park landscape was considered

advantageous in reducing risk to visitor safety. Additionally, lethal removal puts significant strain on Park staff and budget resources. Sharp-shooting is achieved through a contract with USDA/Wildlife Services and initially costs approximately $200,000 per year (including meat processing) when number of deer removed annually was 500-600 individuals. Fertility control is attractive because it can be achieved with NPS staff rather than contractors and may be conducted during the day rather than at night as sharp-shooting is currently done. Ideally, fertility control would have been implemented prior to sharp shooting to most easily access and treat does; however, an appropriate product was not available.

During plan development many animal rights and welfare groups provided input to the draft EIS. One important issue was to have assurance from the park that if an appropriate fertility control option was identified, VAFO was prepared to implement this as a management tool. This was the first NPS unit to incorporate the use of fertility control as a deer management tool in a management plan (previous uses were limited to research) although it has not yet been implemented and a product which meets Park requirements does not yet exist.

2.4 Cape Lookout National Seashore, NC (CALO; Sue Stuska)

Public interest in the horses at the seashore has significantly influenced feral horse management at CALO. While language to maintain a representative herd of horses appeared in the park's 1982 General Management Plan, the first horse management actions did not occur until 1996 after an EA was completed. The EA's preferred alternative was to remove a large portion of the horses for adoption and maintain the herd with pZP immunocontraception. The EA's preferred alternative was to maintain 50-60 individuals; the final EA stated a range of 75-100 horses. At that time, 76 of 184 horses tested positive for equine infectious anemia (EIA) and, by state law and lack of a suitable quarantine facility, were euthanized. There was public outcry regarding this action. This led to amendments to the park's enabling legislation in 1998 and again in 2005. Legislation directs that the seashore "allow a herd of free-roaming horses, with a target population of between 120 and 130" within the park and "enter into an agreement with the Foundation for Shackleford Horses…or another qualified nonprofit entity" for cooperative management.

Contraception using pZP vaccination began in 2000. The contraceptive is administered as needed, based on the mortality and birth rate in the population and with the goal of maintaining genetic diversity. The reversible nature of this contraceptive is very important for adaptive management. Periodic removal has also been used as a management tool, particularly in earlier years, but the numbers removed have significantly decreased due to the contraception program. Uncharacteristically high mortality one year along with lasting effects of contraception where it has been used over multiple years has decreased the population below the management range. Ideally, the population will be able to be managed only with contraception without the less desirable removals.

2.5 Biological Resource Management Division, WASO (BRMD; Jason Ransom)

There is a free-ranging horse population managed by the Bureau of Land Management (BLM) which resides seasonally on National Park Service lands within Bighorn Canyon National Recreational Area, MT (BICA). This herd is very popular with the public and many documentaries and popular

media programs feature these horses. The BLM decided to implement a fertility control research project in this herd to minimize the number of horses they needed to remove via round-up and adoption. Despite extensive strategic planning and research design, the project was nearly unsuccessful because litigation interrupted pZP vaccination during the study. Litigants sought to keep the horses "wild" and protect the full range of genetic resources within the herd. Advocates wanted to prevent the BLM from treating mares. The BLM prevailed but in the aftermath decided to treat mares based on animal welfare grounds rather than population objectives to mollify the objecting public. Additionally, treatment schedules were interrupted due to the litigation. They treated only old and young animals, to remove the burden of lactation from these demographic groups. The individual-level efficacy of the treatments was lower than expected, presumably due in part to interruptions in treatment schedule (Ransom et al., 2011). Additionally, because the treatment regimen did not include the most fecund age cohort, the treatments had little effect on population growth. Effects of treatment on the population included apparent suppression of births in 2-5 year old untreated females (presumably because behavioral changes associated with pZP presence in the herd shifted stallion reproductive focus to treated females), nominally increased survival of adults age 1-19, and a 300% increase in presence of animals ≥ 20 years old (Ransom, 2012).

Swelling was observed subcutaneously in approximately 1% of mares, but no debilitating situations were detected (Roelle and Ransom 2009). Approximately one third of injections resulted in a swelling that was assumed to be a granuloma. These swellings did not cause any clinical signs to indicate it was debilitating to the mares.

One of the main lessons learned was that human dimensions are very important with respect to fertility control. People care about horses and what management is applied to them. There was both support for and objection to fertility control in this herd and there was a wide breadth of reasons for their dissenting opinions.

2.6 Fire Island National Seashore, NY (FIIS; Lindsay Ries)

The park was established in 1964 when the white-tailed deer population was relatively small. In 1974 the population numbered approximately 50. This largely closed population increased in the following decades, and was estimated to be between 500 and 700 in 2003. Within Park boundaries both federal and non-federal tracts of land exist (17 private communities) so there are many year-round and seasonal human residents. Two of the main concerns with a large deer population are, 1) food conditioning of deer in communities that leads to increased human-deer interactions (both negative and positive), and 2) the impact of deer browsing on native vegetation, particularly the globally rare ecological community present on the island (The Sunken Forest, a maritime holly forest). Long-term monitoring of permanent vegetation plots indicates deer have a severe impact on this unique ecological community as well as other maritime forests on Fire Island and at the William Floyd Estate.

In the winter of 1988-1989 the park initiated an experimental hunt in cooperation with NY State Department of Conservation to investigate whether the deer population could be successfully reduced using hunters. The hunt occurred on NPS land, but was highly controversial and residents went to

great lengths to prevent deer from being killed. The hunt was discontinued after only 60 animals had been taken.

Some residents did recognize that deer overabundance was a problem and this initiated the investigation of fertility control (pZP vaccination) in deer on Fire Island. At the outset (phase I: 1993-1997), fertility control was being applied within the communities on private land and the park was not a participant. The Humane Society of the United States (HSUS) worked directly with the communities to identify and apply pZP vaccine on an individual animal basis (each treated doe was known by residents and could be identified). In phase II (1998-2002) and phase III (2003-2009), the Park became more involved in the project and was primarily responsible for remotely applying the vaccine via darts on both the federal and non-federal tracts of land within the park (Fire Island Lighthouse to Fire Island Pines, roughly 8 miles long and less than 0.5 mile wide). In these phases, individual study animals were not permanently marked; however, they were temporarily marked with dye delivered from marker darts (so that the same animal was not treated twice in the same season). The areas and intensities of application remained fairly consistent from 1998-2009; however, the number of treatments decreased over time, from 246 in 1998, to 180 in 2003, to 115 in 2009.

The project has been conducted as a population-level research project since 1998 with varying degrees of success. The deer population declined approximately 50% from 1998-2003 in the western communities (Kismet-Lonelyville) from 79-127 deer/km^2 to 44 deer/km^2. This area has had the longest treatment history, the longest record of monitoring, and the best access to breeding-age females. In other treatment areas the population responses have been much less dramatic and/or have displayed no discernible trend. Other factors that could have influenced deer populations in these areas (e.g., deer movement) have not been evaluated.

It was decided in 2010 that the project be discontinued because research objectives had been accomplished and planning for deer management is currently being pursued. If fertility control is selected as part of a preferred alternative it may again be used in the park in the future. Fertility control is seen by some residents as more acceptable than lethal removal of the deer. The park partners with the United States Geological Survey (USGS) to conduct remote distance sampling population estimates.

The park is currently developing a Deer Management Plan/ EIS to determine the best alternative to resolve impacts associated with deer. This process has made the park critically examine problems associated with deer overabundance in a holistic manner in regards to human-deer interactions, vegetation browsing, and development of measurable objectives that can be monitored to gauge success.

Published literature indicates that pZP vaccination has had moderate population level effects at FIIS (Naugle et al., 2002; Rutberg and Naugle, 2008). These effects are not homogeneous across the seashore. The nearly two decade fertility control project has not restored natural regeneration of maritime forests or resolved the impacts associated with food-conditioned deer on the seashore.

2.7 Rock Creek Park, DC (ROCR; Ken Ferebee)

The situation at ROCR is similar to VAFO, but the park is more urban and completely within city limits. There were no deer documented within Park boundaries before the 1960s. However, by the 1990s managers began considering the need for deer management due to adverse impacts associated with deer. In 2005 ROCR began an EIS process to determine the best course of action to resolve human-deer conflicts including vehicle collisions, destruction of personal property in the areas surrounding the park, and forest degradation within the park. In DC, the park is very visible and is heavily scrutinized by media and the public.

The deer plan (EIS) outlines two alternatives that include fertility control. The first, non-lethal alternative is to fence areas of 10 – 25 acres (for a total of ~10% of the park), then remove deer from inside of fence to allow vegetation to recover and rotate fenced areas every 10 – 12 years. At the same time, deer numbers will be gradually reduced by reproductive control of does either by sterilization or an appropriate fertility control method which meets the criteria established in the EIS if it becomes available. The second alternative is a combination of sharp shooting to reduce the population and fertility control to maintain population size if a product becomes available which meets outlined criteria. The second is the preferred alternative.

Criteria outlined in the ROCR plan for fertility control use are similar to VAFO. The agent needs to be federally approved, have demonstrated multiple-year efficacy (3-5 years), ability to be administered through remote delivery, leave no harmful residue in the meat to protect hunters and predators/scavengers, and have substantial proof of success in limiting population growth with limited impact on behavior in a free-ranging open population. Currently, there is not an agent that meets all of these criteria. In the meantime sharp-shooting will be used to reduce the population and also to maintain lower population numbers until a reproductive agent becomes available and feasible.

When the draft EIS was released in 2009, the Park received many comments about deer management and reproductive control, but there was not a clear public/stakeholder consensus on what should be done. The public was tired of damage to landscaping, hitting deer with their cars, the abundance of ticks, and the assumed, positive relationship between deer and Lyme disease.

A Record of Decision was signed in May 2012 (after a 6 year planning process) and the preferred alternative includes fertility control as an option, but not a requirement, if criteria outlined above are met. Park management expects litigation from animal rights and animal welfare organizations.

2.8 Voyageurs National Park , MN (VOYA; Steve Windels)

The park has not used nor has it considered the use of fertility control.

2.9 Yellowstone National Park, WY (YELL; Rick Wallen)

Fertility control has not been considered as an overabundance management tool but is being investigated as a disease management tool. Fertility control is not a proven disease management technique at this time. The Park has partnered with USDA/APHIS/WS/National Wildlife Research Center to investigate the use of the GnRH vaccine GonaCon to prevent pregnancy and break the brucellosis (*Brucella abortus*) transmission cycle. It is important to YELL to know that the animal

can recover from disease and reverse from infertility in order to maintain the female and her genetics in the breeding population. Permanent sterility could interfere with the conservation goals. No results are yet available from this study.

2.10 Theodore Roosevelt National Park, ND (THRO; Bill Whitworth)

Native Ungulates

Theodore Roosevelt National Park tries to be consistent with NPS policy and allow natural processes to dictate populations, unless those populations, if left unchecked, would result in a single-species domination of the system or impairment of park resources/values. The only instance that THRO has considered the use of contraceptives on native species was in the Park's recent Elk Management Plan/EIS. The population in the fall of 2010 was approximately 1,200 elk and desired management level is approximately 100-200. The Park's elk population was increasing at approximately 25% / year. It was clear that action was needed to protect park resources. The Park chose to implement its Elk Management Plan/EIS which outlined a preferred alternative of elk reduction using skilled volunteers along with NPS employees.

The Park's elk reduction plan has two distinct phases for removal. The first was a reduction phase. This was used to reduce the population to less than 200 elk. The second is a maintenance phase and involves the removal of 20-25 cow elk each year or every other year to maintain the population. Park management considered contraceptive use in the Elk plan/EIS only as an option for the maintenance phase. Fertility control as an initial reduction alternative was rejected because management believed that a contraceptive, even if an acceptable one were available, would not reduce the population to the desired level within the timeframe of the plan/EIS (15 years). This is based on the fact that the population in the fall of 2011 (when the contraceptive could have been applied) could easily have exceeded 1500 animals. Therefore, the population would continue to grow before the reduction in births combined with mortality could begin to reduce elk numbers. Additionally, the population is open and moves freely out of the park. The mortality rate in THRO's elk population is low as forage is not limited and there are no significant predators. Given the timeframe to significantly reduce the population by using fertility control would likely exceed 15 years, this alternative was dismissed as unfeasible. However, once the maintenance phase was reached, contraceptive use was considered as a potential tool. This was done for a number of reasons, but primarily because technological advances could conceivably result in a vaccine being developed during the plan's shelf life that would meet park requirements. The park believed it was important to evaluate a broad range of alternatives because NEPA requires this, and to remove reasons to litigate the plan and subject the park to further delay in taking action. While contraception use was an option fully considered in the plan/EIS, the park recognized logistical difficulties with contraception including; frequent round-ups (~ 3 year intervals) are expensive, they are hard on the animals (morbidity and mortality), and the Park is unlikely to get the required number of female elk in the pens. For the above reasons the fertility control alternative was not selected as a maintenance phase option.

Non-Native Ungulates

At present the only animals on which THRO is considering using contraceptives is for management of the cultural resource/demonstration herd of feral horses (desired population of 70-90; currently at

~ 200). The park is participating in a study to test an experimental vaccine (GonaCon) for safety and efficacy in free-ranging horses. From the park's perspective, the study was initiated because this population of feral horses is of great interest to visitors (even more so than the elk) and the park wanted to consider all population management tools rather than be forced into expensive roundups every 3-4 years. In contrast to elk, we have a good chance at getting all feral horses into the holding pens and there is the possibility that the contraceptive could be administered without the need for a roundup, so logistically it might be a feasible tool.

2.11 Rocky Mountain National Park, CO (ROMO; Therese Johnson)

Rocky Mountain National Park relies on a variety of conservation tools including fencing, vegetation restoration, culling, and elk redistribution to reduce the impacts of elk on vegetation and to restore the natural range of variability in the elk population and affected plant and animal communities. Implementation of the Park's Elk and Vegetation Management Plan (EVMP, 2007) began in 2008 and will continue adaptively over a 20 year timeframe through 2028. Within the life of the plan fertility control agents could be implemented as an adaptive management tool to control the population size if an effective, logistically feasible agent becomes available. In addition, within the life of the plan and given appropriate interagency cooperation, redistribution techniques could include adaptive use of wolves as a management tool.

The EVMP/EIS analyzed five alternatives to manage elk and vegetation in the park that included different combinations of lethal reduction via shooting (culling), fencing, non-lethal redistribution, vegetation restoration methods, fertility control, and intensively managed wolves. The selected alternative relies on gradual lethal reduction of elk by NPS staff and authorized agents of the NPS to reduce an estimated population of about 3,000 elk to the high end of the natural range of variation, between 1,600 and 2,100 animals (600 to 800 in the park subpopulation; 1,000 to 1,300 in the town subpopulation). Up to 200 elk could be removed per year as needed to achieve and maintain the population target.

An alternative was evaluated that would have emphasized treating female elk with a fertility control agent to the greatest extent possible, given technological and logistical capabilities, to achieve a target elk population at the same high end of the natural range of variation by the end of the 20 year plan. Because of logistical constraints on the number of elk that could feasibly be treated it was determined that, although the number of treated animals would be less than under the selected alternative, lethal reduction of elk would still be needed each year to reach plan objectives. This alternative considered the use of a single-year, multi-year, or life-time fertility control agents. It was determined that using a single-year agent (e.g., leuprolide) up to 400 elk could be treated annually during the first four years of the plan and 200 for each of the remaining 16 years. Under this alternative lethal reduction of 80 to150 elk per year would still have been necessary to supplement fertility control. For longer-lasting fertility control agents, either the number of elk treated or the number of elk lethally removed could be reduced.

Several fertility control agents that might be effective for implementing the alternative were in development at the time the ROMO EVMP was developed, and it was recognized that new agents could become available in the future. The Plan identified the characteristics that any treatment agent

must have before it is deemed acceptable for implementation. These included that the agent must 1) be effective with a single treatment, 2) be at least 85% effective, 3) have appropriate regulatory approvals, 4) be safe for treated animals, 5) result in no recognizable behavioral effects (e.g. reduced or increased courtship, rutting, and breeding behavior), and 6) be safe for non-target animals or human consumption.

Stakeholders identified issues related to the use of fertility control as a management tool, which included ethical concerns as well as concerns about the biological effects of fertility control agents. Specific concerns included: 1) the use of fertility control to manage elk populations would be artificial and that humans do not have the right to interfere with the reproductive processes of wild animals, 2) not enough is known about the long-term effects of fertility control agents on elk and other species that could be exposed to the control agent or its derivatives, and 3) the safety of consuming elk meat that has been exposed to fertility control agents. From 2008-2011 staff from BRMD field tested the efficacy of a multi-year reversible agent, GonaCon, in the park under a research permit (Powers et al. 2014).

2.12 Environmental Quality Division, WASO (EQD; Dan Niosi)

Over the last decade, fertility control has been considered in nearly every plan (EA or EIS) to address resource concerns related to ungulate population overabundance. The one ungulate related plan where it was not considered as an option was the Antietam and Monocacy National Battlefields chronic wasting disease (CWD) response plan. This plan was about managing CWD concerns rather than population concerns, and it was concluded fertility control would not meet disease detection or management objectives. Other ungulate management plans (including those for non-native ungulates) have included fertility control as part of the planning process and have either carried it forward for detailed analysis or dismissed it in the plan for various reasons. Either way, this is an important methodology which should be systematically evaluated. This speaks to the need for consistent service-wide guidance on use of ungulate fertility control as a management tool.

Appendix 3. Workshop Discussion

This section reflects the group discussion of the fertility control workshop participants.

3.1 Should ungulate fertility control be used in NPS units?

A general question "Are there situations in which ungulate fertility control should be used in NPS units, assuming that the technical hurdles can be surmounted?" was posed to the group. Everyone agreed that the NPS values non-intervention whenever possible. Nevertheless, in many cases the environment has been altered to a point of ecological imbalance and the mission of the NPS is to restore, to the extent possible, natural processes within the context of the purpose and intent of the park. The NPS implements a broad range of ungulate management options from non-intervention to active management and manipulation of ungulate populations and their habitats using a variety of tools to achieve this goal. Stakeholders may interpret this disparity in management as inconsistency in NPS policy and decision-making; however, park managers consider such flexibility critical to meeting the diverse purposes and mandates associated with NPS units. Some of this confusion and concern about differing management approaches may be resolved with consistent decision-making processes, and thoughtful dialog with stakeholders to not only explain NPS rationale but consider their values along with our own in the decision.

The group agreed that maintaining fertility control as a potential management tool was important, but emphasized that these techniques are likely not appropriate in many situations. Participants also agreed that using a rigorous adaptive management approach for retrospective evaluation was not only appropriate but an essential part of fertility control programs, given that these methods have been used sparingly in non-captive settings or open populations. There was acknowledgement that fertility control programs require extensive planning, funding, and expertise; they are resource intensive processes.

After listening to the three presentations on the physiology, ecology, and ethics of wildlife fertility control, the group was asked to brainstorm reasons they believe stakeholders might object to fertility control in ungulates. Many of these reasons have been heard by the participants in conversation with stakeholders or at public meetings where ungulate management plans were discussed.

3.2 Reasons why stakeholders (including the NPS) may not want to use fertility control

Principles of nature considerations. This is the concept that we should not interfere with natural processes, including evolution. We should maintain ecosystems which allow for natural selection pressures to exert forces on reproduction. This also incorporates the idea that manipulation of individual animals or populations of ungulates diminishes their perceived value as wildlife. The NPS strongly associates with the idea of nature and puts a high value on preserving the natural ecology and biology of native ungulate species. Active management practices which are less manipulative, invasive, or contrived and more self-sustaining are likely to be preferred with this value set.

Pragmatic considerations: Birth rate must drop below mortality rate *in a closed population* before a declining population will occur. Open populations will require more treatment effort to control given untreated animals can enter the population which may dilute treatment effect and treated animals may leave the population which represent wasted effort. Additionally, most treatments require handling or finding the animal at close range at least once and potentially as often as twice in a year which can be difficult to achieve, tempering the effect on population numbers. It may be impossible to treat a sufficient number of animals and maintain them within the population to experience a negative population growth rate or even hold the growth rate at zero (Hobbs et al., 2000; Merrill et al., 2006). Much depends on the survival, immigration and emigration rates as to when population size will decline when fertility rates decline. In situations where desired population objectives are well below biological carrying capacity the intrinsic population growth rate is likely to be high and bringing this rate below zero using fertility control will require treating large proportions of the female population. Finally, fertility control agents may change fertility, survival, and immigration or emigration rates in both predictable and largely unpredictable ways (Ransom et al., 2014a). For example, long-term fertility control increased survival in horses presumably by decreasing the stress of pregnancy (Kirkpatrick and Turner, 2007, 2008). Alternately, fertility control was associated with decreased body condition in female elk possibly due to lack of anabolic hormones accompanying pregnancy (Conner et al., 2007) which in turn could negatively influence survival.

These logistical difficulties and delay in meeting population objectives may not meet management goals for protecting or restoring vegetation or mitigating human-wildlife conflicts. Long and short-term costs should be evaluated (e.g., product costs, personnel time, repeated applications, post-treatment population monitoring, political capital, etc.). Delivery of fertility control agents is labor intensive, particularly when compared to lethal removal, and requires long-term commitment to realize results.

Humane and animal rights considerations: Administration of contraceptives can be stressful or painful to the animal. For example, if physical or chemical capture and restraint is necessary to apply fertility control, animals will experience increased acute stress and possibly an increased mortality rate (Kreeger and Arnemo, 2012). Negative side effects of the fertility control treatment itself may include abscesses at the site of injection (Powers et al., 2011, Gionfriddo et al., 2009), changes to home range size and movement (Gilman et al., 2010), or changes in social or reproductive behaviors (Nunez et al., 2010; Nunez et al., 2009; Heilmann et al., 1998). Finally, animal rights advocates may consider contraception inappropriate as it infringes on the animals' right to reproduction and self-determination.

Utilitarian considerations: Fertility control, like any population reduction method, may decrease hunting opportunities and/or decrease the opportunity for wildlife viewing due to reduced animal densities. Additionally, there is often concern or perception that once an animal is treated with a fertility control agent it is no longer fit for human consumption. Therefore, it is important to have regulatory approval for fertility control products to assure the hunting public that the meat is appropriate for consumption with or without a withdrawal period.

Objectivity considerations: Fertility control or any ungulate population management may be seen as unjust if it is perceived as camouflage for the underlying problem of human encroachment on wildlife habitat. It may be viewed as an artificial or contrived solution. For example, the logical solution to human encroachment on wildlife habitat or eradication of predators which has led to localized high ungulate densities is habitat or predator restoration. However, these solutions may not be feasible given the socio-political environment. The need for fertility control may be a collateral effect of the real problem; lack of a fully functioning ecosystem. The NPS strives to preserve or restore natural ecosystems; however, this is often not possible and collateral effects must still be addressed.

3.3 Reasons why stakeholders (including the NPS) may advocate for the use of fertility control

Pragmatic considerations: Results from simulation modeling suggest that long-term fertility control agents, applied to a functionally closed population, could be more efficient than culling alone in maintaining a stable ungulate population density when used in conjunction with culling (Hobbs et al., 2000; Porter et al., 2002). Additionally, fertility control may eliminate or reduce the need for use of firearms.

Humane and animal rights considerations: Humane arguments supporting fertility control draw on empathy values and the assumption that animals are sentient beings. Parallels are often drawn among wild animals, domestic animals and people. If contraception is an acceptable form of population control in humans and domestic animals, it should be equally appropriate in wildlife. Additionally, some people, who may otherwise support lethal options of population management, find it inhumane to hunt or cull habituated animals because the element of "fair chase" has been removed. Finally, animal rights arguments are based on the idea that animals not only have a right to avoid suffering but also have a right to life.

Objectivity considerations: Fertility control in ungulates may be considered warranted if there is a recognition that humans not only instigated the problem (e.g., habitat encroachment, predator eradication) but also have good intentions of alleviating it by using contraception to manage the growth of wild ungulate populations.

As one component of a larger plan: There is a unique management scenario that often leads to acceptance of both culling and fertility control as a means of managing ungulates. This occurs when multiple techniques (e.g. fencing, habitat modification, ungulate redistribution, fertility control) are combined with lethal removal as a part of a larger, long-term solution to minimize the negative effects of large numbers of ungulates. It is a compromise and balances the need to induce a rapid change in the population and protect the resource with the desire to minimize culling. However, this may cause change in animal behavior which may decrease the effectiveness of repeat treatment efforts.

3.4 Situations in which Parks may find fertility control appropriate to use:

Participants were asked to brainstorm and generate examples of acceptable and unacceptable uses of fertility control for managing populations of wild ungulates. The answers were written on note cards and submitted anonymously and then discussed as a group. The group consensus was that yes, it is acceptable to use fertility control, under certain circumstances and for specific reasons.

As noted by a person in the group: "No action is perfect, without impact, and universally acceptable. If such a perfect, obvious answer was available, there would not be a need for these discussions." So, it is important to recognize that there are tradeoffs for every method, including fertility control and culling. A full and honest accounting of the trade-offs for any considered action is needed to make a good decision. Only by carefully considering management objectives, science, and NPS and stakeholder values can an acceptable decision be made. Communicating the decision making process may be as important as the decision itself.

3.5 Circumstances in which the group generally supported implementing fertility control in ungulate populations:

First and foremost participants believed that there must be a high likelihood of achieving management goals. For example, for population management, target animals must be relatively easily accessible, they should reside within closed or functionally closed populations, and the park should have estimates of population vital rates for predictive modeling, a plan for monitoring the success, and the ability to adapt to changing scenarios. Alternatively, if the goal is disease management in addition to animal access and vital rate information, additional data requirements would likely include an understanding or supported hypothesis of the target disease ecology and plan for long-term disease surveillance. The NPS continues to value practical solutions to problems given limited funding to resolve impacts associated with ungulates; therefore only solutions that have a high likelihood of success are considered worthy of attention. In addition to the primary requirement to achieve management goals participants believed that one or more of the following should apply to fertility control programs within the NPS:

- Targeted at non-native species (exotic species as well as domestic feral species)
    - Manipulating the reproductive ecology of non-native species was considered less egregious than similar actions applied to native species. Reasons for this viewpoint included currently or historically altered natural selection pressures in non-native and domestic species, willingness to accept a higher level of risk with regards to extinction, less emphasis on maintaining the natural ecology of the species given they are already in a non-native habitat, and less emphasis on preserving the "wild" character of animals.
- Within populations already substantially altered by humans.
    - Manipulation of ungulate fertility and natural ecology in populations already significantly affected by anthropogenic influence was more acceptable than in relatively less effected populations. The rationale behind this viewpoint was that there

are already many unnatural stressors on population ecology in these situations; therefore, natural selection is already likely to be altered and effects of fertility control on the population may be negligible when compared to other human derived pressures.

- When fertility control offers unique advantages to other management methods.
    - If removing reproductive capability offers a solution to problems other than too many ungulates such as disease transmission, maintenance of unique genetic alleles within a population, or other unforeseen beneficial biological effects.
- In situations where fertility control is more acceptable to the suite of stakeholders than lethal methods.
    - While the NPS does not manage by public opinion, we do seek to partner with state wildlife agencies, local and national land management agencies, wildlife conservation groups, and other interested stakeholders to cooperatively manage shared resources such as most ungulate populations. When fertility control offers a tool which can be used to build better relationships with partners and stakeholders it is more likely to be considered.

3.6 Circumstances under which the group believed it was generally not acceptable to implement fertility control in managing ungulate populations:

- When fertility control agents have significant effects on the natural ecology and behavior of native species. For example, changes to social status, reproductive behaviors, birth season, migration, or time budgets could be considered significant depending on the intensity, prevalence, and distribution of the effects. Scientific studies investigating these effects should be conducted before widespread use is implemented at a population level in a NPS unit.
    - The current state of the science regarding fertility control products often has conflicting conclusions with regards to secondary side-effects and determining the significance of these effects is not trivial. Often measuring small but biologically consequential changes is challenging and expensive.
- In open populations where there is little or no control over animal movements or where emigration/immigration is likely to be significant; because management goals are not likely to be achieved.
    - Populations need only be functionally closed rather than physically closed with fences or in an island situation; however, immigration and emigration rates are difficult and expensive metrics to acquire. Furthermore, these rates may be affected by a wide range of influences including historic migration, habitat availability, matrilineal group fidelity, density-dependence, and stochastic events among others. Therefore, site specific data, modeling, and monitoring are crucial to understand population dynamics.

- When the consequences of fertility control could lead to irretrievable damage to the ecosystem (i.e., when the uncertainty in the outcome is high and could lead to native species population extinction or genetic bottleneck).
    - For example, if the breeding population becomes too small and is functionally inbred.
    - Or if permanent sterilization is employed and the population cannot recover from a catastrophic event.

To address the concerns described above, the group generally agreed that an acceptable fertility control method considered for management should be:

- Effective (80-100% depending on site specific needs)
- Long lasting (≥3 years; dependent on site specific modeling and management objectives).
- Safe for individual animal and ecosystem health (including non-target species)
- Safe for human consumption in a food producing species
- Regulated by a governing agency and approved for use in free-ranging species
- Feasible for delivery (e.g., remote delivery preferred)
- Cost-effective when compared to alternative methods used for ungulate management; including field personnel time, materials, equipment, and post-treatment monitoring
- Have minimal impacts on daily activity patterns, reproductive behaviors, and general species ecology

It was also recommended that NPS units implement the use of fertility control as an option (versus a requirement) in management planning efforts. There are at least two reasons for this. First, the long-term effects of currently available technology are poorly understood in free-ranging animals and there could be unanticipated effects or reasons to reject fertility control. Second, circumstances may make it logistically impossible to successfully implement a fertility control program (e.g., if a previously 'closed' population exhibits substantial changes in their movement patterns). It is important to be clear with stakeholders that if unforeseen circumstances arise that there is the flexibility to change management techniques.

Appendix 4. Overview of Fertility Control Methods in Ungulates

For all abbreviations, acronyms and scientific names of mentioned species refer to the glossary (Appendix 5). For a more in depth presentation of the pros and cons of each fertility control agent please see the National Academy of Sciences comprehensive review of current fertility control products in their report to the Bureau of Land Management, Wild Horse and Burro Management Program (NAS 2013).

4.1. Regulation and use of fertility control products

Regulatory responsibility for fertility control products is shared between the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) (Fagerstone et al., 2010; Eisemann et al., 2006). The FDA regulates fertility control agents intended for use in humans, domestic species, and captive wildlife under the authority of the Federal Food, Drug, and Cosmetic Act (1938). The EPA regulates fertility control agents (e.g., OvoControl, GonaCon, Zonastat-H) for use in free-ranging wildlife, under the Federal Insecticide, Fungicide and Rodenticide Act (1947). Once an agent is registered for use nationally by the EPA it must then be approved for use within individual states.

Although registration, approval, and labeling of products are regulated by the above agencies, the decision to manage wildlife falls under the jurisdiction of the state and federal wildlife agencies. State and federal agencies have the authority to manage wildlife in the public trust. Wildlife fertility control agents applied in NPS units must be used in accordance with applicable federal and state laws. Additionally, any food producing animals captured using immobilizing agents must be marked to prevent them from entering the human food chain until meat withdrawal periods have passed. The same marking requirement applies for fertility control agents if necessary. Finally, the above regulatory agencies must determine the appropriate meat withdrawal period for fertility control agents used in food producing animals if a withdrawal period is necessary.

Fertility control products

Currently there are three general methods for suppressing fertility in free-ranging ungulates. These include:

1. Immunocontraceptive vaccines
2. Pharmaceuticals (including hormone derivatives)
3. Physical sterilization

4.2. Immunocontraceptive vaccines

Immunocontraception is the process by which a target animal is vaccinated against a protein required for normal reproduction, develops a strong immune response to the protein, and is temporarily or permanently unable to reproduce. Immunocontraceptive vaccines are not pharmaceuticals (drugs) or hormone derivatives (analogous to human contraceptives). In concept they are similar to disease vaccines but instead of preventing infectious disease they prevent reproduction. The two most

extensively studied wildlife contraceptive vaccines are porcine zona pellucida (pZP) and gonadotropin releasing hormone (GnRH) vaccines. Research involving both the pZP and GnRH vaccines has investigated many vaccine constructs, adjuvants (immune stimulants), and dosing regimens. It is important when comparing the safety, efficacy, and duration of vaccines that these differences are noted. At this time, all immunocontraceptive vaccines must be delivered via an injection. None are compatible with oral delivery. See the National Academy of Sciences report for full descriptions (NAS, 2013).

a. Porcine zona pellucida (pZP) vaccine (suspension)

Description: The zona pellucida is a membrane that surrounds the ovum (egg) and contains sperm receptors which are needed for fertilization. By blocking these receptors with antibodies it is possible to prevent pregnancy. The zona pellucida (ZP) vaccines are generally made with pig ovaries which are processed to remove the oocytes (immature eggs) which contain the ZP. This mixture of antigen(s) is then combined with an adjuvant and injected into the recipient animal to stimulate an immune response. Recombinant vaccines, that utilize proteins produced in the laboratory rather than derived from pig ovaries (Miller et al., 2000a), have also been investigated though none are currently in use.

Mechanism of action: Vaccination with pZP vaccines induces an immune reaction that stimulates antibody production against ZP proteins. When anti-ZP antibody binds to the sperm receptors on the ovum in the vaccinated female, it prevents fertilization. Antibody titers naturally decline with time if no booster vaccination is given. Generally, females are infertile only as long as antibody titers are sufficiently high to prevent sperm binding (Miller et al., 2000b); however, it is possible to induce long-term or permanent sterility after multiple vaccine applications (Ransom et al., 2013; Kirkpatrick and Turner, 2002). The mechanism of very long or permanent infertility is unknown; however, it may be due to suppression of developing follicles (Bechert et al., 2013). There may be other more chronic and less well described mechanisms of infertility when females remain infertile for extended periods (reviewed in: Ransom et al., 2013). For example, an absence of developing follicles and a reduction in primordial follicles was observed in domestic sheep (Stoops et al., 2006) and white-tailed deer (Curtis et al., 2002) and may have contributed to the longer infertility periods in bighorn sheep, mountain goats, and other species (Frank et al., 2005; Kirkpatrick et al., 1992) as well as altered ovarian function in mares (Bechert et al., 2013; Kirkpatrick et al., 1992).

Administration: Porcine zona pellucida vaccine is available as a small volume (1ml) intramuscular injection that can be given via dart delivery. It is distributed as two parts (agent and adjuvant) that are mixed to produce an emulsion. It should be mixed immediately prior to use. The vaccine should remain frozen (-20°C) until use. After appropriate mixing, the emulsion can be transferred to a dart for remote delivery or into a syringe for hand injection. When delivered remotely, the vaccine can be administered in 1 ml barbless darts (Pneu-Dart, Williamsport, PA) which are often delivered through a Pneu-Dart or Dan-Inject (Børkop, Denmark) dart rifle. Typically, an initial dose is administered, followed by a booster 2 - 4 weeks later to induce one year of infertility. Annual boosters are required thereafter (Kirkpatrick and Turner, 2007). In some instances after multiple applications over several

years mares have remained infertile for substantially longer than one year without revaccination (Kirkpatrick and Turner, 2002; Ransom et al., 2013).

Efficacy: In white-tailed deer, intramuscular injection (500 µg first dose + 300 µg booster) resulted in 89% reduction in fawning rate during the first year of application (Miller et al., 2000b). Additionally, fawning rate in white-tailed deer that were given three intramuscular injections at 3 week intervals was reduced from 86% (six of seven) in control does to 0% (zero of seven) in treated does (Turner et al., 1992). In feral horses that received initial and booster inoculations, efficacy ranged between 83-100% (Kirkpatrick et al., 1997; Ransom et al., 2011). In free-ranging burros receiving initial dose / booster treatment as well as a booster at one year, 100% of treated females were infertile for the following year and 54% were infertile in the second year. Pregnancy rates in non-treated feral burros were approximately 50% (Turner et al., 1996); the population was considered effectively reversed two years after the last booster injection. High efficacy has also been demonstrated in other non-domestic captive equids including Przewalski's horses and zebra (Frank et al., 2005) as well as elk (Heilmann et al., 1998, Shideler et al., 2002). Variable efficacy has been demonstrated in a wide variety of ungulates (reviewed in: Kirkpatrick et al., 2009).

Biological effects: Because pZP antibodies interfere primarily with fertilization, pregnancy is prevented but the female generally continues to experience estrous cycles. In the absence of pregnancy, estrous cycles endure throughout the breeding season and extend into the post-breeding season (Heilmann et al., 1998; McShea et al., 1997; Curtis et al., 2002). Vaccinated mares received approximately 50% more reproductive behaviors from stallions than non-treated mares during the breeding season (Ransom et al., 2010), presumably due to continued cycling. Similar results were observed in elk (Heilmann et al., 1998) and deer (McShea et al., 1997). As a consequence of extended breeding activity, when females regain fertility late in the season the birthing period may become extended and mismatched with forage availability (Ransom et al., 2013; Nunez et al., 2010; McShea et al., 1997); however in a small horse population on Assateague Island National Seashore this was not observed (Kirkpatrick and Turner, 2003). In addition to continued cycling and extended breeding seasons, horses treated with pZP experienced decreased band fidelity (Nuñez et al., 2009; Madosky et al., 2010). The long-term social consequences of these effects are not fully understood.

Other biological effects associated with the use of pZP include an increase in body condition and increased longevity (Kirkpatrick and Turner, 2007; Ransom, 2012). This change in longevity coupled with a decrease in births will eventually lead to a population skewed toward older age classes. This may or may not have important population consequences.

Vaccination against pZP does not interrupt existing pregnancies or affect fetal health or the fertility of female offspring (Kirkpatrick and Turner, 2002). There are no known contraindications to using pZP vaccination during pregnancy or lactation. Pre-pubertal or juvenile animals treated with pZP vaccines are most likely to be fertile as adults when antibody concentrations recede.

Finally, vaccination with pZP may lead to injection site reactions. Reports of injection site reactions following treatment with pZP are limited; although, injection site lesions (granulomatous reactions, sterile abscesses) can occur (Bechert et al., 2013; Roelle and Ransom, 2009; Curtis et al., 2007). One

study found histologic lesions in white-tailed deer two years after vaccination (Curtis et al., 2007). However, noticeable negative effects on animal welfare are rare and appear to be related to method of delivery; dart delivery has a higher incidence than hand-injections (Roelle and Ransom, 2009).

Reversibility: As antibody titers decline females often regain fertility. When females are treated for multiple years, they may take substantially longer to return to fertility or may remain infertile. When mares were treated for one year, 88% returned to fertility within one year, when treated for 3 consecutive years 69% of mares had returned to fertility by 4 years after the last treatment, and none of the mares treated for 7 consecutive years had returned to fertility by 8 years after the last treatment (Kirkpatrick and Turner, 2002). In a another study involving 1–5 consecutive pZP annual inoculations, an estimated 55% of mares never produced offspring in 7 years post-treatment (Ransom, 2012). The length of time to return to fertility was strongly positively influenced by the duration of treatment. Additionally, foals born to treated females were born later in the year than to untreated females (Ransom et al., 2013).

Non-target effects: Porcine zona pellucida vaccine poses little risk to non-target species or the environment because the vaccine is individually administered via darting or hand-injection and because the vaccine is a protein; if consumed it is expected to be degraded and metabolized in the gastrointestinal tract. Ingestion of pZP did not result in measurable pZP antibody concentrations or decreased fertility in rabbits (Barber and Fayrer-Hosken, 2000). There are no known negative effects of ingesting the adjuvant (modified Freund's Complete Adjuvant and Freund's Incomplete Adjuvant). For more detail about adjuvants please refer to section 4.2.d.

Regulation: Current use of pZP vaccine in free-ranging species *other than horses* requires an experimental use permit (EUP) obtained from the EPA by the product sponsor, the Humane Society or the United States (HSUS). Recently, the EPA has granted registration status of ZonaStat-H, a pZP vaccine, as a restricted use pesticide for use in limiting populations of feral horses and burros. The vaccine is approved for application via hand, jab-stick, or dart delivery by wildlife management personnel from the following agencies and organizations:

- National Park Service, Bureau of Land Management, U.S. Fish and Wildlife Service, and other Federal Land Management Agencies
- State departments of agriculture / livestock and wildlife, and their designated agents
- Federally recognized Indian tribes, and their designated agents
- Department of Defense and its designated agents
- Public and private feral horse sanctuaries and reserves
- The Humane Society of the United States and designated agents

Prior to EPA registration the vaccine was used as an Investigational New Animal Drug (INAD) and regulated by the Food and Drug Administration (FDA) (Kirkpatrick and Turner, 2007). Studies were

conducted in NPS units at both the individual animal and in some locations population level in: feral horses on Assateague Island National Seashore (MD) (Kirkpatrick and Turner, 2008), Cape Lookout National Seashore (NC), and Bighorn Canyon National Recreation Area (WY/MT) (Ransom, 2012), burros at Virgin Islands National Park (VI) (Turner et al., 1996), deer at Fire Island National Seashore (Naugle et al., 2002; Rutberg and Naugle, 2008), and elk at Point Reyes National Seashore (CA) (Shideler et al., 2002).

Species: The pZP vaccine has been used in horses (Kirkpatrick and Turner, 2002), burros (Turner et al., 1996), Przewalski's horses and zebra (Frank et al., 2005; Ransom et al., 2013), white-tailed deer (Naugle et al., 2002; Rutberg and Naugle, 2008; McShea et al., 1997; Miller et al., 2000b), elk and moose (Shideler et al., 2002; Frank et al., 2005), fallow deer (Deigert et al., 2003), as well as other exotic ungulate species (Frank et al., 2005; Kirkpatrick et al., 2009). Recombinant ZP vaccines have been used in white-tailed deer (Miller et al., 2000a). Although sample size is small, it seems that sheep and goats sustain contraceptive titers for longer periods of time; one injection was sufficient to maintain infertility for more than 2 years in captive bighorn sheep and mountain goats (Frank et al., 2005).

Source: The pZP vaccine ZonaStat-H is produced and distributed by the Science and Conservation Center, Montana (http://www.sccpzp.org/).

b. Porcine zona pellucida (pZP) vaccine – slow release

Description: Single dose, multiyear formulations of pZP have been delivered as microspheres (McShea et al., 1997), in pelleted form (Rutberg et al., 2013; Ransom et al., 2011; Roelle and Ransom, 2009; Turner et al., 2008), as liposomes (SpayVac) (Bechert et al., 2013; Rutberg et al., 2013; Fraker et al., 2002; Killian et al., 2008; Brown et al., 1997), and as an emulsion (Miller et al., 2009).

Mechanism of action: Repeated/ continuous antigenic stimulation is achieved by the slow or controlled release of the various vaccine preparations which enhances or prolongs the antibody effect. This is similar to booster vaccination, but does not require re-dosing or prolongs the interval between doses.

Administration: Liposome encapsulated pZP formulations (SpayVac) were delivered to captive (Miller et al., 2009) and free-ranging (Rutberg et al., 2013) white-tailed deer, fallow deer (Fraker et al., 2002), and feral horses (Killian et al., 2004) by intramuscular hand injection. These products have not yet been fully tested for administration via dart. Reports on dart use of pZP microspheres are variable as one study reports that they settle out in the carrier medium and clog syringes and needles (Kirkpatrick and Frank, 2005) and in another study microspheres were successfully delivered to white-tailed deer via dart injection (McShea et al., 1997). The pelleted form is two injections delivered by hand, one via trocar the other using regular needle and syringe (Rutberg et al., 2013; Ransom et al., 2011).

Efficacy: When **liposomes** (SpayVac) were used in white-tailed deer there was a 96% reduction in fecundity and was effective for up to 5 years (Miller et al., 2009). Alternately, it was approximately 70% effective in free-ranging deer over 3 years (Rutberg et al., 2013). In feral fallow deer, SpayVac was 100% effective for at least 3 years (Fraker et al., 2002). Contraception rates in horses decreased from 100% to 83% over 4 years (Killian et al., 2008). No long-term data on population level effects exists for SpayVac. One study (Miller et al., 2009) compared four slow release formulations in **emulsion** form (5 female deer each treatment), the efficacy of these formulations were: a) SpayVac (liposomes) 100% efficacy up to year 3, then 80% of does remained infertile for years 4 and 5; b) a non-liposome emulsion formulation was 100% effective for year 1, and 80% effective each year up to year 7, it is not clear if the 20% reversal represents the same female; c) emulsion formulation without the adjuvant AdjuVac (see section 4.2.d for information on adjuvants) 80% of does were infertile for the first year and none were infertile in subsequent years and d) emulsion formulation (500µg) without AdjuVac 100% of does were infertile the first year. By year 2 only 20% of does remained infertile (Miller et al., 2009). In non-contracepted deer herds, many of the untreated females gave birth to twins, whereas many of the treated-reversed females had singletons. Therefore, although the doe was no longer infertile, her fecundity was suppressed. The **pelleted** formulation (made by cold-evaporation or heat extrusion, Turner et al., 2008) reduced individual foaling rates in a feral horse herd from 75% to 32% (Ransom et al., 2011) and decreased pregnancy rates in white-tailed deer from approximately 80% before treatment to 30% after treatment (Rutberg et al., 2013).

Biological effects: Same as for suspension pZP (see above). Long term effects are still largely unknown for the multiyear experiments. Ovarian suppression effects may be more prominent given the more robust antigenic stimulation (Bechert et al., 2013).

Reversibility: In mares treated with one dose of the **liposome** formulation (SpayVac), 17% returned to fertility by the second year (this percentage did not increase over the course of years 2-4) and serum antibody concentrations in the 2 (of 8) mares that became pregnant were significantly lower than in the contracepted mares (Killian et al., 2008). Prior work found, treated mares returned to fertility 2 years after treatment (Killian et al., 2006). White-tailed deer treated with SpayVac remained infertile for at least 2 years (0% reversal) (Locke et al., 2007). One study (Miller et al., 2009) compared four slow release formulations in **emulsion** form (see results above). In another study, none of the treated fallow deer does that were examined were pregnant at the end of a 3 year study (Fraker et al., 2002). In 5 years of post-treatment monitoring of horses treated with the 22-month **pelleted** formulation (made by cold-evaporation), only 47% of treated females produced offspring. Ninety-two percent of those females had demonstrated fertility prior to treatment (Ransom, 2012; Ransom et al., 2013).

Non-target effects: Same as for suspension pZP (see above).

Regulation: Slow release pZP vaccines are not yet registered for use in any species. For research purposes, an experimental use permit (EUP) is likely required by the EPA.

Species: The **liposome formulation** (SpayVac) has been used in: feral horses (Killian et al., 2008), white-tailed deer (Rutberg et al., 2013; Locke et al., 2007; Miller et al., 2009), and fallow deer

(Fraker et al., 2002). The **emulsion** formulation with and without AdjuVac as well as in lyophilized form has been used in white-tailed deer (Miller et al., 2009). The **pelleted** formulation has been used in feral horses (Ransom et al., 2011; Roelle and Ransom, 2009; Turner et al., 2008) and white-tailed deer (Rutberg et al., 2013).

Source: None of the slow release technologies are available commercially. All are being produced and used in an experimental / research context. ImmunoVaccine Technologies (IVT) of Halifax, Nova Scotia, Canada, developed liposome encapsulated pZP (SpayVac) as well as the antigen portion of the vaccine used by Miller et al. (2009). The adjuvant (AdjuVac) used in the emulsion formula was developed by the USDA, APHIS, Wildlife Services at the National Wildlife Research Center, Fort Collins, CO, USA. Time-release pelleted pZP vaccine is currently being developed at the University of Toledo, College of Medicine in conjunction with the Science and Conservation Center, Montana (http://www.sccpzp.org/).

c. GnRH vaccine

Description: Gonadotropin releasing hormone (GnRH) is a small neuropeptide (a protein-like molecule) produced in the hypothalamus of the brain and is a necessary part of the reproductive hormonal cascade (Figure 1.1.1). Vaccines directed against GnRH create an antibody response against this hormone. Because GnRH is a small endogenous or "self" peptide, it is not naturally immunogenic and must be conjugated to a large, highly immunogenic carrier protein (Nett et al., 1973; Miller et al., 2008) then combined with a potent adjuvant to stimulate antibody production. The current GnRH vaccine produced for wildlife contraception is called GonaCon.

Mechanism of action: Immunization against GnRH elicits antibodies that when bound to endogenous GnRH prevent it from binding to pituitary receptors and suppresses the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) (two hormones that stimulate the function of the gonads), leading to atrophy of the gonads and concomitant infertility in both sexes (Miller et al., 2000c).

Administration: The GnRH vaccine can be applied to either males or females; however, little empirical data is available on its effects in suppressing fertility in male wild ungulates. Most studies have been directed toward evaluating its effect on reproduction and side-effects in females. Dose is species dependent. One to 3 ml of emulsified vaccine is generally given. Intramuscular injection via hand-held syringe is currently the only method of delivery in deer; however, the vaccine can be delivered via dart to horses (see Appendix 6). Typical application is a single injection without booster vaccinations for several years.

Efficacy: In white-tailed deer does, vaccination with GonaCon resulted in 88% reduction in fawning rate (Miller et al., 2000c). In a multi-year study, the pregnancy rate in GonaCon-treated white-tailed deer was 12% compared to 85% in controls one year post-treatment and 53% (vaccinates) compared to 100% (controls) two years after vaccination (Gionfriddo et al., 2009). In a small study in white-tailed deer, two formulations of a one-shot vaccine were tested and resulted in 100%, 60%, 50%, 50%, and 25% contraception in years 1-5. (Miller et al., 2008). Captive elk vaccinated once with

GonaCon showed a 90% decrease in fertility the first year following treatment, 75% the second year, 50% the third year and 25% the fourth year following treatment (Powers et al., 2011). The vaccine was less efficacious in free-ranging elk where effects only lasted 2 years (Powers et al., 2014). Efficacy rates for captive mares vaccinated with GonaCon were 94% after 1 year, then 60% and 53% for years two and three, respectively (Killian et al., 2006; Killian et al., 2008). However, free-ranging feral horses had only an approximate 30% decrease in foaling rates for 2 years post-vaccination when compared to untreated mares (Powers, 2014). Feral swine inoculated with GonaCon reduced pregnancies from 100% in control to 10% in treated females in a 36 week trial (Killian et al., 2003). A group of pregnant bison was administered GonaCon, they calved normally and the year after vaccination 0 of 6 treated female bison were pregnant after being exposed to fertile males (Miller et al., 2004).

Biological effects: Sterile pyogranulomatous injection site abscesses were observed in elk (Powers et al., 2011; Powers et al., 2014) and white-tailed deer (Curtis et al., 2008; Gionfriddo et al., 2008; Gionfriddo et al., 2011) although the injection site lesions did not appear to affect locomotion or general health. In one small horse study in Theodore Roosevelt National Park, ND approximately 80% of mares had evidence of swelling at the injection site that lasted 1-4 years (Powers, 2014). **Female**: Female elk vaccinated with GonaCon continued to show pre-copulatory behaviors throughout the normal breeding season (September – October), which suggests that vaccination only partially suppresses the hormones responsible for driving reproductive behavior as well as ovulation (Powers et al., 2011). Vaccination did not affect pregnancy when administered to mid-gestation pregnant elk (Powers et al., 2011), or feral pigs (Killian et al., 2003), but may have affected pregnancy success in white-tailed deer (Miller et al., 2000c). Additionally, there were no adverse effects noted in calves born to treated female elk (Powers et al., 2012). When administered to pregnant bison, 3 of 4 delivered healthy calves, the fourth one presented with dystocia, as did one cow in the control group (Miller et al., 2004). Mean body condition scores in treated adult female white-tailed deer were greater than in non-treated females (Gionfriddo et al., 2011). There were minimal treatment effects on time budgets, and reproductive behaviors were similar in GnRH vaccinated and saline control mares, likely due to suppressed estrous cycling in treated mares and pregnancy in control mares (Ransom et al., 2014b). **Male**: Captive feral pigs had reduced testicular weights and reduced testosterone concentrations after vaccination (Killian et al., 2003), but there were no changes in daily activity time budgets or blood chemistry parameters (Massei et al., 2008). Immunized male white-tailed deer demonstrated no sexual activity towards untreated females (Miller et al., 2000c). Vaccination with GonaCon negatively affected antler development and testes morphology (Curtis et al., 2008; Miller et al., 2000c). Mean body condition scores in treated adult males were greater than in non-treated males (Gionfriddo et al., 2011).

Reversibility: Seventy-five percent of captive female elk vaccinated with GonaCon returned to fertility by 4 years post-treatment (Powers et al., 2011). Forty seven percent of captive mares vaccinated with GnRH vaccine had returned to fertility by 3 years post-treatment (Killian et al., 2006). In a small study in white-tailed deer, two formulations of a one-shot vaccine were tested and return to fertility was 0%, 40%, 50%, 50%, and 75% in year 1-5 respectively (Miller et al., 2008).

Non-target effects: Similar to pZP vaccines, the GnRH vaccine has a protein based antigen and does not pose a threat to non-target species including humans. Current label does not address human consumption issues; however, an internal EPA memorandum (see Appendix 2) concludes there are no concerns for human health.

Regulation: In 2009, GonaCon was registered by the EPA as a restricted use pesticide for use in free-ranging female white-tailed deer. The vaccine is approved for use by hand injection only by USDA/APHIS/Wildlife Services or state wildlife management agency personnel or by persons working under their authority. The vaccine must meet state regulatory requirements for pesticide use prior to purchase or shipping within a state.

In 2013 GonaCon was registered for use in free-ranging horses and burros. In equids the vaccine can be administered by employees of:

- USDA/APHIS/WS or Veterinary Services, National Park Service, Bureau of Land Management, U.S. Fish and Wildlife Service
- State wildlife agencies with responsibility for wild or feral horse or burro management
- Federally recognized Indian tribes
- Department of Defense
- Public and private feral horse sanctuaries
- Designated agents of the above entities

Species: GonaCon has been evaluated in captive and free-ranging white-tailed deer (Miller et al., 2000c; Gionfriddo et al., 2009; Gionfriddo et al., 2011), captive and free-ranging elk (Powers et al., 2011; Killian et al., 2009; Powers et al., 2014), captive bison (Miller et al., 2004), captive feral swine (Massei et al., 2008), captive and free-ranging horses (Killian et al., 2008; Killian et al., 2006; Killian et al., 2004). No large scale population level field trials have been conducted.

Source: GonaCon is currently manufactured by the USDA/APHIS/WS National Wildlife Research Center and is distributed commercially by Pocatello Supply Depot.

d. Adjuvants

An immunologic adjuvant is defined as any substance that acts to accelerate, prolong, or enhance antigenic-specific responses when used in combination with specific vaccine antigens (Stills, 2005). Adjuvants are needed for immunocontraception, because the intent is to develop antibodies to a "self" protein, which are inherently of low antigenicity. One mechanism by which adjuvants work is the "depot" effect. One of the components of the adjuvant, generally the oil base, prevents the body from diluting, degrading, and eliminating the antigen; thus causing continuous and prolonged exposure of the immune system to low levels of antigen (Stills, 2005). Another method of stimulating the immune system is to add killed bacteria to the adjuvant. The body recognizes the bacteria or

bacterial components as foreign and mounts a much stronger immune response. Finally, in addition to an adjuvant some antigens, particularly small ones, require a carrier molecule to successfully present the antigen to the immune cells and ensure a biologically significant response. In general, GnRH vaccines require a protein carrier molecule to stimulate an antibody response (Miller et al., 2008) whereas pZP vaccines do not.

The following is a list of the most commonly used adjuvants and carrier proteins in fertility control vaccines.

- **Freund's complete adjuvant** contains paraffin oil, a crude mineral oil (~85%), the emulsifying agent mannide monooleate (Arlacel A) (~15%), and heat-killed *Mycobacterium tuberculosis* in the original formulation of Freund's adjuvant (Freund et al., 1937). Although it is still called FCA, modifications have been made over time, in particular regarding the purity of the oil used; therefore it is difficult to compare reactions caused by FCA (Stills, 2005). This is one of the most immunogenic adjuvants available. In immunocontraception it has been used to administer the initial or priming dose of many vaccines. Its use can be accompanied by injection site reactions such as granulomatous inflammation and sterile abscesses (Curtis et al., 2007). Due to the *M. tuberculosis* contained in FCA, it can lead to false positive results on intradermal tuberculosis tests (Lyda et al., 2005). As a consequence of the injection site reactions as well as false positive tuberculosis results, its use has been discontinued as better alternatives have been identified (Roelle and Ransom, 2009).

- **Freund's incomplete adjuvant** differs from FCA in that FIA lacks the bacterial fraction (Stills, 2005). This form is used to give boosters after the initial dose. For a more in-depth review of other oil-in-water and water-in-oil adjuvants, the reader is referred to Stills (2005).

- **Freund's complete adjuvant, modified** contains *Mycobacterium butyricum* rather than *M. tuberculosis*, and therefore does not lead to false positive results on intradermal tuberculosis tests (Lyda et al., 2005). However, Freund's modified still incites a robust inflammatory response and can lead to nodules which may be granulomas (Roelle and Ransom, 2009).

- **AdjuVac** is an oil-based, proprietary adjuvant which contains killed *Mycobacterium avium* (Dunbar et al., 1989). AdjuVac is a modification of the USDA-licensed Johne's disease vaccine, Mycopar (Fort Dodge Animal Health, Fort Dodge, IA, USA) (Miller et al., 2008). Because Mycopar is already approved for use in food animals, the concern about the use of AdjuVac in ungulates that may be hunted for human consumption is decreased (Miller et al., 2008). The amount of mycobacteria contained in AdjuVac is three orders of magnitude less than FCA (Dunbar et al., 1989). AdjuVac can cause false positive on assays for antibodies to Johne's disease (Powers et al, 2011), which may complicate management.

4.3. Pharmaceutical / Hormonal

a. GnRH agonist

Description: This method can be potentially effective in both male and female wild ungulates; however, due to its effects on secondary sex characteristics (e.g., antler growth, male behavior) it is usually a female-directed technology. A slow-release implant or depot injection with a synthetic GnRH agonist, down-regulates the secretion of LH and FSH from the pituitary and inhibits function of the gonads. This result is similar to the GnRH vaccine; however, GnRH agonists are not vaccines and do not induce an immune reaction. The most common GnRH agonist tested in free-ranging wildlife is leuprolide.

Mechanism of action: Administration of GnRH agonists provides continuous stimulation of the pituitary which first temporarily increases then causes long-term suppression in production of key reproductive hormones (LH and FSH). This interferes with gonad function inducing infertility. Although, in theory, this method should have an effect on both males and females, some agonists are not effective in male ungulates. Studies indicate that treatment with GnRH agonists failed to sufficiently down-regulate LH and testosterone in bovids [nafarelin (Melson et al., 1986); deslorelin (Aspden et al., 1997; D'Occhio et al., 2000)], and antelope species [deslorelin (Penfold et al., 2002)].

Administration: Slow release implants or depot injections need to be placed intramuscularly or subcutaneously using either dart or hand injection. In elk, long-term implants last 7 – 8 months (Baker et al., 2005; Baker et al., 2002). Therefore, ungulates must be treated prior to breeding season to prevent 1 year of reproduction.

Efficacy: In female elk, leuprolide suppressed ovulation and achieved 100% contraception in clinical trials with captive (Baker et al., 2002) and free-ranging (Conner et al., 2007) elk and captive mule-deer (Baker et al., 2004).

Biological effects: Agonists block the final maturation of ovarian follicles and ovulation, and decrease the production of gonadal steroid hormones; however, no changes in breeding behaviors were observed in elk (Baker et al., 2002). Similarly, no changes in systemic blood parameters were observed. Agonists cause an initial stimulation of the ovary followed by suppression; therefore females could become pregnant if the agonist is administered at a time when the follicles are capable of ovulation (e.g., early autumn). Consequently, the agonist must be administered prior to the breeding season for it to be effective.

Reversibility: When slow-release implants no longer deliver biologically active GnRH agonist, females regain fertility. Leuprolide implants were completely reversible after 1 year in female elk (Baker et al., 2002; Baker et al., 2005; Conner et al., 2007) and mule-deer (Baker et al., 2004).

Non-target effects: No known non-target effects; however, no studies with oral exposure to depot or long-term implants in non-target species have been conducted.

Regulatory issues: Leuprolide is not labeled for use in free-ranging ungulates at this time. It has been used in an experimental fashion in the past.

Species: Used experimentally in female elk (Baker et al., 2002; Baker et al., 2005; Conner et al., 2007) and mule deer (Baker et al., 2004). Leuprolide has not been tested at the population level.

Source: No GnRH agonists are currently being formulated for commercial use in free-ranging wildlife in the United States. Slow-release deslorelin (Suprelorin) 6 month implants (4.7mg) are made by Peptech Animal Health (Australia). Virbac has a product for ferrets and it is available in the US (Suprelorin F). Leuprolide (Lupron Depot) is labeled for use in humans and is not widely available for animal use.

b. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

Description: Prostaglandin $F_{2\alpha}$ is a female directed method of contragestion which terminates pregnancy. Prostaglandin $F_{2\alpha}$ occurs naturally in females and is the physiologic pathway to lyse the corpus luteum after non-fertile estrous cycles.

Mechanism of action: Prostaglandin $F_{2\alpha}$ interrupts pregnancy by lysing the corpus luteum which is responsible for progesterone production and the maintenance of pregnancy.

Administration: Prostaglandin $F_{2\alpha}$ has been used in white-tailed deer by delivery in a "bio-bullet" (DeNicola et al., 1997b) and in elk by hand-injection (Powers et al., 2011; Bates et al., 1982).

Efficacy: Can be up to 100% efficacious but may require repeated doses during one season. Effective use of $PGF_{2\alpha}$ has been reported in white-tailed deer treated with the bio-bullet formulation (one treatment); pregnancy rate in treated does was 13% compared to 90% in untreated does (DeNicola et al., 1997a). In captive elk $PGF_{2\alpha}$ was 100% effective after 2 hand-injected doses 6 hours apart (Powers et al., 2011).

Biological effects: Prostaglandins induce termination of pregnancy (abortion) by eliminating (lysing) the natural source of progesterone from the ovaries (corpus luteum). Females may return to estrous cycling and conceive if the breeding season has not ended. Also, this method may require multiple doses to be effective.

Reversibility: Prostaglandin $F_{2\alpha}$ affects only the corpus luteum present at the time of administration; therefore the female will likely be fertile the next estrous cycle.

Non-target effects: No non-target issues. Prostaglandins are metabolized quickly through the target animal's respiratory system and leave no residue. There is no meat withdrawal period.

Regulatory issues: Use of $PGF_{2\alpha}$ analogs such as dinoprost tromethamine (Lutalyse) or cloprostenol (Estrumate) are not labeled for use in free-ranging wildlife as fertility control agents at this time.

Species: Has been used effectively used in small numbers of free-ranging white-tailed deer (DeNicola et al., 1997a) and captive elk (Powers et al., 2011).

Source: Biobullets were manufactured by Antech Laboratories (DeNicola et al., 1997a). Dinoprost tromethamine is a synthetic form of $PGF_{2\alpha}$ and is sold commercially by veterinary suppliers as Lutalyse. Cloprostenol is likewise sold commercially as Estrumate.

c. Steroid hormones (Progestins)

Description: Progestins are synthetic forms of progesterone, one of the steroid hormones, and have been used as contraceptives in ungulates. Progestins are very effective contraceptive agents in captive wildlife; however, they are not likely to be approved for use in free-ranging ungulates due to perceived human health concerns. Synthetic progestins target female contraception. There are various compounds; the most commonly used are melengestrol acetate (MGA), medroxyprogesterone acetate (MPA), megestrol acetate (MA), levonorgestrel (LNG), and norgestomet.

Mechanism of action: Progestins act in several ways to interfere with conception and pregnancy. Constant systemic levels cause negative hormonal feedback to the hypothalamus and pituitary which interferes with ovulation. Progestins also alter the uterine environment making it more difficult for sperm to reach the ovum and for a conceptus to implant.

Administration: Administration varies depending on the formulation and specific progestin. There are surgically implanted long-term implants (MGA) which last approximately 2 years, depot injections (MPA) which last approximately 3 months, and daily administration pre-mixed feed for ungulates (MGA feed) (Patton et al., 2005). Also, norgestomet implants can be delivered remotely into the muscle in biobullets (DeNicola et al., 1997b). Other progestins are available but have not been investigated in free-ranging wildlife.

Efficacy: In ungulates, MGA implants are effective in many zoo species (not in equids), with a failure rate of ~ 4%. In white-tailed deer, norgestomet implants were 92-100% effective (DeNicola et al., 1997b). In black-tailed deer norgestomet was effective in preventing pregnancy in all (n = 7) females for one breeding season (Jacobsen et al., 1995). Feral mares treated with ethinylestradiol and progesterone implants had foaling rates between 6 and 16% compared to controls where foaling rates were 42-45% (Eagle et al., 1992). Levonorgestrel implants were not an effective contraceptive in white-tailed deer (White et al., 1994; Plotka and Seal, 1989). Another synthetic progestin implant (DRC-6246) was used with some efficacy in white-tailed deer; 23% pregnancy rate in treated does compared to 75% in control does (Matschke, 1980).

Biological effects: Folliculogenesis can occur in animals treated with progestins and females may continue to exhibit estrous behavior. Endometrial hyperplasia, hydrometra, and uterine infections have occurred in MGA treated captive exotic ungulates; however, these diseases occasionally occur in non-treated animals in captivity (Munson et al., 2005). The association between progestin treatment and risk of these diseases in ungulates is being investigated. Oral MGA administration to pregnant white-tailed deer was not associated with interrupted pregnancies, changes in gestation length, stillbirth, or parturition difficulty (dystocia) (Roughton, 1979). In white-tailed deer MGA implants did not interrupt pregnancy but did interfere with parturition (Plotka and Seal, 1989). Progestins should not be used in pregnant animals.

Reversibility: In zoo ungulates, reversal time for MGA treated animals (time between removal of implant and time of estimated conception) ranged from 1 - 31 months. Moose (n= 2) treated with MPA for 3 months conceived after 11 months (Patton et al., 2005).

Non-target effects: There is potential to affect non-target species because steroids remain systemically bioactive after administration. While similar preparations are used in commercial food producing animals (e.g., domestic cattle, sheep, and swine) to promote growth, public perception of risk to predators, scavengers and human hunters likely precludes their use in free-ranging wildlife.

Regulation: There are no steroid hormones labeled for use as contraceptives in free-ranging wildlife.

Species: Progestins have proven to be effective contraception in many species of captive ungulates, including bovids and cervids and specifically in white-tailed deer (Roughton, 1979) and black-tailed deer (Jacobsen et al., 1995; DeNicola et al., 1997b).

d. Gonadotropin releasing hormone toxins

This contraceptive consists of a highly active analog of GnRH (e.g., GnRH agonist) coupled to a cellular toxin, for example, pokeweed antiviral protein (PAP) (Yang et al., 2003) or derivatives of doxorubicin (Kovacs et al., 1997). The cytotoxin is carried to the gonadotroph cells in the anterior pituitary. The toxin is internalized into the cell when the GnRH analog binds to the GnRH receptor. The toxin disrupts cellular protein synthesis or initiates cell death. The cell can no longer produce LH and FSH interrupting the reproductive hormone cascade. The GnRH-PAP conjugate has been investigated in domestic male dogs (Sabeur et al., 2003), domestic sheep (Nett et al., 1999) and female mule deer (Baker et al., 1999). The chemotherapeutic doxorubicin derivative has been tested in rats (Kovacs et al., 1997). This technology is still in the research and development stages but may be available in the future.

4.4. Surgical / Physical

a. Ovariectomy/Orchiectomy (Castration)

Description: Ovariectomy is removal of the ovaries. Orchiectomy is removal of the testes. (Described in: Youngquist, 1997)

Mechanism of action: When the gonads are removed, the animal is sterilized because there are no ovarian or testicular hormones (estrogens and progesterone or testosterone) and there are no gametes (ova/sperm).

Administration: Surgical sterilization requires capture, anesthesia and surgery on individual animals. A sterile surgical field and a licensed veterinarian are generally required to perform surgery. The female surgery can be performed either through a standard incision or with a laparoscope. The male surgery is less invasive and is performed through an incision in the scrotum.

Efficacy: This method is 100% effective at preventing reproduction in the individual if the surgery is performed properly.

Biological effects: The animal loses ovarian or testicular hormones and all reproductive hormone driven behaviors and secondary sex characteristics. Estrous behavior, mounting, pair-bonding and territoriality may be lost; however, these behaviors may be both learned as well as influenced by hormones and some behaviors may remain. The animal is permanently removed from the breeding population.

Reversibility: This method is not reversible.

Non-target effects: Animals must be marked to alert hunters to withdrawal times associated with anesthetic agents.

Regulation: A qualified veterinarian is generally required.

Species: Orchiectomy was used on a small scale at Point Reyes National Seashore on fallow bucks (N. Gates personal communication), and more recently ovariectomy has been used experimentally to limit deer populations (A. DeNicola personal communication, White Buffalo Inc. http://www.whitebuffaloinc.org/).

b. Tubal ligation or transection

Description: Tubal ligation or transection, involves the cutting the oviduct (uterine or Fallopian tubes - the distal-most part of the uterine horn) to prevent the ovum from reaching the uterus after ovulation (MacLean et al., 2006).

Mechanism of action: By transecting the oviduct, the ovum is prevented from reaching the uterus and the sperm cannot reach the ovum; therefore, conception is prevented.

Administration: Surgical sterilization requires capture, anesthesia and surgery on individual female animals. A sterile surgical field and a licensed veterinarian are generally required to perform the surgery. The surgery can be performed either through a standard incision or with a laparoscope.

Efficacy: This method is 100% effective at preventing reproduction in the individual if surgery is performed properly.

Biological effects: Treated females cannot conceive yet are hormonally intact; therefore, they continue to cycle and show repeated estrous behavior during the breeding season. The animal is permanently removed from the breeding population.

Reversibility: This method is not reversible.

Non-target effects: Animals must be marked to alert hunters to withdrawal times associated with anesthetic agents.

Regulatory issues: A qualified veterinarian is generally required.

Species: This technique was successfully used in a small population of white-tailed deer in a study in Illinois (Mathews et al., 2005) and at Point Reyes National Seashore in a few fallow deer does (N. Gates, personal communication).

c. Vasectomy/Epididyectomy

Description: This male contraception method removes part of the vas deferens or the epididymis. The vas deferens is the tube connecting the testes with the urethra and the epididymis is the sperm storage area at the base of the testes. By removing a part of this tubular system sperm cannot be ejaculated. Although, in canids vasectomy reversals have been performed when the vas ends are left open (DeMatteo et al., 2006), this is most often a permanent method of sterilization. (Described in: Youngquist, 1997)

Mechanism of action: Pregnancy is prevented by removing the ability of sperm to reach the female reproductive tract. Animals are hormonally intact.

Administration: Surgical sterilization requires capture of individual animals, a sterile surgical field, and generally a licensed veterinarian to perform the surgery.

Efficacy: If done properly, vasectomy or epididymectomy will render 100% of treated males infertile. In feral horses vasectomy of the band stallion resulted in a reduction of the percentage of bands with foals from 80-86% prior to treatment to 17-30% post-treatment (Asa, 1999); however, due to the polyandrous nature of horses it may not have a population level effect (Eagle, 1993; Garrott and Sniff, 1992).

Biological effects: The male will no longer be able to introduce sperm to the female reproductive tract. Because the testes are not removed, the animal is hormonally intact and testosterone driven behaviors as well as secondary sex characteristics (e.g., antlers) will still be present. No studies have evaluated the collateral effects of male vasectomy on female behavior. However, a model was developed to assess the efficacy of vasectomy in feral horses (Garrott and Siniff, 1992). This model presumed that non-pregnant females (as a consequence of the dominant stallion being infertile) would continue to cycle which would lead to an extended breeding season providing opportunity for mating with non-dominant stallions (subordinate or bachelors) and shifting the foaling season to later in the year (Garrott and Siniff, 1992).

Reversibility: Although vasectomy reversal has been used successfully in canids (DeMatteo et al., 2006) and it is routinely done in humans, reversal requires that a) the vasectomy be done with an open-ended technique, b) the specific individual must be located and c) specialized training is required to perform the reversal surgery. Therefore, within the context of free-ranging wildlife this method is considered a permanent method of contraception.

Non-target effects: Animals must be marked to alert hunters to withdrawal times associated with anesthetic agents.

Regulation: A qualified veterinarian is generally required.

Species: In free-ranging species this technique has only been used in very limited situations in horses and deer.

d. Intrauterine Devices (IUD)

Description: This method can only be used in females. Inert foreign bodies (e.g., silastic O-rings, round glass balls, copper T-devices) are inserted into the uterine lumen (Daels and Hughes, 1995).

Mechanism of action: Foreign bodies create a mild inflammation in the uterus which interferes with pregnancy (Daels and Hughes, 1995).

Administration: To place the intrauterine devices it is necessary to handle the animal and in most cases will require chemical immobilization. Treating before the breeding season is recommended in white-tailed deer (Malcolm et al., 2010).

Efficacy: In mares treated with copper-containing IUDs, 80% were infertile after year 1, but only 25% and 14% were infertile and after years 2 and 3 (Killian et al., 2006). In another study using horses, 20% of treated mares became pregnant, compared to 75% of controls, expulsion of IUD from the uterus was also reported for some of these mares (Killian et al., 2004). In a small trial in white-tailed deer does treated with copper IUDs 25% conceived, compared to 100% of controls; this failure was presumably due to loss of the vaginal implant (Malcolm et al., 2010).

Biological effects: Estrous cycles were less common in females treated with copper T-devices than those treated with a pZP vaccine (Killian et al., 2006). With silastic O-rings, mares showed reproductive behaviors and had more estrous cycles (mean 5 cycles per mare) compared to untreated mares (which became pregnant after a mean of 2 cycles); however estrous cycle length varied more than in untreated mares (Daels and Hughes, 1995). The study on copper T-devices did not report any side effects (although histopathology was not performed) (Killian et al., 2006). Silastic O-rings were reported to cause mild chronic endometritis but no lasting effects (Daels and Hughes, 1995).

Reversibility: This method is presumably effective until the device is removed, which requires re-capture of the animal. Although the study was not designed to measure reversibility, 75% of mares returned to fertility after 2 years and 86% were fertile after 3years, most likely due to loss of the IUD (Killian et al., 2006). Retention with silastic O-rings was good, 5 of 6 mares maintained the IUD until removal (Daels and Hughes, 1995). The effects of this method on behavior of the population (including males) have not been studied.

Non-target effects: Because each animal is individually treated, accidental exposure to this contraceptive is not anticipated.

Regulation: Intra-uterine devices are not currently regulated or sold for use in free-ranging species. To date they have only been used experimentally.

Species: This method has been used in captive horses (Daels and Hughes, 1995; Nie et al., 2001; Killian et al., 2006) and captive white-tailed deer (Malcolm et al., 2010). This method has not been tested in free-ranging ungulates.

4.5. Fertility control product comparison table

Summary comparison of key characteristics of fertility control products most likely to be used in ungulates.

Agent	Federal/State Approved for use in ungulates	Multi-year efficacy (3+) with single application	Capable of remote administration (dart or biobullet delivery)	Meat Safe for Humans	Success in controlling the size of Free-ranging Populations
Immunocontraceptives					
pZP vaccine (two dose initial + yearly booster regimen)	Yes (horses)	No (although there are residual effects with long-term use)	Yes	Likely, but need EPA approval in food producing species	Yes, but only in closed, small populations over long periods of time (>10yr; horses, white-tailed deer)
Slow release technologies	No	Likely[a]	Unknown		Untested
GnRH vaccine	Yes (white-tailed deer, horses)	Possibly[b]	Species dependent[c]	Yes	Untested
GnRH Agonists					
Leuprolide Acetate	No	No	Yes	Likely but need EPA approval	Untested
Histrelin Acetate	No	No	No	Likely but need EPA approval	Untested
Other					
Physical/surgical	Not applicable (may require a veterinarian)	Yes – but permanent	No	Yes, after anesthesia withdrawal time	Untested
Steroid Hormones	No	No	Unknown	Unlikely, but need regulatory guidance	Untested
Contragestives ($PGF_{2\alpha}$)	No	No	Yes	Yes	Not likely but untested

a Long-term studies (>5 years) have been conducted only in captive deer with small sample sizes (Miller et al., 2009); however, antibody levels suggest long-term infertility (Fraker et al., 2002) and recent research suggests up to 3 years of contraception in free-ranging white-tailed deer (Rutberg et al., 2013)

b The multi-year formulation was less effective in free-ranging vs. captive deer (Miller et al. 2008; Gionfriddo et al., 2009, 2011) and in free-ranging (Powers et al., 2014) vs. captive (Powers et al., 2011) elk.

c The label for white-tailed deer requires hand injection; whereas the label for horses allows for hand-injection, jab-stick, or dart delivery (Appendix 6.4).

Appendix 5. Glossary

5.1. Definitions, acronyms and abbreviations

AMDUCA	Animal Medicinal Drug Use Clarification Act
CE	Categorical Exclusion
CL	Corpus luteum
contragestion	Any contraceptive method that prevents the gestation of a fertilized egg either by making the implantation site uninhabitable or by promoting the expulsion of the conceptus.
corpus luteum	Area that remains in the ovary after ovulation took place. There is one corpus luteum for every follicle that ovulated. Consists of cells that produce progesterone.
CVM	Center for Veterinary Medicine
EA	Environmental Assessment
ecology	The study of interactions between organisms and their environment
EIS	Environmental Impact Statement
EPA	Environmental Protection Agency, since 2006 is responsible for regulation of fertility control products for use in free-ranging wildlife, as they are now considered pesticides.
estrogens	This group of steroid hormones (primarily estradiol) is produced by the dominant follicle prior to ovulation and in some species the corpus luteum (CL) post-ovulation. The primary actions are to support follicular development and provide negative and positive feedback to the hypothalamus and pituitary for maintenance of the reproductive cycle.
FCA	Freund's Complete Adjuvant, includes particles of dead *Mycobacterium tuberculosis,* used as the adjuvant for the initial dose of pZP vaccination in early studies but can cause false positive tuberculin tests so is no longer used.
FDA	Food and Drug Administration, regulates drugs (pharmaceuticals) for use in humans and animals.
FIA	Freund's Incomplete Adjuvant, does not include *Mycobacterium tuberculosis,* used as the adjuvant for the follow-up doses of pZP

	vaccination.
FMA	Freund's Modified Adjuvant, includes particles of dead *Mycobacterium butyricum,* used as adjuvant for the initial dose of pZP vaccination. Does not result in false positive results in tuberculin skin tests.
follicle stimulating hormone	Follicle stimulating hormone induces development of follicles and oocytes (eggs) (folliculogenesis/ oogenesis) in the ovaries of females. In the males it induces the development and maturation of sperm (spermatogenesis) in the testes. It is produced in the pituitary and production of FSH is stimulated by GnRH.
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone, a peptide hormone from the hypothalamus, responsible for the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. Also known as LHRH (luteinizing hormone releasing hormone).
GnRH-blue	GnRH peptide conjugated to Blue Carrier protein derived from the Chilean mollusk (*Concholepas concholepas*; CCH), to increase immunogenicity and make the vaccine more efficacious.
GnRH-KLH	GnRH conjugated to keyhole limpet hemocyanin (KLH) to increase immunogenicity and make the vaccine more efficacious.
gonadotroph	One of the many cell types within the anterior pituitary gland. They produce gonadotropins or hormones with an affinity for the gonads. The gonadotropins include LH and FSH.
gonadotropin releasing hormone	(GnRH), luteinizing hormone releasing hormone (LHRH), and luteinizing hormone releasing factor (LHRF) are all synonyms for the same protein hormone. GnRH is secreted in variable frequency pulses from the hypothalamus at the base of the brain and stimulates the gonadotroph cells in the anterior pituitary (attached to the base of the brain by the hypothalamic stalk). These cells then produce and secrete LH and FSH. GnRH is at the beginning of the reproductive hormone cascade.
hypothalamus	Part of the brain that produces gonadotropin releasing hormone.
INAD	Investigational New Animal Drug
KLH	Keyhole limpet hemocyanin, a large protein derived from a mollusk. The protein is conjugated to the small GnRH to increase

	immunogenicity and make the vaccine more efficacious.
lactotroph	Cell type within the anterior pituitary that produces prolactin.
LH	Luteinizing hormone
LHRF	Luteinizing hormone releasing factor is a synonym for Gonadotropin releasing hormone (GnRH), see gonadotropin releasing hormone for definition.
LHRH	Luteinizing hormone releasing hormone is a synonym for Gonadotropin releasing hormone (GnRH), see gonadotropin releasing hormone for definition.
luteinizing hormone	Luteinizing hormone is responsible for inducing maturation and ovulation of a mature egg (oocyte) from the ovaries in females. In the males it is responsible for stimulating testosterone production from the testes. It is produced in the pituitary and production of LH is stimulated by GnRH.
lyophilize	To freeze-dry, a process used to stabilize and increase shelf life of biological products.
MA	Megestrol acetate, synthetic progestin, available as oral, daily pills (Megace, Ovaban).
MGA	Melengestrol acetate, synthetic progestin. Most common formulation is a slow release implant, but has also been used as an oral liquid and milled in feed for ungulates.
MPA	Medroxyprogesterone acetate, synthetic progestin, frequently part of oral contraception pills, also available as depot injections (DepoProvera).
natural condition	The condition of the resource "that would occur in the absence of human dominance over the landscape." (Management Policies 2006 chapter 4).
NEPA	National Environmental Policy Act
norgestomet	A synthetic progestin, available as an implant.
NPS	National Park Service
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$

PRL	Prolactin
progesterone	This steroid hormone is initially produced principally by the tissue of the corpus luteum (CL). This hormone is primarily responsible for maintaining pregnancy. In different species variable amounts of progesterone are produced by the placenta later in gestation.
progestin	A progesterone-like molecule, it includes the endogenous progesterone as well as synthetic progesterone analogs.
prolactin	Hormone produced in the anterior pituitary and responsible for milk production and letdown in mammals.
prostaglandin	These fatty acid derived hormones are produced in various areas of the body. The two primary prostaglandins of importance in reproduction are $PGF_{2\alpha}$ and PGE_2. Prostaglandins work closely with corticosteroid hormones (primarily cortisol) to accomplish these reproductive biological effects.
prostaglandin E_2	This prostaglandin regulates many physiological functions; one of them is the rupture of the mature follicle and subsequent ovulation.
prostaglandin $F_{2\alpha}$	This prostaglandin signals the ovary to induce luteolysis of the corpus luteum. In this way it allows the start of a new estrous cycle or initiates early pre-term abortion or full-term parturition.
pZP	Porcine zona pellucida, zona pellucida from pig (porcine) origin, see also *zona pellucida.*
testosterone	This steroid hormone is the primary androgen (masculinizing hormone) responsible for supporting both primary (e.g. spermatogenesis, libido, etc.) and secondary (e.g. coloration, seasonal growth, antler growth, etc.) reproductive characteristics in males. Females also produce androgens most of which are then converted to estrogen. Testosterone provides negative feedback to the hypothalamus and pituitary causing suppression of both GnRH and LH secretion.
zona pellucida	The acellular layer around an ovum or egg cell, where the protein receptors that bind sperm for fertilization are located. Binding of antibodies to this receptor inhibits fertilization.
ZP	zona pellucida

5.2. Scientific names of referent species

Antelope, pronghorn	*Antilocapra americana*
Bison	*Bison bison*
Burro	*Equus africanus asinus*
Caribou	*Rangifer tarandus*
Cattle, domestic	*Bos taurus*
Deer, fallow	*Cervus dama*
Deer, mule (black-tailed)	*Odocoileus hemionus*
Deer, Sika	*Cervus nippon*
Deer, white-tailed	*Odocoileus viriginianus*
Elk	*Cervus elaphus nelsoni*
Goat, Mountain	*Oreamnos americanus*
Horse, Przewalski	*Equus ferus przewalskii*
Horse, feral /domestic	*Equus caballus*
Moose	*Alces alces*
Musk Ox	*Ovibos moschatus*
Pig, feral / domestic	*Sus scrofa*
Sheep, Bighorn	*Ovis canadensis*
Zebra, Grevy's, Burchelli's, and Mountain	*Equus grevyi, E. burchelli,* and *E. zebra*

Appendix 6. Product Labels

6.1. Memorandum on GonaCon exposure risk

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Health Effects

MEMORANDUM

Date: August 4, 2009

SUBJECT: Gonacon™ Immunocontraceptive Vaccine for use in White-Tailed Deer. Section 3 Registration.

PC Code: 116800
Decision No.: 404955
Petition No.: N/A
Risk Assessment Type: Non-food use
TXR No.: N/A
MRID No.: N/A

DP Barcode: D363061
Registration No.: N/A
Regulatory Action: Section 3
Case No.: N/A
CAS No.: 9034-40-6
40 CFR: N/A

Ver.Apr.08

FROM: Kit Farwell, DVM, DABT
Risk Assessment Branch VII
Health Effects Division (7509P)
Office of Pesticide Programs

Kit Farwell

THROUGH: Michael Metzger, Branch Chief
Risk Assessment Branch VII
Health Effects Division (7509P)
Office of Pesticide Programs

TO: Autumn Metzger, Product Manager
Insecticide/Rodenticide Branch
Registration Division (7505P)
Office of Pesticide Programs

I. CONCLUSIONS

HED has no objections to the Section 3 registration of Gonacon™. There are no risk concerns because of the very limited potential worker and dietary exposure.

II. BACKGROUND

The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) has applied for a Section 3 registration for Gonacon™. Gonacon™ is an injectable immunocontraceptive vaccine containing the active ingredient gonadotropin releasing hormone (GnRH). The application is for use of Gonacon™ by USDA APHIS Wildlife Services or state wildlife agency personnel or persons working under their authority to control the populations of white-tailed deer. Gonacon™ was formerly being developed as an investigational new animal drug under authority of the Food and Drug Administration, however, regulatory authority for contraceptives used in wild and feral animals has since been transferred to the EPA.

III. DISCUSSION

Ingredients: Gonacon™ contains GnRH as the active ingredient. GnRH is a 10 amino acid peptide hormone with the same amino acid sequence in most mammals. Because injection of GnRH alone would not stimulate an immune response, it is conjugated with a large carrier protein which is recognized by the body as "foreign" and will cause an immune response. Gonacon™ also contains an adjuvant. Adjuvants are used in vaccines to provide a local inflammatory response and enhance the immune response to a vaccine. The carrier protein and adjuvant are listed in the confidential statement of formula.

Mode of Action: Gonacon™ contains gonadotropin-releasing hormone (GnRH) to be hand injected intramuscularly by syringe. The injection stimulates an antibody response against GnRH. GnRH normally stimulates the production of the sex hormones, estrogen, progesterone, and testosterone. By blocking GnRH, the deer's body produces less of these sex hormones and becomes infertile for one or more years. Gonacon™ thus functions by stimulating an immune response and not by hormonal action.

Dietary Exposure: There is little likelihood of exposure to hormonally active compound from deer meat because GnRH is a protein which is digested and not absorbed intact. Like other proteins, GnRH is too large and polar to pass through the membranes of the gastrointestinal tract. Proteins are digested into their component amino acids in the stomach and small intestines. For these reasons, GnRH when used therapeutically in people and animals is always injected and not administered by the oral route.

Occupational Exposure: Applicators could be exposed to Gonacon™ by accidental self-injection which could result in the same effects as occur in deer, *i.e.* infertility. Granulomas, a type of tissue reaction, due to the adjuvant may also occur. The likelihood of accidental self-injection will be minimized because applicators trained in wildlife management and injecting of wild animals will be hand injecting Gonacon™.

Hazard: Toxicology data requirements for Gonacon™ were waived because of the very limited possibility of human exposure. No endpoints were selected and there are no concerns for sensitivity of infants and children because exposure to children is not expected. No public health

or epidemiology data or reports in the public literature relevant to this assessment were found in a PubMed® literature search.

Other products containing GnRH: GnRH injections are used in humans to induce ovulation and to test hypothalamic-pituitary function. GnRH injections have also been used to treat prostate cancer in humans and benign prostatic hyperplasia in dogs. GnRH injections have been injected into boars in Australia to reduce odor in meat.

GnRH is approved by the FDA/Center for Veterinary Medicine to treat ovarian cysts in dairy cattle. There is no tolerance in tissues, withdrawal time is zero, and an official analytic method was not required because there is no withdrawal period.

Data needs: There are no data gaps for Gonacon™. Toxicology and exposure data are waived.

Regulatory recommendations: HED has no objections to the Section 3 registration of Gonacon™. There are no risk concerns because of the very limited potential worker and dietary exposure.

6.2. GonaCon Label (white-tailed deer)

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

Keep away from humans, domestic animals and pets. Wear protective gloves when handling. If pregnant, do not handle or administer product. Accidental injection may cause infertility in women. Wash all implements used for handling or applying product with detergent and water. Do not use these implements for mixing, holding, or transferring food or feed.

ENVIRONMENTAL HAZARDS

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark.

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Applicators and other handlers must wear:

-long sleeved shirt and long pants
-gloves
-shoes plus socks

USE RESTRICTIONS

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. A copy of this label must be in the possession of the user at the time that the product is applied.

READ THIS LABEL: Read this entire label and follow all use directions and precautions.

IMPORTANT: Do not expose children, pets, or other non-target animals to this product. To help prevent accidents:

1) Keep children out of areas where this product is used.

2) Store product not in use in a location out of reach of children and pets.

3) Apply product only according to the directions authorized.

4) Dispose of product container and spoiled or unused product as specified in the "STORAGE AND DISPOSAL" section on this label.

GonaCon™ Immunocontraceptive Vaccine is for use in female white-tailed deer 1 year of age or older.

Caution is required to prevent accidental self-injection when administering GonaCon™ immunocontraceptive vaccine to white-tailed deer.

Pregnant women should not be involved in the handling or injection of GonaCon™. Do not ingest. Avoid contact with eyes.

Do not apply this product to food or feed.

Applicators should be aware that additional State regulations (including wildlife laws) and permitting may apply to the use of this product. All applicable State authorities must be contacted prior to use.

(See right panel for DIRECTIONS FOR USE)

RESTRICTED USE PESTICIDE

DUE TO NON-TARGET INJECTION HAZARD

For use by USDA APHIS Wildlife Services or state wildlife management agency personnel or persons working under their authority

GONACON™
IMMUNOCONTRACEPTIVE VACCINE

Immunocontraceptive vaccine for use in white-tailed deer (Odocoileus virginianus)

ACTIVE INGREDIENT

Mammalian Gonadotropin Releasing Hormone	0.03%
OTHER INGREDIENTS	99.97%
TOTAL	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

Have the product container or label with you when calling a poison control center or doctor, or when going for treatment

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
Riverdale, MD 20737-1237
EPA Est. No. 56228-CO-1
EPA Reg. No. 56228-40
Net Contents: 1 milliliter (0.033 fl. ounce)
Batch Code No.: _____

DIRECTIONS FOR USE

GonaCon™ is intended to be used in combination with other population management techniques.

GonaCon™ renders a vaccinated female white-tailed deer infertile for a minimum of one year following vaccination.

GonaCon™ should not affect existing pregnancy, but should cause infertility of the vaccinated animal in the subsequent year and possibly longer.

Administer a single vaccination (1 ml) of GonaCon™ at least two to three months prior to the onset of rut for full contraceptive effect.

If longer contraceptive effect is desired, a second vaccination may be given 30 to 60 days after the first injection or during the following year with no known adverse health effects to the vaccinated animal. Mark vaccinated animals to ensure that they are not unintentionally reinjected.

The effects of the vaccine may wear off the second year or sometimes longer, and vaccinated females may once again become fertile.

However, re-immunization with GonaCon™ can extend infertility.

There is a chance some vaccinated females will become permanently sterile.

Accidental injection of males will result in antler deformities and infertility.

One-mililiter (1 ml) doses of GonaCon™ are packaged in pre-loaded, 3-ml plastic syringes.

GonaCon™ must be administered by hand injection. Inject each female with 1.0 ml of GonaCon™, using an 18- or 19-gauge stainless steel hypodermic needle, by intramuscular injection into a large muscle mass.

Syringes must be individually labeled with the following language:

Restricted Use: Injection Hazards
CAUTION
GonaCon Immunocontraceptive Vaccine
Active Ingredient: Gonadotropin Releasing Hormone (0.03%)
KEEP OUT OF REACH OF CHILDREN
EPA Reg. No. 56228-40, EPA Est. No. 26228-ID-1
See Full Product Label for Application Instructions.
Vaccine expires 6 months from: _____

STORAGE AND DISPOSAL

PESTICIDE STORAGE: Keep preloaded GonaCon™ Immunocontraceptive Vaccine in a refrigerator (36 °F to 45 °F) until ready for use. In the field, keep preloaded GonaCon™ Immunocontraceptive Vaccine in a cooler on ice as long as possible prior to use.

PESTICIDE DISPOSAL: If not used within 6 months of manufacture when held under refrigeration (36°F to 45°F), or if not maintained on ice in the field, disable and dispose of unused GonaCon™ Immunocontraceptive Vaccine material and preloaded syringes as medical waste according to applicable Federal, State, and/or Local regulations.

CONTAINER DISPOSAL: Nonrefillable container. Do not reuse or refill container. Disable and dispose of expired material, preloaded syringes, used syringes and needles as medical waste according to applicable Federal, State, and/or Local regulations.

Revised 11-09

6.3. pZP Label (horses)

86833-1 1/30/2012 1/10

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Registration Division (7505P)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

EPA Reg. Number:	Date of Issuance:
86833-1	JAN 30 2012

NOTICE OF PESTICIDE:
_X_ Registration
____ Reregistration
(under FIFRA, as amended)

Terms of Issuance:
Unconditional

ZonaStat-H

Name and Address of Registrant (include ZIP Code):

Humane Society of the United States
c/o Morgan, Lewis & Bockius LLP
1111 Pennsylvania Ave., NW
Washington, DC 20004

Attention: Kathleen M. Sanzo

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is unconditionally registered in accordance with FIFRA section 3(c)(5) provided that you:

Signature of Approving Official:

John Hebert
Product Manager (07)
Insecticide-Rodenticide Branch
Registration Division (7505P)

Date:
JAN 30 2012

EPA Form 8570-6

Notice of Registration (continued)
EPA Reg. No. 86833-1

A. Submit and/or cite all data required for registration/reregistration of your product when the Agency requires all registrants of similar products to submit such data.

B. Make the following label changes before you release the product for shipment:

1. Revise your registration number to "EPA Reg. No. 86833-1",
2. Add "Department of Interior, and all its designated agents" before "National Park Service…" located in the first bullet of the certified applicators section,
3. Add a bullet in the certified applicators section that reads "USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service),
4. Delete "Federal Land Management Agency" as there is no such entity,
5. Remove "Draft" from "Draft Package Insert for Zonastat-H", "DRAFT LABEL FOR ZONASTAT-H BAG", and "DRAFT LABEL FOR ZONASTAT-H VIAL".
6. Place a box around the restricted use section.
7. Revise "SEE OTHER PANEL FOR…" to read "SEE BACK PANEL FOR PRECAUTIONARY STATEMENTS".
8. Add an "S" to ACTIVE INGREDIENT.
9. Under "Other ingredients" add "Total" and then add "100%" under "99.9%".
10. On page 4, change "Avoid contact with eyes" to read "Do not contact with eyes."
11. Revise the second sentence under the section title Application Rate to read "Efficacy is maintained by annual booster doses."
12. Revise "SEE PACKAGE INSERT FOR PRECAUTIONARY STATEMENTS" found on the label for the bag and vial to read "SEE PACKAGE INSERT FOR PRECAUTIONARY STATEMENTS AND DIRECTIONS FOR USE".
13. Remove "Store loaded darts in a cool dry area. In humid areas of the country, store in plastic sealable bags with a desiccant." from the Pesticide Storage paragraph of the Storage and Disposal section,
14. Add a reference to dart in the Pesticide Disposal section,
15. Create a second paragraph in the Pesticide Storage section that reads:

"Storage: The vials containing PZP solution are stored frozen. The frozen PZP solution expires two years after freezing. After defrosting, the PZP solution expires after 24 hours. When transporting for use in the field, store the PZP solution in a cooler with ice packs. If transportation of the PZP solution takes longer than 8 hours, store the PZP solution on dry ice in the cooler. Store loaded darts in a cool dry place. In humid areas of the country, store in plastic sealable bags with a desiccant."

C. Submit one (1) copy of final printed labeling for the record before you release the product for shipment.

A copy of your label stamped "Accepted with Comments in EPA Letter Dated January 30, 2012" is enclosed for your records.

Reference to Website on Label

Should you wish to add a reference to the company's website on your label, please be aware that the website becomes labeling under the Federal Insecticide Fungicide and Rodenticide Act and is subject to review by the Agency. If the website is false or misleading, the product would be misbranded and unlawful to sell or distribute under FIFRA section 12(a)(1)(E). 40 CFR 156.10(a)(5) list examples of statements EPA may consider false or misleading. In addition, **regardless of whether a website is referenced on your product's label**, claims made on the website may not substantially differ from those claims approved through the registration process. Therefore should the Agency find or if it is brought to our attention that a website contains false or misleading statements or claims substantially differing from the EPA approved registration, the website will be referred to the EPA's Office of Enforcement and Compliance Assurance.

Confidential Statement of Formula

The acceptable Confidential Statement of Formula (CSF) for this product is dated September 12, 2011 (Basic Formulation). All other versions are obsolete.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

If you have any questions or comments regarding this letter, please contact Jennifer Gaines by phone (703-305-5967) or e-mail (gaines.jennifer@epa.gov).

Enclosures: 1. Stamped Label

4/10

DRAFT PACKAGE INSERT FOR ZONASTAT-H

ACCEPTED
with COMMENTS
In EPA Letter Dated
JAN 30 2012
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 86933-1

FRONT PANEL

RESTRICTED USE PESTICIDE

For retail sale to and use by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicators certification:

- **National Park Service, Bureau of Land Management, U.S. Fish & Wildlife Service, and Federal Land Management Agency**
- **State departments of agriculture/livestock and wildlife, and their designated agents**
- **Federally recognized Indian tribes, and their designated agents**
- **Department of Defense and its designated agents**
- **Public and private wild horse sanctuaries and reserves**
- **Humane Society of the United States and designated agents.**

Each Responsible Authority for wild horses and/or burros intended to be treated with ZONASTAT-H must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this Package Insert.

ZONASTAT-H

Product information: ZonaStat-H is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of wild and feral horses (*Equus caballus*) and burros (*Equus asinus*).

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID
HAVE LABEL WITH YOU WHEN OBTAINING TREATMENT ADVICE

If on skin: Take off contaminated clothing.
Rinse skin immediately with plenty of water for 15-20 minutes.
Call a poison control center or doctor for treatment advice.

If inhaled: Move the person to fresh air.
If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
Call a poison control center or doctor for treatment advice.

DBI/ 67193892.2

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes.
Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

SEE OTHER PANEL FOR PRECAUTIONARY STATEMENTS

RESTRICTED USE PESTICIDE

ZONASTAT-H

ACTIVE INGREDIENT:
Porcine zona pellucida (ZP3)(0.1%)..... 0.071%
Porcine zona pellucida (ZP1, ZP2, ZP4)(0.1%).....0.029%

Other ingredients..... 99.9%

Batch Code:

EPA Registration No. TBD

If pregnant, take precaution when preparing, loading, and recovering darts to not self-inject.

Humane Society of the United States
2100 L Street NW
Washington, DC 20037
202-452-1100

Net Contents 0.5 mL
Single dose

BACK PANEL

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

Keep away from humans, domestic animals, and pets. Wear protective gloves when handling. If pregnant, take necessary precautions when preparing, loading, and recovering darts to not self-inject. Accidental injection may cause infertility in women. Wash all implements used for handling or applying product with detergent and water. Do not use these implements for mixing, holding, or transferring food or feed.

In the event of an accidental needle stick or cut, clean wound immediately with soapy water and disinfect wound with alcohol or other bactericidal solution. In the event of accidental contact with Modified Freund's Complete Adjuvant, wipe skin clean with an ethanol soaked towelette and wash with soapy water.

ENVIRONMENTAL HAZARDS

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water by cleaning of equipment or disposal of wastes.

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Applicators and other handlers must wear:

- long sleeved shirt and long pants
- gloves
- shoes plus socks

USE INFORMATION

When injected into a female horse or burro, ZonaStat-H stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment, thereby preventing conception.

USE RESTRICTIONS

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. A copy of this label must be in the possession of the user at the time that the product is applied.

READ THIS LABEL: Read this entire label and follow all use directions and precautions.

IMPORTANT: Do not expose children, pets, or other non-target animals to this product. To help prevent accidents:

1) Keep children out of areas where this product is used.
2) Store product in use in a location out of reach of children and pets.
3) Apply product only according to the directions authorized.
4) Dispose of product container and spoiled or unused product as specified in the "STORAGE AND DISPOSAL" section on this label.

ZonaStat-H is for use only in female wild and feral horses and burros, which are defined as free-roaming horses or burros, privately or publicly owned, that are capable of doing environmental damage.

Caution is required to prevent accidental self-injection when administering ZonaStat-H.

Pregnant women should take necessary precautions when preparing , loading , and recovering darts to not self-inject. Do not ingest. Avoid contact with eyes.

Do not apply this product to food or feed. Do not apply ZonaStat-H to horses or burros being used as food.

DIRECTIONS FOR USE

Mixing PZP Solution and Adjuvant:
This activity takes place in the field.

Equipment Needed:
2 BD #2311 glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
BD 1.5-inch 18 g disposable sterile needle
Vial of Adjuvant (supplied separately)
Vial of PZP Solution
Luer-Loc connector

FOR HAND DELIVERY
BD 3cc disposable plastic syringe with Luer-Lok
BD 1.5-inch 18 g disposable sterile needle
BACK PANEL (Continued)

FOR JAB-STICK DELIVERY
Dan-Inject® Fiskars Combi-Click Jab Stick
BD 3cc disposable plastic syringe with Luer-Lok
Monoject 1.5-inch 14 g disposable sterile needle

FOR REMOTE (DART) DELIVERY
BD 2.0 inch 18 g disposable sterile needle

1.0-cc C-type or P-type Pneu-Dart dart with 1.25-inch or 1.5-inch barbless needle

Procedures:

1. Examination gloves must be worn during mixing and loading of PZP solution.
2. Attach the Luer-Lok connector to one of the glass syringes.
3. Place the 1.5-inch needle on the second glass syringe.
4. Draw out 0.5 cc of adjuvant (supplied separately).
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution.
6. Holding the syringe containing the vaccine very carefully (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.
8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

FOR HAND DELIVERY (INJECTION), attach a 2.0 or 3.0cc plastic syringe to the glass syringe via the Luer-Lok, and inject the emulsion into the plastic syringe. After loading the plastic syringe, disconnect the glass syringe and connect an 18 g 1.5-inch needle to the plastic syringe containing the emulsion.

FOR JAB-STICK DELIVERY, place the nose of the plastic syringe tightly into the Luer-Lok and inject the emulsion from the glass syringe into the plastic syringe. After filling the plastic syringe, remove the glass syringe and attach the Monoject 14g 1.5-inch needle to the plastic syringe containing the emulsion. Place the plastic syringe into the jab-stick.

FOR REMOTE (DART) DELIVERY

- Attach the 18 g 2-inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

- After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-H intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

- Use the Pneu-Dart 1.0-cc dart with a 1.25-inch or 1.5-inch barbless needle for delivery.

- The darts can be delivered using any of the following rifles, depending on the logistical requirements of the particular targeted population:

  - Dan-Inject® CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
  - Dan-Inject® Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5-20 meters)
  - Pneu-Dart® model 193 rifle (for use at ranges of up to 50 meters)
  - Pneu-Dart® model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)

- The applicator must make every attempt to recover all darts. If possible, all darts that are discharged and drop from the horse at the shooting site must be recovered before another darting occurs. In exceptional situations, such as an onset of inclement weather, loss of daylight, applicator safety concerns, or other urgent circumstances, the site of a lost dart may be noted and marked, and recovery efforts made at a later time. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its vaccine contents.

Application Rate:

For maximum efficacy, ZonaStat-H is administered as an initial priming dose followed by a booster dose at least two weeks later. Full efficacy is maintained by annual booster doses.

Initial Priming Dose

The initial treatment (priming dose) of ZonaStat-H consists of 0.5 cc of the PZP solution emulsified with 0.5 cc modified Freund's Complete Adjuvant If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of the mating season.

Booster Dose

A booster dose of ZonaStat-H consists of 0.5 cc of the PZP solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant. Administration of a single booster treatment at least two weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose.

PACKAGING

Packaging:
PZP antigen dissolved in phosphate buffered saline solution is packaged in screw-top, non-refillable plastic vials containing single 0.5 mL doses.

Adjuvant is provided separately for the initial priming dose and the booster dose. The adjuvant is provided in multidose bottles.

STORAGE AND DISPOSAL

Pesticide Storage:
Keep vials of PZP antigen (i.e., PZP + phosphate buffer solution) frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2°C to +8°C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area. In humid areas of the country, store in plastic sealable bags with a desiccant.

Pesticide Disposal:
If the PZP solution is not used within 24 hours of defrosting, or if not properly stored while in the field, dispose of unused ZonaStat-H material and loaded syringes as medical waste according to applicable Federal, State, and/or Local regulations.

Container Disposal:
Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes, darts, and needles as medical waste according to applicable Federal, State, and/or Local regulations.

Storage:
The vials containing PZP solution are stored frozen. The frozen PZP solution expires two years after freezing. After defrosting, the PZP solution expires after 24 hours. When transporting for use in the field, the PZP should be stored in a cooler with ice packs. The cooler should contain dry ice if transportation of the PZP takes longer than 8 hours.

The adjuvant should be refrigerated +2°C to +8°C, but not frozen.

Store loaded darts in a cool dry area. In humid areas of the country, it is recommended that they be stored in plastic sealable bags with a desiccant.

Disposal:
Used darts: Used darts should be disposed of in a sharps container, and further disposed of in accordance with state laws regarding disposal of medical waste.

6.4. GonaCon Label (horses)

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Chemical Safety and Pollution Prevention
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

NOTICE OF PESTICIDE:
_X_ Registration
___ Reregistration
(under FIFRA, as amended)

EPA Reg. Number:	Date of Issuance:
56228-41	JAN 10 2013

Term of Issuance: Unconditional

Name of Pesticide Product: Gonacon - Equine

Name and Address of Registrant (include ZIP Code):

U.S. Department of Agriculture, Animal and Plant Health Inspection Service
Environmental Services, Unit 149
4700 River Road
Riverdale, MD 20737

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is unconditionally registered in accordance with FIFRA section 3(c)(5) provided that you:

1. Submit and/or cite all data required for registration/reregistration of your product when the Agency requires all registrants of similar products to submit such data.

2. Make the following label change before you release the product for shipment:
   - Revise the EPA Registration Number to read, "EPA Reg. No 56228-41."

Signature of Approving Official:

for Meredith Laws, Chief
Insecticide-Rodenticide Branch, Registration Division (7505P)

Date: JAN 10 2013

EPA Form 8570-6

3. Submit one copy of your final printed labeling before you release the product for shipment.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. If you have any questions, please contact Autumn Metzger at 703-305-5314 or metzger.autumn@epa.gov.

A stamped copy of the label is enclosed for your records.

Meredith Laws, Chief
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

Keep away from humans, domestic animals and pets. Wear protective gloves when handling. If pregnant, do not handle or administer product. Accidental injection may cause infertility in women. Wash all implements used for handling or applying product with detergent and water. Do not use these implements for mixing, holding, or transferring food or feed.

ENVIRONMENTAL HAZARDS

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Applicators and other handlers must wear:
-long sleeved shirt and long pants
-gloves
-shoes plus socks

DIRECTIONS FOR USE

Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. A copy of this label must be in the possession of the user at the time that the product is applied.

READ THIS LABEL: Read this entire label and follow all use directions and precautions.

IMPORTANT: Do not expose children, pets, or other non-target animals to this product. To help prevent accidents:

1) Keep children out of areas where this product is used.
2) Store product not in use in a location out of reach of children and pets.
3) Apply product only according to the directions authorized.
4) Dispose of product container and spoiled or unused product as specified in the "STORAGE AND DISPOSAL" section on this label.

GonaCon™ - Equine is used to manage fertility in reproductively mature female wild or feral horses *(Equus caballus)* and burros *(Equus asinus)*.

Use caution to prevent accidental self-injection when administering GonaCon™ - Equine to wild or feral horses and burros.

Pregnant women should not be involved in the handling or injection of GonaCon™. Do not ingest. Avoid contact with eyes.

Do not apply this product to food or feed.

Applicators: Additional State regulations and/or permitting may apply to the use of this product in wild or feral horses and burros. All applicable State authorities must be contacted prior to use. GonaCon™ renders vaccinated reproductively mature female wild or feral horses and burros infertile for a minimum of one year following vaccination.

(See right panel for application instructions)

RESTRICTED USE PESTICIDE

DUE TO NON-TARGET INJECTION HAZARD

For use by employees of USDA APHIS Wildlife Services and Veterinary Services, U.S. Bureau of Land Management, U.S. Fish and Wildlife Service, U.S. National Park Service, U.S. Department of Defense, Federally recognized Indian Tribes, State agencies responsible for wild or feral horse and burro management, public and private wild horse sanctuaries, or persons working under their authority.

GONACON™ - EQUINE

For managing fertility in female wild or feral horses (Equus caballus) and burros (Equus asinus)

ACTIVE INGREDIENT

Mammalian Gonadotropin Releasing Hormone	0.03%
OTHER INGREDIENTS	99.97%
TOTAL	100%

ACCEPTED
JAN 10 2013
Under the Federal Insecticide, Fungicide and Rodenticide Act, as amended, for the pesticide registered under:
EPA Reg. No: 56228-41

KEEP OUT OF REACH OF CHILDREN

CAUTION

Have the product container or label with you when calling a poison control center or doctor, or when going for treatment

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

PESTICIDE STORAGE: Keep preloaded GonaCon™ - Equine in a refrigerator (36 °F to 45 °F) until ready for use. In the field, keep preloaded GonaCon™ - Equine in a cooler on ice as long as possible prior to use.

PESTICIDE DISPOSAL: If not used within 6 months of manufacture when held under refrigeration (36°F to 45°F), or if not maintained on ice in the field, disable and dispose of unused GonaCon™ - Equine material and preloaded syringes as medical waste according to applicable Federal, State, and/or Local regulations.

CONTAINER DISPOSAL: Nonrefillable container. Do not reuse or refill container. Disable and dispose of expired material, preloaded syringes or darts, used syringes, darts and needles as medical waste according to applicable Federal, State, and/or Local regulations.

APPLICATION INSTRUCTIONS

GonaCon™ can be administered at any time throughout the year and should not adversely affect an existing pregnancy, but should cause infertility of the vaccinated animal in the subsequent year and possibly longer.

Administer a single vaccination (2 ml) of GonaCon™ at least two to three months prior to the onset of breeding for full contraceptive effect. If longer contraceptive effect is desired, a second vaccination may be given 30 or more days after the first injection or during the following year with no known adverse health effects to the vaccinated animal. The effects of the vaccine may wear off during the second year or sometimes later and vaccinated females may once again become fertile. However, re-immunization with GonaCon™ can extend infertility.

There is a chance some vaccinated females will become permanently sterile. Accidental injection of males will result in infertility.

Two-milliliter (2 ml) doses of GonaCon™ are packaged in pre-loaded, 3-ml plastic syringes.

GonaCon™ can be administered by hand injection, jab stick or remote delivery (darting). Inject 2.0 ml of GonaCon™ by intramuscular injection (IM) into a large muscle mass (e.g., rump, neck).

Hand Injection: Inject IM 2 ml GonaCon™ using the packaged preloaded syringe and a 1.5-inch 18G or 19G stainless steel hypodermic needle.

Jab Stick Delivery: Transfer 2 ml GonaCon™ from the preloaded syringe into the jab stick syringe. Inject IM using a 1.5-inch 14G stainless steel hypodermic needle.

Remote Darting: Recommended dart specifications for this use are a 2 cc dart with a 1.25- or 1.5-inch 14G gelatin barb needle. Transfer 2 ml GonaCon™ from the preloaded syringe into the dart. Deliver IM using an appropriate projection device.

If remote delivery is used, the applicator must make every attempt to recover all darts. If possible, all darts that are discharged and drop from the horses at the shooting site must be recovered before another darting occurs. In exceptional situations, such as an onset of inclement weather, loss of daylight, applicator safety concerns, or other urgent circumstances, the site of a lost dart may be noted and marked, and recovery efforts made at a later time. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its vaccine content.

Syringes must be individually labeled with the following language:

Restricted Use: Injection Hazards
CAUTION
GonaCon™ - Equine
Active Ingredient: Gonadotropin Releasing Hormone (0.03%)
KEEP OUT OF REACH OF CHILDREN
EPA Reg. No. 56228-XX, EPA Est. No. 26228-CO-1
See Full Product Label for Application Instructions.
Vaccine expires 6 months from: _____

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
Riverdale, MD 20737-1237
EPA Est. No. 56228-CO-1
EPA Reg. No. 56228 XX
Net Contents: 2 milliliter (0.066 fl. ounce)
Batch Code No.:

Draft 12-12-2012

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