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REVIEW

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The status of fertility control for rodents—recent achievements and future directions

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Abstract

Management of overabundant rodents at a landscape scale is complex but often required to sustainably reduce rodent abundance below damage thresholds. Current conventional techniques such as poisoning are not species specific, with some approaches becoming increasingly unacceptable to the general public. Fertility control, first proposed for vertebrate pest management over 5 decades ago, has gained public acceptance because it is perceived as a potentially more species-specific and humane approach compared with many lethal methods. An ideal fertility control agent needs to induce infertility across one or more breeding seasons, be easily delivered to an appropriate proportion of the population, be species specific with minimal side-effects (behavioral or social structure changes), and be environmentally benign and cost effective. To date, effective fertility control of rodents has not been demonstrated at landscape scales and very few products have achieved registration. Reproductive targets for fertility control include disrupting the hormonal feedback associated with the hypothalamic-pituitary-gonadal axis, gonad function, fertilization, and/or early implantation. We review progress on the oral delivery of various agents for which laboratory studies have demonstrated efficacy in females and/or males and synthesize progress with the development and/or use of synthetic steroids, plant extracts, ovarian specific peptides, and immunocontraceptive vaccines. There are promising results for field application of synthetic steroids (levonorgestrel, quinestrol), chemosterilants (4-vinylcyclohexene diepoxide), and some plant extracts (triptolide). For most fertility control agents, more research is essential to enable their efficient and cost-effective delivery such that rodent impacts at a population level are mitigated and food security is improved.

Key words: ecologically based rodent management, levonorgestrel, quinestrol, triptolide, 4-vinylcyclohexene diepoxide

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INTRODUCTION

Invasive weeds, insects, and vertebrate pests constrain pastoral and agricultural production worldwide through economic and environmental impacts (Ngiem *et al*. 2013) affecting food security, human health, and biodiversity

(Jacob *et al*. 2008; Swanepoel *et al*. 2017). Rodents in both developed and developing countries are common and engender major impacts at the economic and socio-political level in urban and rural habitats, the latter especially during population outbreaks (Singleton *et al*. 2005, 2010a,b; Jacob & Tkadlec 2010; Sudarmaji *et al*. 2010; Ngiem *et al*. 2013). Furthermore, in tropical climates, increased intensity of agricultural production will be necessary to meet the increased food requirements of increasing human populations. This could require planting more crops per year and will lead to an increase in the duration of breeding of pest rodent species (see review, Singleton *et al*. 2021). The basis for the occurrence of such outbreaks is the high reproductive potential of small rodents that allows them to produce many large litters in a short time (Andreassen *et al*. 2020). In the future, other factors such as increasing frequency of extreme weather events and projected climate change worldwide will likely increase the frequency of pest rodent outbreaks (Singleton *et al*. 2010a; Imholt *et al*. 2015) as well as the impacts of invasive weeds, insects, and animals in general (Zhang 2001; Singleton *et al*. 2007, 2010a) and challenge our ability to effectively manage them.

Management of exotic or native invasive mammals at a landscape scale is complex and requires a good understanding of the biology and ecology of the pest species (Singleton *et al*. 2007, 2010a). Large-scale management of outbreaks of rodents can result in environmental problems and non-target risk due to the usually non-specific lethal methods used for control. Current conventional techniques involving lethal control often require repeated effort and application. Most of these methods (trapping, poisoning) are becoming increasingly unacceptable to the general public, particularly in urban and peri-urban environments, and their use may also be questionable with respect to "clean and green" food production, food contamination, and potential effects on human health. This is not suggesting that lethal control is ineffective nor that it should not be used as part of a pest management approach, just as not all non-lethal methods (e.g. translocation) are effective or more humane. Therefore, the major requirement for each pest species is to develop and adopt an efficient and practical management strategy—a combination of both lethal and non-lethal management techniques is likely to be the most cost effective (Pepin *et al*. 2017; Croft *et al*. 2020, 2021).

In this review, we focus on developments in fertility control approaches which could be used as non-lethal applications and included as part of an integrated management approach for rodent pest species. We provide a brief background on the rationale for the use of fertility control for vertebrate pest management and its relevance for highly fecund short-lived rodents. We also outline the approaches considered to date before focusing on recent progress in 2 areas: orally delivered anti-fertility agents and options for large scale bait delivery. We synthesize these aspects to define research gaps and work needed to suggest how fertility control of rodents could be utilized in the future.

WHY FERTILITY CONTROL FOR RODENT PEST MANAGEMENT?

Fertility control was proposed as another potential tool for pest management about 5 decades ago (Knipling 1959; Davis 1961), specifically the use of sterile males in insect control and chemosterilants. Indeed Knipling (1972), using computer modeling, compared the use of rodenticides and that of an irreversible chemosterilant deemed effective in male and female rats, and showed that a chemosterilant was theoretically at an advantage. Since then, a range of fertility control approaches have been under development and the overall concept has gained public acceptance because it has been perceived as a more species-specific and humane approach (Oogjes 1997). Fertility control has been considered as a potential management tool in species with high fecundity (Caughley *et al*. 1992; Shi *et al*. 2002), high natural adult mortality rates, and rapid turnover (Bomford 1990; Barlow *et al*. 1997).

Ideally, a fertility control agent should either induce permanent sterility or induce infertility at least for part of the breeding season(s) leading to reduced recruitment in the pest population. The timing of application, before or during a breeding season will depend on the means of delivery and the rapidity of effect of the agent used. It also must be easily delivered to reach an appropriate proportion of the target population, be species specific with minimal side-effects (behavioral or social structure changes), and be environmentally benign and cost effective (Chambers *et al*. 1997). Social structure, including the mating system (monogamy, polygamy) of a pest species, is predicted to also affect the efficacy of a fertility control agent (Zhang 2000).

Bomford (1990) in her review of the rationale for fertility control for wildlife management concluded that methods requiring individual capture (e.g. surgical sterilization, insertion of hormonal implants) would not be practical for the control of all overabundant species. Such methods could be practical for vertebrate pests of large body size but would be highly impractical for rodent pests

where animals are difficult to target individually. Thus, for rodents, which are short-lived and have a short, defined breeding season, oral delivery of permanent or semi-permanent fertility control agents is essential.

Increasing mortality in a population using lethal control has an immediate impact on population size and by inference on the damage caused (Shi *et al*. 2002). The same is true for human infection risk when correlated with rodent vector abundance, for example, the zoonotic *Puumala orthohantavirus* (Reil *et al*. 2017) which is transmitted by the bank vole [*Clethrionomys glareolus* (Schreber, 1780)]. If only fertility control is applied, there is a delay in response before natural mortality begins to reduce population size. This may not be optimal in a commensal rodent situation where swift eradication is the primary aim, particularly when human health is at risk. However, in agricultural or pastoral systems where pest rodent populations increase rapidly during a defined reproductive season, a delay in mortality of infertile animals may not be an issue: minimizing the proliferation of a small founder population could be sufficient to reduce crop damage during the crop cycle. Therefore, in species where population outbreaks are experienced, extreme population peaks and associated crop damage may be prevented, or at least dampened, if fertility control can be applied before the onset of the breeding season thereby reducing the number of litters produced (Shi *et al*. 2002; Davis *et al*. 2003).

Nevertheless, some intrinsic population processes can partially compensate the effects of fertility control. The survival of juveniles and infertile adults can be increased (Sinclair 1997; Chambers 1999; Williams *et al*. 2007), the survival of offspring improved (Jacob *et al*. 2008), and subordinates can be released from breeding suppression (Caughley *et al*. 1992). Conversely, when infertile individuals still compete for space, food, and social status, their presence can reduce the reproductive success of fertile individuals or other subordinates (Caughley *et al*. 1992; Zhang 2000). Therefore, it is important that infertile individuals remain in the population as shown for ricefield rats [*Rattus argentiventer* (Robinson & Kloss, 1916)] (Jacob *et al*. 2004a). Breeding activities (gestation and lactation) are also metabolically demanding—for example, pregnant and lactating ricefield rats feed more intensively on rice crops than non-reproducing individuals (Jacob *et al*. 2004b). Similarly, female bank vole (*Clethrionomys glareolus*) infected with cowpox virus do not reproduce and then show higher survival than uninfected (and reproducing) animals (Telfer *et al*. 2002). Thus, if infertile animals cause less damage than fertile animals, there would be a benefit in the short term in addition to the smaller increases in population size. The latter is a result of both the foregone reproduction of founders and their unborn offspring and the ultimate die-off of infertile animals. Given these combined effects of fertility control on rodent abundance, feeding activity, and damage, fertility control should be part of an integrated program and be used in conjunction with other control methods to achieve reductions in damage similar to that achieved by using lethal control alone.

WHICH TARGETS FOR REPRODUCTIVE CONTROL?

There are many key components within the reproductive system and the hormones of the hypothalamic-pituitary-gonadal (HPG) axis which regulate reproductive success in both males and females. Thus, fertility could be reduced by directly inhibiting the function of the gonads in terms of successful spermatogenesis and/or ovarian follicular or oocyte development. Targeting subsequent events such as fertilization, and/or early pregnancy and implantation in females, or affecting the hormonal feedback associated with the HPG axis could also indirectly impair the overall functioning of the reproductive system. A summary of the characteristics, effects, and oral delivery potential for promising fertility control agents for rodents is presented in Table 1. As mentioned above, for animals of small body size, the challenge is to find a delivery approach that is effective and economic for field application.

Hormone implants

The use of steroidal (e.g. synthetic progesterone) and non-steroidal hormone implants (e.g. agonists or antagonists against gonadotropin releasing hormone, GnRH) to disrupt hormonal regulatory feedback has been quite successful in larger wildlife species, including many zoo animals (Herbert & Trigg 2005). Such implants are effective for as long as the agent is being actively released. However, at a wildlife population level, efficient delivery is problematic and expensive because individuals must be captured for treatment. For numerous small, short-lived rodents, delivery of such implants would be impractical.

Immunocontraceptive vaccines

Another approach has been the development of immunocontraceptive vaccines in which the body's immune

Table 1 Summary of the characteristics, effects and potential of fertility control agents for rodents

Agent	Site of action and effects	Species-specific/ sex-specific?	Duration of effect	Potential for oral delivery for broadscale management of rodents
Immuno-contraceptive vaccines				
Gonadotrophin releasing hormone, GnRH	Down regulation of hormones of pituitary-gonadal axis	No/No	Unknown, but could last for breeding season?	Moderate: Promising results for oral delivery of GnRH constructs plus added adjuvants; still requires development
Female reproductive antigens such as zona pellucida proteins, (ZP), bone morphogenetic protein (BMP15), growth differentiation factor 9 (GDF9)	Ovary and oocytes, uterus; disrupts oocyte development, blocks fertilization	Yes, if species specific antigens used. No—females only	Permanent or semi-permanent	Moderate: Requires an efficient oral delivery system to be developed (e.g. bacterial ghosts, disseminating vector such as virus); protection of antigen in gastrointestinal tract; immune response generated may require boosting treatments
Male reproductive antigens	Testis, epididymis—inhibition of spermatogenesis and/or maturation of sperm in epididymis	Yes, if species specific antigens used. No—could be effective in females also	Semi-permanent	Low-moderate: Limitations as for female reproductive antigens (see above); would need to treat all males to achieve effect
Gene drives				
CRISPR-based systems	Gene drive system not fully defined yet though likely to select for male offspring	Yes/Yes	Likely permanent in individual	Low: Requires introduction of the rodents expressing the system and then its rapid inheritance throughout the population by sexual reproduction
Hormones				
Synthetic steroids: Levonorgestrel (P), Quinestrol (E) EP-1 combination Product registered	Uterus—edema of the uterus; reductions in conceptions and litter sizes Inhibits the function of the testis, epididymis, and seminal vesicles; effects on spermatogenesis	No/No	Variable; depends on dose and period of consumption—effects can carry over into next breeding season in males.	Moderate-high: Palatability may be limiting at concentrations required to achieve efficacy in some species EP-1 used in grasslands species of China. EP-1 product registered in Tanzania
Chemosterilants				
4-vinylcyclohexene diepoxide, VCD	Primordial follicles of the ovary Disrupts spermatogenesis and epididymal function in males	No/Yes Most effective in females	Permanent in females as primordial follicles are targeted and cannot be replenished. Reversible in males	Low to moderate: Dose-dependent effects in different rodent species. Further work on palatability needed as duration of delivery must be continuous and prolonged.

(*Continued*)

Table 1 (Continued)

Agent	Site of action and effects	Species-specific/ sex-specific?	Duration of effect	Potential for oral delivery for broadscale management of rodents
Plant extracts				
Extract from Paw-Paw Seeds	Disrupts ovulation and estrous cycle, causes primary and secondary follicle depletion. Reduces sperm count; increases sperm abnormalities	No/No	Reversible within 30 days after treatment	Low: Requires continuous treatment and has serious side effects
Extracts of Neem tree	Disrupts spermatogenesis. Disrupts estrous cycle; inhibits follicle development, implantation; induces abortion. Disrupts hypothalamic pituitary gonadal endocrine axis.	No/No	Reversible after treatment ceases	Low: Requires continuous treatment, palatability affected by high doses; has some side effects
Gossypol	Inhibits spermatogenesis, sperm concentration, and motility in several non-rodent species Disrupts pregnancy and implantation; induces abortions	No/No	Reversible after treatment ceases	Very low: Safety concerns due to toxicity. No effect on spermatogenesis in rats and mice
Triptolide	Disrupts spermatogenesis Disrupts primary and secondary follicle development and delays estrous; no effect on primordial follicle development	No/No	Longer duration of effects in males than females	Moderate to high Products have been registered in China for rodent control
Combination of VCD and Triptolide—ContraPest®—liquid formulation registered in USA	See specific effects for individual components above	No/No	Duration of effects extended due to combined effects of chemicals.	Moderate-high: Product is registered for specific uses in built environments in the United States. Not yet assessed for management of populations at landscape scale; unlikely to be possible as product uptake requirements are continuous
Viruses and bacteriophages				
Replication-incompetent recombinant adeno-associated viruses	Express high affinity antibodies targeting reproductive antigens such as GnRH	Yes/Yes	Unknown	Moderate: Trials of intramuscular treatment are positive but practical oral delivery remains problematic
Specific phage peptides	Bind to granulosa cells; inhibit adhesion of sperm to zona pellucida by binding and blocking key sperm proteins; increase apoptosis of target cells Use to enhance the low immunogenicity of GnRH	Yes/Yes	Unknown	Moderate: Oral delivery possible; under development

response targets a self-hormone (e.g. GnRH) or another reproductive antigen (such as follicle or egg coat proteins, sperm proteins, implantation, or other uterine or oviduct proteins) (Gupta *et al*. 2004; Hardy *et al*. 2006; Kirkpatrick *et al*. 2011; Sharma & Hinds 2012). While GnRH and porcine egg coat (zona pellucida) injectable immunocontraceptive vaccines have been shown to be very effective, their delivery requires individual capture and, in some cases, booster immunizations (Massei & Cowan 2014). Remote delivery using darts has been successful (Turner *et al*. 1992) for some vaccines, and research for these large species is ongoing (Rutberg *et al*. 2017; Wimpenny & Hinds 2018).

Approaches which require individual capture, treatment, and release and which may be feasible for some large, long living species are neither feasible nor practical for rodent pests. However, an approach using self-disseminating species-specific viruses expressing reproductive genes to deliver immunocontraceptive vaccines (Tyndale-Biscoe 1994) was extensively researched for European rabbits (*Oryctolagus cuniculus*), red foxes [*Vulpes vulpes* (Linneaeus, 1758)], and house mice (*Mus musculus domesticus* Schwarz and Schwarz, 1943) in Australia. Similarly, in New Zealand, a recombinant vaccinia virus has been assessed for delivery of disease vaccines and immunocontraceptive vaccines to possums, *Trichosurus vulpecula* (Duckworth *et al*. 2007; Cross *et al*. 2011). Although both areas of research have ceased for a range of technical reasons such as attenuation and reduced transmission of engineered vectors (Tyndale-Biscoe & Hinds 2007; Redwood *et al*. 2007), a naturally disseminating or non-disseminating species-specific recombinant virus still has appeal as an approach for delivering fertility control. Achieving regulatory approval and public acceptance for such genetically modified agents remains a difficult challenge.

An alternative virus-vectored approach under development involves the use of replication-incompetent recombinant adeno-associated viruses. These vectors are designed to directly express high affinity antibodies targeting reproductive antigens such as GnRH (see review—Hay *et al*. 2018). Trials of intramuscular treatment in laboratory mice are positive but practical oral delivery remains problematic.

Orally delivered fertility control agents

Effective delivery of fertility control agents is extremely important to achieve effects at the population level. For rodents, agents which can be delivered via baits that are highly palatable and environmentally stable are essential, as oral delivery generally requires continuous or repeated administration to induce and maintain sufficient inhibition of the reproductive system. Reproductive targets that inhibit the fertility of females are considered more efficient for population management than those affecting only males because a high proportion of infertile females will result in greater declines in population growth than if there was a similar proportion of infertile males (Bomford 1990). However, if an agent affects both females and males, that could be of considerable added benefit.

Potential candidates for oral delivery include synthetic hormones, plant compounds, chemicals, and potentially, immunocontraceptive vaccines. In addition, bacteriophages expressing reproductive antigens could be used in bait (see section below) (Hall *et al*. 2017; Samoylova *et al*. 2017).

Other newly emerging technologies include gene drives such as CRISPR-based systems (Prowse *et al*. 2017). These are being explored for use in eradicating invasive rodents on islands. However, no functional gene drive system is yet available for mammals and the technology would require introduction of the genetically modified rodents expressing the system and for subsequent rapid inheritance throughout the population (Campbell *et al*. 2019; Godwin *et al*. 2019). The use of gene drives may also raise conservation concerns if there was unintended movement or dispersal of modified individuals released for pest control in one country back to the country of origin of a desired native species (Webber *et al*. 2015). Similar concerns were raised regarding the proposal to use disseminating viral vectored immunocontraception for introduced vertebrate pests in Australia (Williams 1997).

Synthetic steroids: Levonorgestrel (P) and quinestrol (E)

Early studies using orally active estrogens, progestagens, and androgens demonstrated major disruptive effects on the uterus, ovulation, and implantation, and on spermatogenesis in rodents (Howard 1967; Marsh 1988). In laboratory studies, Gao and Short (1993) showed that continuous exposure to steroids was required to maintain the effects but this was difficult to achieve in bait delivered forms which were unpalatable at the concentrations required for efficacy. Furthermore, side-effects were also apparent in most individuals, the effects were not species specific, and some of the steroids at the concentrations used posed an environmental hazard.

The anti-fertility effects of a combination of synthetic estrogen (E) and synthetic progesterone (P) (EP-1) for a

range of doses (1–10 mg/kg, 10–50 ppm) delivered by oral gavage or baits have been reported for several rodent species (Zhang *et al*. 2004; Zhao *et al*. 2007; Wang *et al*. 2011; Liu *et al*. 2012a,b, 2013; Massawe *et al*. 2018; Selemani *et al*. 2021; Stuart *et al*. 2021; Chen *et al*. 2021). Generally, a treatment period of about 7 days in the laboratory is required to induce effects in the reproductive system, but a single baiting is adequate in field conditions (3 kg/ha, 0.005% EP-1; Liu *et al*. 2012a,b). In females, the most common response to E and EP-1 is enlargement (edema) of the uterus in a dose-dependent manner. This leads to reductions in conceptions and/or litter sizes, but the effects are temporary and fully reversible. In males, E and EP-1 inhibit the function of the testis, epididymis, and seminal vesicles for different periods of time depending on dose (Liu *et al*. 2012b,c). EP-1 on cereal baits is palatable to rodents in laboratory and field trials (Wang *et al*. 2011; Liu *et al*. 2012b; Massawe *et al*. 2018). In the field, a single baiting with EP-1 or E in spring significantly reduced reproduction in plateau pikas [*Ochotona curzoniae* (Hodgsen, 1858) (Liu *et al*. 2012a,b). In some species, cached bait may be present in burrow systems until the next breeding season (Liu *et al*. 2012a,b).

Estrogen is decomposed quickly by microbes in soil, by ultraviolet radiation, or visible light and acids in water (Zhang *et al*. 2014). The half-life of P and E in soil is 6–16 and 9–15 days, respectively (Tang *et al*. 2012a,b). EP-1 decomposes quickly under natural conditions, with a half-life of a few hours in water and 1–2 weeks in soil (Tang *et al*. 2012a,b). Few studies have examined impacts of EP-1 on non-target species. In a laboratory-based study, the production of eggs by domestic chickens was delayed in a dose-related manner after oral gavage with a range of concentrations of EP-1 (He *et al*. 2021). Baiting with products containing 0.005% E, 0.005% P, and 0.005% EP-1 showed little effect on bird abundance and diversity in the Qinghai–Tibet Plateau, with the exception that E reduced the abundance of white-rumped snowfinch (*Montofringilla taczanowskii*), likely in response to the reduced abundance of active plateau pika burrows which they co-habit (Qu *et al*. 2015). Further assessments of the impacts on non-target species of consumption of EP-1 in the field are still required. Recently, EP-1 was registered as a fertility control product for use in rodent control in Tanzania (Registration No. RO/012, Ministry of Agriculture, Tanzania).

Chemosterilants

Chemosterilants have always been of interest, with one industrial chemical, 4-vinylcyclohexene diepoxide (VCD), being assessed for its reproductive toxicity. VCD causes depletion of the finite pool of ovarian primordial follicles in female rodents (Mayer *et al*. 2002, 2004) and disrupts spermatogenesis and epididymal function in male rats (Adedara *et al*. 2017) through increased oxidative stress and apoptosis. It also induces short-term inflammation and cell death in other organs such as the liver and kidneys (Abolaji *et al*. 2016; Adedara *et al*. 2017). While VCD is not species specific, rodents are more sensitive to its effects compared to other species. However, to effectively impair reproduction, VCD must be delivered over a prolonged period (>10 days) and its effects are dose-dependent (Hinds *et al*. 2014). Mice seem more susceptible to its ovotoxic effects, as the degeneration of follicles is initiated earlier than in rats (Kao *et al*. 1999). Although formulation for oral delivery could be feasible, the challenge remains to specifically target the chosen pest species for a sufficient period of time to achieve permanent effects at a population level. The combination of a chemosterilant and a plant extract in a palatable bait could enhance the effects of both agents (see section below) and more rapidly lead to infertility.

Plant extracts

Many plant compounds are known for inducing various contraceptive effects in humans (Unny *et al*. 2003; Qureshi *et al*. 2006; Pradhan *et al*. 2013) whereby short-term disruption of uterine and/or ovarian function affects implantation, induces abortion, or suppresses lactation. Some effects (abortion, suppression of lactation) raise welfare concerns. However, the recurrent problem is the rapid reversibility of the effects of the plant extract after treatment ceases, and poor palatability at the required doses. Plant extracts are of interest for more permanent interference of male and female reproductive function, particularly for rodent pests (Tran & Hinds 2012). However, to achieve a relatively permanent effect, the selected compound(s) should induce primordial follicle degeneration and interfere with overall ovarian function (Tran & Hinds 2012). Extracts can induce negative side effects, and most require continuous consumption for long periods to induce and maintain infertility. Usually fertility is restored within days after withdrawal of treatment (Tran & Hinds 2012).

An extract obtained from the seeds of pawpaw (*Carica papaya* L.) induces infertility in both sexes. In laboratory studies of *R. norvegicus*, oral administration for 18 days disrupts ovulation and the estrous cycle, induces follicular atresia, reduces ovarian weights and litter size, and inhibits implantation. It reliably prevents pregnancies

within one breeding cycle, but the effects are reversible within 30 days after treatment (see review—Tran & Hinds 2012). In males, the extract reduces sperm count and increases sperm abnormalities. Although no mortalities in rats have been reported for pawpaw root extracts (up to 2000 mg/kg), serious side effects like lethargy, ataxia, and edema have been observed (Nwaehujor *et al*. 2014).

Extracts of the neem tree (*Azadirachta indica* A. Juss) also have various effects on the fertility of males and females. They disrupt spermatogenesis and the estrous cycle, inhibit follicle development and implantation, and induce abortion. However, ovaries are affected only indirectly as the neem tree extracts influence the synthesis and release of hormones that regulate ovarian follicle development. Furthermore, they have side effects at higher doses and reduce bait palatability (Tran & Hinds 2012).

Another plant extract is the racemic Gossypol, which occurs naturally in seeds and roots of cotton plants (Malvaciae) (Qian & Wang 1984). It irreversibly inhibits spermatogenesis in dogs (*Canis lupus familiaris* Linnaeus, 1758) and spermatogenesis, sperm concentration, and sperm motility in monkeys [*Macaca fascicularis* (Raffles, 1821); *Macaca mulatta* (Zimmermann, 1780)]. However, there are no such effects in European rabbits (*Oryctolagus cuniculus* Linnaeus, 1758), house mice, and Norway rats [*Rattus norvegicus* (Berkenhout, 1769)] but it prevents pregnancy in house mice and hamsters [*Mesocricetus auratus* (Waterhouse, 1839)] and implantation in rats (Qian & Wang 1984). There are safety concerns about Gossypol due to its high toxicity leading to damage to kidneys and associated hypokalemia (Waites *et al*. 1998).

Plant extracts that induce follicle depletion are of high interest for the reasons mentioned above. However, most of them induce atresia of growing follicles at a later stage and do not affect the primordial follicle population. Nevertheless, they might be useful in combination with other antifertility agents that deplete primordial follicles and they could help to find new approaches to inhibit ovarian function in a more rapid and permanent way (Tran & Hinds 2012).

Many plant extracts have been screened for their effects on gonadal function, implantation, and/or the subsequent progress of a pregnancy. Others such as triptolide (TP) have been shown to have medium-term effects in males, and shorter-term effects in females. It impairs spermatogenesis and reduces the diameter of seminiferous tubules as well as sperm motility and viability (Huynh *et al*. 2000; Li *et al*. 2009; Singla & Challana 2014; Dhar & Singla 2014a; Witmer *et al*. 2017). Singla and Challana (2014) found that TP causes severe structural and morphological changes in sperm, such as head–tail separation, a degenerated mitochondria sheath, absent plasma membrane, or the aggregation of sperm tails. Furthermore, a decrease in caudal epididymal sperm count (Singla & Challana 2014) was observed, but there is no evidence that TP affects the endocrine status of male rats (Huynh *et al*. 2000). Xu and Zhao (2010) focused on the effects of TP on ovarian follicles and observed an increased apoptosis in secondary follicles and a reduced number of developing follicles (Dhar & Singla 2014b) but no effect on primordial or antral follicles (Xu & Zhao 2010). TP prolongs the estrous cycle and affects the morphology of uterus and ovary in the lesser bandicoot rat [*Bandicota bengalensis* (Gray and Hardwicke, 1833)] (Dhar & Singla 2014b).

Effects of combinations of VCD and TP

Assessment of combinations of VCD (1%) and various doses of TP (25, 50, or 100 μg/kg body weight) resulted in reduced primordial follicle counts at lower TP doses and a more rapid effect when the combination was used compared to results with either of the 2 compounds alone (Dyer *et al*. 2013). This leads to the assumption that the effects of VCD and TP together are complementary and additive (Dyer *et al*. 2013). In males, the exposure to a combination bait leads to reduced sperm count and lower sperm viability (Witmer *et al*. 2017). In laboratory rats, bait containing VCD and TP is less palatable than control bait (Dyer *et al*. 2013). However, a 50-day voluntary uptake of a VCD-TP combination bait by male and female rats leads to infertility for up to 4 months (Witmer *et al*. 2017). No pups were born (Witmer *et al*. 2017), or the litter size was reduced (Dyer & Mayer 2014) if males and females were treated with a VCD-TP combination bait. There is no evidence for an irreversible sterilization after a 58-day exposure to bait containing VCD and TP (Siers *et al*. 2020).

This combination product, ContraPest®, is now registered for the management of Norway rats in the United States. The liquid bait is palatable to rats and renders males and females infertile (Pyzyna *et al*. 2018). In 2 pilot studies, where ContraPest® was used in combination with a rodenticide, consecutive baiting for 100 days was required to decrease rat populations by 46% and it required 133 days in an urban setting to reduce the rat population by 67% (Pyzyna *et al*. 2018). The relative contribution of ContraPest® and the rodenticide to the apparent decrease in population size is unknown. The long baiting period is not practical if swift eradication is the aim. The effectiveness of ContraPest® when applied at landscape scale has not been assessed.

Bacteriophages

Bacteriophages can be engineered to be used as an immunocontraceptive tool (Samoylova *et al*. 2017). Specific peptides are expressed and displayed on the outside of filamentous bacteriophages (Aitken 2006; Samoylova *et al*. 2017) that bind to murine granulosa cells and reduce fertility of mice. Oral delivery of these peptides might be also a possibility, as formulations are available that can stabilize the peptides in the gastrointestinal tract. Similar to this method, phage peptides can be used to inhibit the adhesion of sperm to the zona pellucida by binding and blocking key sperm proteins (Hall *et al*. 2017). This was initially studied as a contraceptive technique for humans (Eidne *et al*. 2000). Later, this approach was explored in dogs and pigs (*Sus scrofa domesticus* Erxleben, 1777) (Samoylova *et al*. 2012). Moreover, this method has been used to enhance the low immunogenicity of GnRH (Sabeur *et al*. 2003; Samoylova *et al*. 2012). However, in addition to disrupting sperm-oocyte fusion, peptide-displaying phages can also increase apoptosis of target cells by coupling them with redox cycling xenobiotics (Aitken 2006; Hall *et al*. 2017).

CHALLENGES FOR THE FUTURE—RESEARCH GAPS

What proportion of a population needs to be infertile?

To manage overabundant rodents with high reproductive rates efficiently, large proportions of females need to be infertile. Computer simulations suggest that 50–80% of females of eruptive house mice (Chambers *et al*. 1997; Davis *et al*. 2003) and >50% of females of non-eruptive ricefield rats (Jacob *et al*. 2004b) need to be infertile to achieve effects at population level (Jacob *et al*. 2008). This seems challenging but experience with rodenticidal bait indicates that even larger proportions can be targeted (Murphy *et al*. 1998). Therefore, orally delivered agents or vaccines should have priority.

However, these computer simulations do not include compensatory effects. Increased spatial activity of infertile ricefield rats might lead to higher predation risk/mortality in infertile rats and replacement by fertile rats (Jacob *et al*. 2004a). Depending on the mode of fertility control, infertile rats may lose their territories with the risk of being replaced by fertile individuals (Jacob *et al*. 2004a). Another factor that can influence breeding performance is social structure (Chambers *et al*. 1999). Female rodents often have a hormonally controlled hierarchy. Subordinate, young fertile females might replace dominant, sterile females, if they lose their position in the social hierarchy (Chambers *et al*. 1999). In addition, improved survival, increased fecundity of fertile females (Chambers *et al*. 1999), and larger litter sizes (Hinds *et al*. 2003) might also lead to compensation (Ramsey & Wilson 2000).

Delivery of anti-fertility agents

On one hand, any anti-fertility agent must be stable in bait until consumed and have a half-life in the body after consumption that is long enough to cause the desired effect. On the other hand, such compounds should not accumulate in the organism or in the environment.

Oral delivery of most of the agents discussed above and particularly of immunocontraceptive vaccines remains a major challenge. Anti-fertility compounds and reproductive antigens have to be kept stable in bait at various environmental conditions (temperature, humidity, ultraviolet exposure) and once consumed must be protected from degradation before uptake across the gastrointestinal tract. Reproductive antigens must have the capability to stimulate uptake via mucosal immune-active sites to generate sufficient antibody responses to inhibit reproductive processes (Sharma & Hinds 2012). A recent study shows some progress with mucosal delivery via the intranasal route: After several consecutive doses of a multimer of GnRH formulated with *Mycobacterium avium* fragments, rats successfully produce antibodies and those with higher titers produce fewer litters (Massei *et al*. 2020). The issue with this intranasal approach and other potential agents is being able to ensure delivery of only the appropriate dose to individuals as well as eliminate nontarget uptake of the contraceptive.

The delivery of immunocontraceptive effects using a viral vector has been studied in rodents (e.g. Singleton *et al*. 2002; Hinds *et al*. 2003; Redwood *et al*. 2007) and non-rodents (Hardy *et al*. 2006). As noted above, a species-specific viral vector when engineered to express a specific reproductive gene induces infertility in the target species (Chambers *et al*. 1999; Hinds *et al*. 2003; Hardy *et al*. 2006; Redwood *et al*. 2007). The efficacy in experimentally infected house mice was high (Redwood *et al*. 2007; Tyndale-Biscoe & Hinds 2007) but attenuation of the genetically engineered virus resulted in insufficient transmission for it to become a successful self-disseminating fertility control agent (Redwood *et al*. 2007). In addition, there are considerable safety concerns (Williams 2007). The latter makes it unlikely that this

method, even if it was used as a non-disseminating bait-delivered product, will receive much attention in the immediate future.

Similar to rodenticidal products, a bait base is required that is highly attractive in the presence of other food sources to ensure adequate bait uptake for a sufficiently long period (which can be in the order of months for VCD if not replenished). Rodent species, populations, or even individuals vary in food preference (Hansen *et al*. 2016); therefore, the food habits of the taxon in question must be considered (Lund 1988).

A variety of bait formulations are available to deliver rodenticides (Jacob & Buckle 2018), each with several advantages and disadvantages. Not only anti-fertility agents but also the bait base needs to be stable at a wide range of environmental conditions and some of them may be appropriate to deliver an anti-fertility agent. This requires extensive testing in field situations. Such studies would also be able to address the best implementation strategy for each species of interest. The timing of delivery of fertility control treatment(s) may need to be continuous for continuous breeders (such as commensal species in urban environments), versus strategically timed before and during the breeding season for seasonally breeding species, including those which may show irregular outbreaks in agricultural systems (Leirs *et al*. 1996; Chambers *et al*. 1997; Shi *et al*. 2002; Davis *et al*. 2003; Krebs *et al*. 2004; Jacob *et al*. 2004a; Sullivan & Sullivan 2010; Esther *et al*. 2014). Robust prediction of rodent outbreaks in space and time is a valuable tool for decision making and restricting management action to areas where and when it is necessary can result in considerable economic (Davis *et al*. 2004) benefit and is advantageous for the environment.

Species specificity of anti-fertility agents and environmental concerns

Most anti-fertility compounds are not species specific and may have adverse effects on nontarget organisms (Jacob *et al*. 2008) that are exposed to bait directly or indirectly through uptake of prey that have consumed anti-fertility bait. This is a situation similar to primary and secondary exposure of nontarget taxa to anticoagulant rodenticides (ARs) (Brakes & Smith 2005; van den Brink *et al*. 2018). Naturally, there are also concerns in the public when there is a risk of residues entering the human food chain (Massei & Cowan 2014).

However, there are important differences to ARs that should make an anti-fertility approach more environmentally friendly: (1) Anti-fertility agents impair reproduction only and do not cause mortality (Jacob *et al*. 2008). (2) In most cases, anti-fertility effects will be temporary, hence affected individuals will be able to contribute to population growth after the anti-fertility effects cease (Tran & Hinds 2012). This may not matter for short-lived nontarget small mammals. Similarly, effects of consumption by nontarget species, such as longer-lived birds of prey, owls, and large terrestrial predators, would likely be temporary but needs assessment. (3) At least some anti-fertility compounds are rapidly metabolized and do not pose a risk of secondary exposure. (4) A reduction in reproduction is unlikely to cause stress and pain (Massei & Cowan 2014)—unlike the symptoms of AR poisoning—which is an additional benefit with respect to the public's expectation for humane wildlife management.

There are no species-specific bait formulations available (Shore & Coeurdassier 2018). However limited uptake by most nontarget species can be achieved using targeted presentations (tailored bait boxes, covers, burrow baiting) and other restrictions already in place for poison products in several parts of the world (Jacob & Buckle 2018). Placing bait at key times of year and in key habitats for limited durations (Colvin *et al*. 1998; Ramsey & Wilson 2000; van den Brink *et al*. 2018) as well as restricting baiting locations to indoors (where appropriate) (Walther *et al*. 2020) or to in-crop habitats can exclude many nontarget taxa. The availability of orally deliverable but non-species-specific anti-fertility compounds is in sight, so developing species-specific bait delivery boxes (Erickson *et al*. 1990; Motomco 2019) is essential to prevent nontarget access and undesirable and indirect impacts on other animals consuming the anti-fertility bait (Eason & Spurr 1995; Elliott *et al*. 2014; Shore & Coeurdassier 2018).

Suitable baiting regimes need to be tested to deliver anti-fertility agents safely in urban situations and at landscape scales (Massei & Cowan 2014) where large-scale chronic infestation or rodent outbreaks cause problems. Baiting regimes should also consider short-term versus long-term baiting depending on the anti-fertility agent used. This is an under-researched topic. Field trials at management scale (e.g. Imakando *et al*. 2021) should be conducted to compare baiting strategies (burrow baiting, bait stations, broadcast) regarding their suitability for delivering effective doses to target species and minimizing uptake by nontargets. Bait markers seem a suitable tool for such studies (Jacoblinnert *et al*. 2021).

Registration of anti-fertility compounds

The registration of fertility control products demands much information with respect to their mode of action,

their classification as pesticide, biocide, or veterinary medicine, and their specificity (Humphrys & Lapidge 2008). Different requirements will apply in different countries and several different regulatory agencies within a country may be involved. Rodent anti-fertility agents will need to meet similar requirements of efficacy and environmental safety as rodenticides as part of the registration process. In the European Union (EU), hazard identification for endocrine-disrupting properties is required as set out in EU regulations for biocidal products and plant protection products, respectively (Commission EU 2017, 2018). There are numerous hormone-altering chemicals, mostly derived from industrial chemicals, which mimic the effects of estrogens by strongly binding to estrogen receptors in different tissues. Their adverse impact on environmental health and reproduction can be considerable (Adeel *et al*. 2017).

As noted above the registration of self-disseminating virus-vectored fertility control agents (Tyndale-Biscoe 1994) would be highly complex partly due to public attitudes to genetically modified organisms and partly because once released it cannot be retrieved. Further, the virus may move beyond the country/continent of intended use and affect the same non-pest species (Williams 1997).

CONCLUSIONS

There is growing interest in nonlethal methods for rodent control that could be met by the application of fertility control agents (Fagerstone *et al*. 2010). Fertility control affects only reproduction, induces (reversible) infertility, and should carry fewer risks for nontarget species than lethal methods. Compared to the use of anticoagulant rodenticides (ARs), fertility control has the potential to deliver a higher degree of humaneness in vertebrate management and therefore, gain more acceptance in the general public.

For seasonally occurring high densities of populations, integrated management approaches are needed and may be different for commensal rodent problems in urban environments compared to rodent outbreaks in agricultural systems. While some results are promising, there are several research gaps.

We need to (1) develop an appropriate delivery system that is optimal for target and nontarget species and that can be delivered efficiently and cost effectively at a population level, (2) conduct well-replicated and controlled field trials at management scales to confirm efficacy for the target species and potential exposure risk for nontarget species, and (3) provide data to meet product registration processes which vary markedly in different countries. Fertility control alone may not be sufficient to manage populations and compensatory effects need to be considered, although in conjunction with conventional lethal and nonlethal control methods, it could be part of an effective, long-term solution.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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