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REVIEW

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Developing fertility control for rodents: a framework for researchers and practitioners

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Abstract

Fertility control is often heralded as a humane and effective technique for management of overabundant wildlife, including rodents. The intention is to reduce the use of lethal and inhumane methods, increase farm productivity and food security as well as reduce disease transmission, particularly of zoonoses. We developed a framework to guide researchers and stakeholders planning to assess the effectiveness of a potential contraceptive agent for a particular species. Our guidelines describe the overarching research questions which must be sequentially addressed to ensure adequate data are collected so that a contraceptive can be registered for use in broad-scale rodent management. The framework indicates that studies should be undertaken iteratively and, at times, in parallel, with initial research being conducted on (1) laboratory-based captive assessments of contraceptive effects in individuals; (2) simulation of contraceptive delivery using bait markers and/or surgical sterilization of different proportions of a field-based or enclosure population to determine how population dynamics are affected; (3) development of mathematical models which predict the outcomes of different fertility control scenarios; and (4) implementation of large-scale, replicated trials to validate contraceptive efficacy under various management-scale field situations. In some circumstances, fertility control may be most effective when integrated with other methods (e.g. some culling). Assessment of non-target effects, direct and indirect, and the environmental fate of the contraceptive must also be determined. Developing fertility control for a species is a resource-intensive commitment but will likely be less costly than the ongoing environmental and economic impacts by rodents and rodenticides in many contexts.

Key words: captive studies, field applications, modeling, oral contraceptive delivery, population management, rodents

INTRODUCTION

Worldwide, the economic and environmental impacts of rodents in urban and rural areas include damage to crops and infrastructure, disease transmission, competition with, and predation on native species (e.g. Tompkins *et al.* 2002; Meerburg *et al.* 2009; Singleton *et al.* 2021).

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In developing countries, pre-harvest crop damage by rodents regularly amounts to annual losses of 5–10% while post-harvest rodent damage also accounts for up to 2.5% (Singleton *et al.* 2007, 2010, 2021), and the World Health Organization has estimated that 400 million human cases of rodent-related zoonoses occur every year (Colombe *et al.* 2019). Rodent impacts are also escalating in developed countries, due to changes in farming practices, abandonment of farmlands, and increased diversity and availability of crop types (Singleton & Brown 1999; Massawe *et al.* 2007; Ruscoe *et al.* 2022). A recent review of the total cost related to native and non-native rodents exceeds US$ 23 billion annually (Jacob & Buckle 2018).

Traditional methods of mitigating rodent impacts include poisoning, habitat management, and trap and dispatch. Poisons appear to be the most commonly used method for rodent control, followed by traps and habitat management (Capizzi *et al.* 2014). However, in several contexts, lethal methods have proven ineffective, inefficient due to the need for repeated applications and sustained effort, publicly unacceptable, and environmentally hazardous because of the secondary effects of some rodenticidal compounds on the food chain. Indeed, the environmental risk of second-generation rodenticides has prompted municipalities in British Columbia and in California to consider banning their use, while in several other countries, public pressure is mounting to protect predators and scavengers by restricting the use of rodenticides (Quinn *et al.* 2019; Hunold & Mazuchowski 2020; Broughton *et al.* 2022) as is the case already in the European Union (Jacob & Buckle 2018). This trend mirrors a global shifting of attitudes from wildlife management to human–wildlife coexistence, particularly in highly developed countries and in urbanized areas (Manfredo *et al.* 2020; Massei & Boyles-Griffin 2022). It also reflects the concept of ecologically based rodent management (EBRM), whereby specific knowledge about the species' behavior, physiology, and ecological impacts are used to integrate different population control methods (Singleton *et al.* 1999; Croft *et al.* 2021a,b).

Public antipathy toward lethal control of wildlife, coupled with the urgent need to identify safe, practical, and environmentally friendly methods to decrease the impact of rodents, have placed a premium on the need to develop fertility control as an alternative or complementary method to culling. Fertility control, which acts by reducing birth rates, rather than by increasing mortality rates, is perceived as being more humane and publicly acceptable than lethal population control. Research is focused on developing oral contraceptives that are practical to use, safe for the target species, and that present little risk to humans, non-target species, and the environment.

Most contraceptives for wildlife are first tested in captive studies or in large enclosures, with a view to progress to field studies. Several reviews on wildlife fertility control (Fagerstone *et al.* 2010; Kirkpatrick *et al.* 2011; Massei & Cowan 2014; Cohn & Kirkpatrick 2015; Wimpenny *et al.* 2021; Jacoblinnert *et al.* 2022b) highlighted desirable features of contraceptives for wildlife and listed a number of points to be addressed when testing the dose, effectiveness, longevity, and safety of a contraceptive.

Transitioning from captive trials to field testing of contraceptives is essential for practical applications of fertility control and involves additional challenges. For instance, Turner and Rutberg (2013) examined the essential steps for field trials aimed at testing contraceptives on wild horse (*Equus caballus*) and white-tailed deer (*Odocoileus virginianus*) populations. These steps include logistics, such as access to and identification of animals, pregnancy testing, behavior and welfare monitoring and training staff in preparation and delivery of drugs and in methods to assess the impact of fertility control at the individual and at population level. For rodents, Tran and Hinds (2012) produced guidelines for standardizing protocols for testing fertility control agents in laboratory trials. These guidelines focused on testing the contraceptives' effect and duration, palatability, and side-effects. More recently, Jacoblinnert *et al.* (2022b) published a critical review of contraceptives for rodents and highlighted research gaps including the need to define population level effects, delivery to target species, risks to non-target species and to the environment, and issues about registration of anti-fertility compounds.

At present, the only fertility control compounds available for large-scale rodent control are oral contraceptives; (1) ContraPest® which is registered in the United States for black rats (*Rattus rattus*) and Norway rats (*R. norvegicus*) and is based on 4-vinylcyclohexene diepoxide and triptolide (Pyzyna *et al.* 2016; Siers *et al.* 2020) and (2) a combination of two synthetic hormones, levonorgestrel and quinestrol, referred to as EP-1 (e.g. Zhao *et al.* 2007; Liu *et al.* 2012b; Shi *et al.* 2020), which is registered in Tanzania for multimammate mice (*Mastomys natalensis*). In addition, the injectable contraceptive GonaCon^{TM} was registered for black-tailed prairie dogs (*Cynomys ludovicianus*) in the United States in 2022 (Yoder & Miller 2010).

So far, no comprehensive framework, which would guide those considering fertility control for rodents through a series of logical steps for testing of a contraceptive from laboratory trials through to field applications,

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has been developed. Such an approach was core to the functioning of the Cooperative Research Centre for Biological Control of Vertebrate Pest Populations which was established in 1992 to develop virus vectored immunocontraception for introduced European foxes (*Vulpes vulpes*) and rabbits (*Oryctolagus cuniculus*), and later house mice (*Mus musculus*) in Australia (Tyndale-Biscoe 1991; Tyndale-Biscoe 1994). From its inception, the Centre established a multidisciplinary approach including reproductive physiology and immunology, virology and molecular biology, ecology and behavior, and mathematical modeling of fertility control with researchers working collaboratively and iteratively across the different disciplines over time. In addition, risk assessments and social acceptance of the approach were investigated (Williams 1997, 2002; Twigg & Williams 1999). At its outset, this project was ambitious, intensive, and complex, and required high levels of funding over 15 years and ongoing commitment by many institutions and stakeholders, with no guarantee of success (Tyndale-Biscoe & Hinds 2007). A very similar multi-disciplinary approach and research strategy was pursued by the Cooperative Research Centre for the Conservation and Management of Marsupials (Marsupial CRC 1995–2003 https://www.eoas.info/biogs/A001950b.htm). The fertility control targets in this case were locally overabundant species in Australia (e.g. eastern grey kangaroos, *Macropus giganteus*) and the brushtail possum (*Trichosurus vulpecula*), a major introduced invasive non-native species in Aotearoa (New Zealand). In this case, oral rather than viral-vectored delivery was the preferred strategy. Although there were at the time emerging oral delivery platforms, these have yet to produce effective vaccines which cause the long-term immunologically mediated contraception/infertility required to be effective at the level of free-living populations. Arguably, application of immunologically based vaccines for marsupials was always a difficult goal given the poor understanding of the marsupial immune response and its manipulation. Although, knowledge of immune function in laboratory rodents is considerable, the marsupial experience emphasizes that substantial fundamental research is likely to be required in the development of fertility-control vaccines for any vertebrate (John Rodger, Director Marsupial CRC, personal communication).

For many researchers today, attracting sufficient resources for a large complex fertility project is difficult, and it is more likely that the scale of a fertility control project for a particular species will involve fewer researchers and institutions than the above examples. It is therefore highly imperative that anyone embarking on a fertility control project for a rodent species has a clear framework and agreed Stop/Go points before commencement.

The first aim of this paper, therefore, is to build on previous reviews, synthesize the research on fertility control of rodents in captive and field contexts, and develop a guiding framework for researchers contemplating taking a fertility control agent from laboratory to field testing and implementation.

Several steps aimed at developing practical applications of contraceptives for rodent populations do not require using the actual contraceptive. For instance, an initial assessment of which proportion of a population could be targeted by using orally delivered contraceptives can be carried out by employing bait markers (e.g. Fisher 1998; Jacoblinnert *et al.* 2022a) or by modeling the impact of contraceptives on population size (Chambers *et al.* 1997; Shi *et al.* 2002; Croft *et al.* 2021a,b). Similarly, as stakeholders are increasingly influencing the acceptability and therefore choice of wildlife management methods, knowledge and public attitudes (Fisher *et al.* 2008; Dunn *et al.* 2018) to fertility control should be assessed for each context before implementing this method.

The second aim of this paper is to provide users with suggestions on research that can be pursued simultaneously when considering the practical aspects of using fertility control to manage rodent populations.

MATERIALS AND METHODS

The framework assumes that fertility control has been selected as the method of choice to reduce the impact and/or number of rodents in an ecosystem or agricultural production area. We have excluded domestic situations, where the use of fertility control seems unsuitable because usually there is zero tolerance for rodents and eradication needs to be realized more rapidly than an anti-fertility compound can achieve. The framework also presumes that a new contraceptive compound "X" is being evaluated for species "Y." The steps suggested are listed as questions to guide the progression of research from initial pilot trials in captivity through to full scale field tests and ultimately to field applications. For ease of illustration, single steps are presented as a sequence; however, several lines of research can and should be run in parallel. For instance, captive studies to test and refine contraceptive compound "X" can be carried out in parallel with field studies which simulate the feasibility of delivery and the effects of contraceptives on the target species "Y" by using bait markers to assess bait uptake, surgical approaches, or removal of different proportions of target animals from the natural environment. Both captive and

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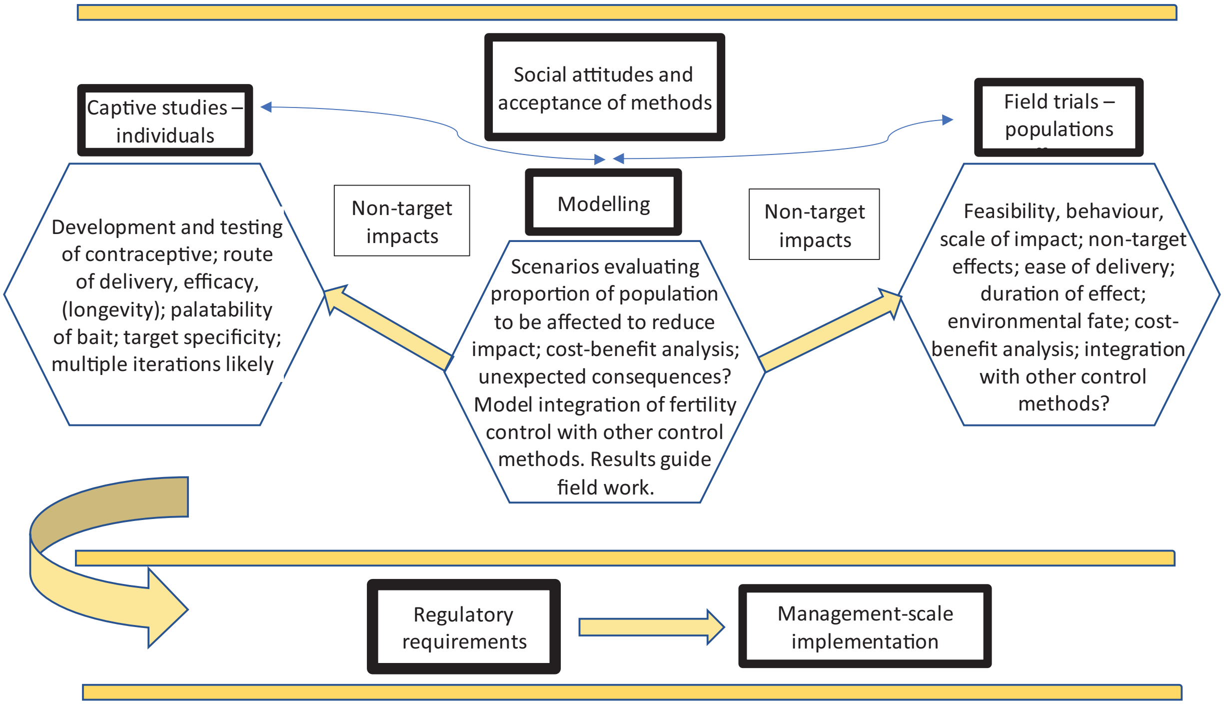

Figure 1 The iterative process required to develop a population-level, efficacious contraceptive for wildlife, including target rodent species.

field studies may also benefit from an independent line of research focused on modeling the impact of fertility control, alone or in conjunction with other population management methods, on population size (Fig. 1).

RESULTS

1. Captive studies

Captive studies should progress from pilot tests on effectiveness, safety, and duration of effects of a contraceptive on the target species, through to formulation of baits and species-specific methods to deliver oral contraceptives, tests on environmental stability of these compounds, and possible effects on the food chain (Fig. 2-2a).

1a. Effectiveness: Is this contraceptive effective on the target species?

In many instances, novel contraceptives are first tested on laboratory rats or mice in laboratory trials or in controlled conditions, even if these species are not necessarily the ultimate target species. Pilot trials are used to select the dose of a candidate contraceptive and to measure its effects on reproduction. These effects are quantified via changes in reproductive physiology, such as ovarian follicle number and type, weight, size, and histology of ovaries and testes, sperm number and quality (morphology, motility), concentration of sexual hormones, and by changes in reproductive output and litter size (Sharma *et al.* 2014; Witmer & Raymond-Whish 2021; Chen *et al.* 2022; Pinkham *et al.* 2022; Selemani *et al.* 2022).

Different species, even those that are closely related, can respond differently to the same contraceptive and not all contraceptives developed for mammals are effective on rodents. For instance, porcine zona pellucida-based contraceptives, effective on many wildlife species, do not affect reproduction in rodents (Fagerstone *et al.* 2010). The best examples of the different responses of rodents to the effects of a contraceptive are found in studies on orally delivered levonorgestrel (P) and quinestrol (E), alone or in combination (EP-1). For example, both EP-1 and quinestrol affect male reproduction of striped field mice (*Apodemus agrarius*) (Chen *et al.* 2022) and male and female reproduction of black rats (Selemani *et al.* 2022). However, in Brandt's voles (*Lasiopodomys brandtii*), treatment with quinestrol or EP-1 resulted in no marked effects on the reproductive status of males and females although quinestrol alone significantly affected male's reproduction (Zhao *et al.* 2007; Shi *et al.* 2020).

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Further, there is no common dose or common ratio of EP-1 or its constituents that equally affect different rodent species (see Jacoblinnert *et al.* 2022b).

Triptolide alone has been shown to have significant effects for more than 60 days on male reproductive parameters (Norway rats: Huynh *et al.* 2000; *Bandicota bengalensis*: Dhar & Singla 2014). As the main objective for fertility control of most wildlife species is to markedly limit recruitment, females are the targeted sex, with effects in males a bonus (see Jacoblinnert *et al.* 2022b).

For these reasons, it is advisable that each contraceptive is first tested on the target species in captive studies or under controlled conditions. These data are also required by the registration authorities if the contraceptive is going to be made commercially available for the target species.

1b. Safety and toxicity: Does the contraceptive have side effects?

A meta-analysis of quantitative studies of the side effects of contraceptives for wildlife showed that secondary

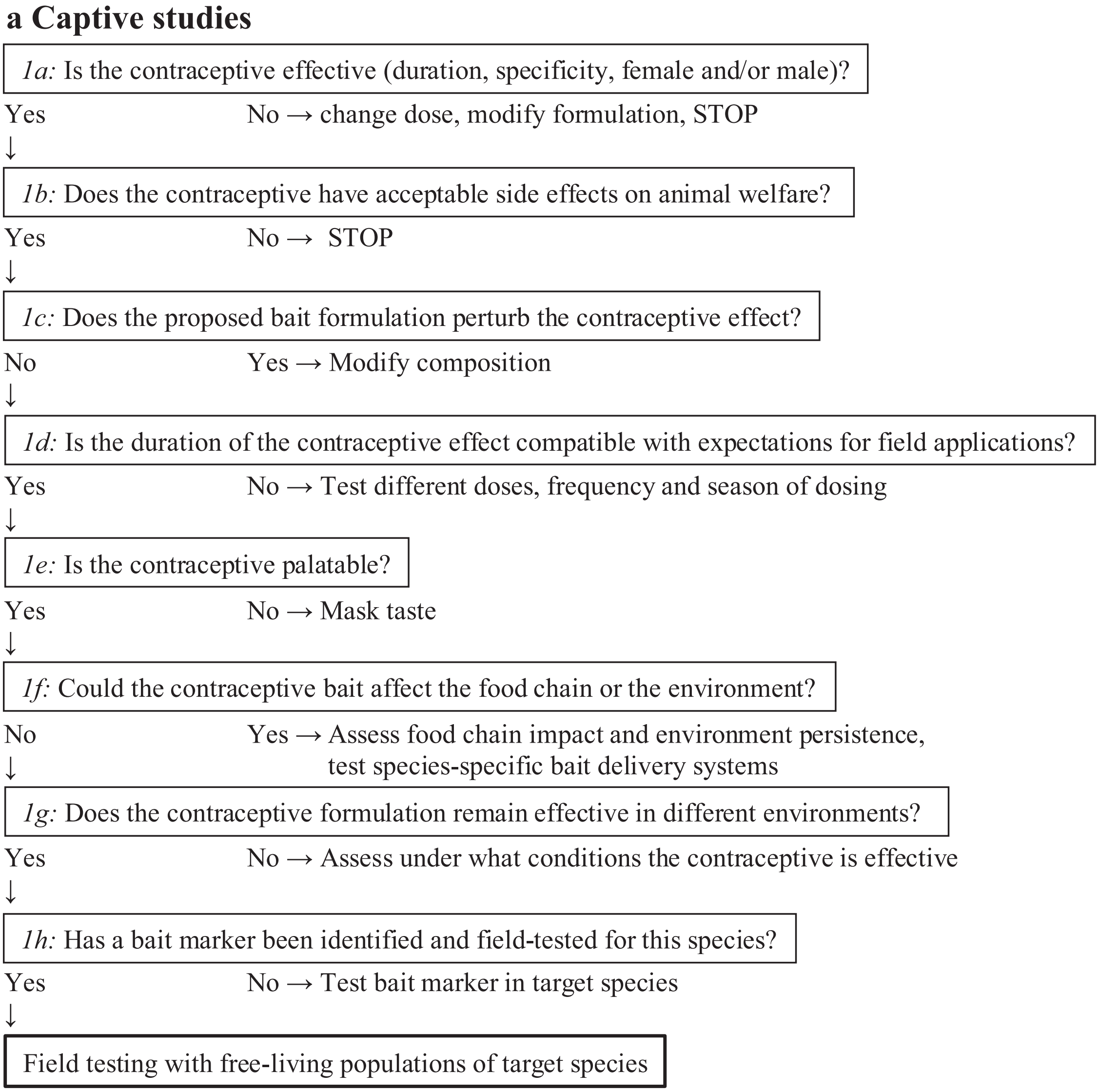

Figure 2 A decision tree to progress the testing of contraceptives for rodents from laboratory to practical field applications. The tree assumes that a candidate contraceptive has been selected for a target rodent species and that public opinion supports the use of fertility control to manage this species. (2a) Captive studies; (2b) field studies; (2c) modeling.

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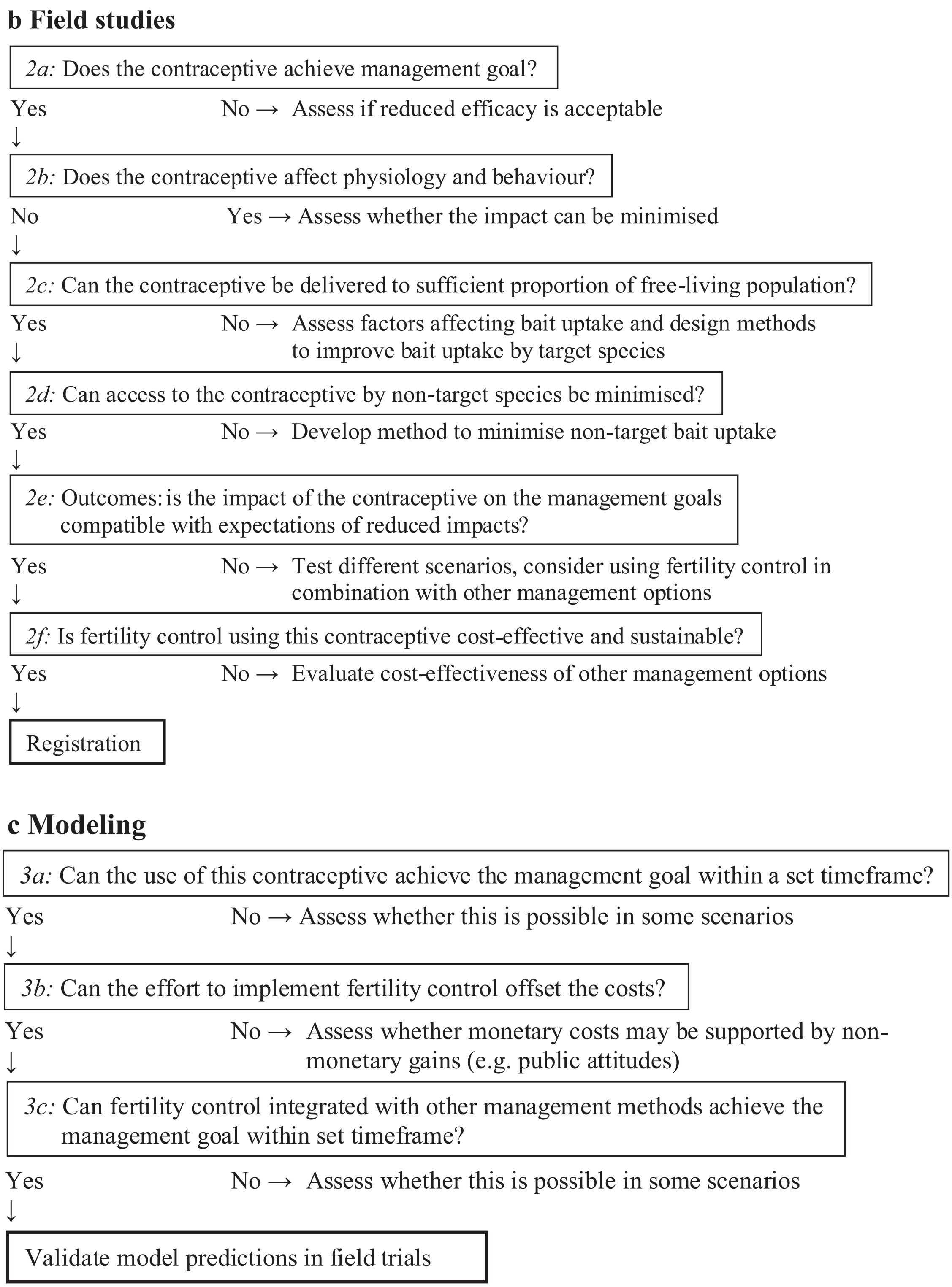

b Field studies

2a: Does the contraceptive achieve management goal?

Yes ↓ No → Assess if reduced efficacy is acceptable

2b: Does the contraceptive affect physiology and behaviour?

No ↓ Yes → Assess whether the impact can be minimised

2c: Can the contraceptive be delivered to sufficient proportion of free-living population?

Yes ↓ No → Assess factors affecting bait uptake and design methods to improve bait uptake by target species

2d: Can access to the contraceptive by non-target species be minimised?

Yes ↓ No → Develop method to minimise non-target bait uptake

2e: Outcomes: is the impact of the contraceptive on the management goals compatible with expectations of reduced impacts?

Yes ↓ No → Test different scenarios, consider using fertility control in combination with other management options

2f: Is fertility control using this contraceptive cost-effective and sustainable?

Yes ↓ No → Evaluate cost-effectiveness of other management options

Registration

c Modeling

3a: Can the use of this contraceptive achieve the management goal within a set timeframe?

Yes ↓ No → Assess whether this is possible in some scenarios

3b: Can the effort to implement fertility control offset the costs?

Yes ↓ No → Assess whether monetary costs may be supported by non-monetary gains (e.g. public attitudes)

3c: Can fertility control integrated with other management methods achieve the management goal within set timeframe?

Yes ↓ No → Assess whether this is possible in some scenarios

Validate model predictions in field trials

Figure 2 *Continued*

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effects consistently occur across all contraceptive types and concluded that research was needed to address fundamental questions about secondary effects of contraceptive treatment (Gray & Cameron 2010).

Physiological effects of contraceptives comprise stillbirth, abnormal offspring, inhibition of parturition or dystocia, and changes in lactation, secondary sex characteristics, bodyweight or body condition, and abscesses or inflammatory reactions. The effects of contraceptives on rodents' reproduction can be more subtle than simply making animals infertile. For instance, some of these effects include reduced fertility, reflected in the production of smaller litters and/or smaller pups in field mice females mated with males dosed with EP-1 (Chen *et al.* 2022), in laboratory rats treated with a GnRH-based oral vaccine (Pinkham *et al.* 2022), and in Brandt's vole females mated with males treated with quinestrol (Zhao *et al.* 2007).

Side effects on behavior include changes in movement and activity patterns, aggression, social disruption, change in social status, and territory loss (Gray & Cameron 2010; Liu *et al.* 2012a,b; Jacoblinnert *et al.* 2022b). For oral contraceptives, the effects of overdosing or underdosing must be tested in captivity as in field conditions the consumption of baits containing contraceptives varies in relation to factors such as gender, age, social status, season, and population density.

Among side effects of contraceptives in rodent species, injection site abscesses were found in eastern gray squirrels (*Sciurus carolinensis*) injected with GonaCon^{TM} (Pai *et al.* 2011) but no effects were observed on time-activity budgets, dominance, and aggression in eastern fox squirrels (*Sciurus niger*) treated with GonaCon^{TM} (Krause *et al.* 2015).

Data on safety and toxicity of a contraceptive, tested on the target rodent species, are required for comprehensive assessment of environmental risk and also by the registration authorities if the contraceptive is going to be made commercially available for the target species.

1c. Bait effect on contraceptive: Does the proposed bait formulation perturb the contraceptive effect?

Bait formulation is likely to influence retention time in and uptake from the gastric tract, as well as the effect of oral contraceptives. For instance, when testing different bait formulations, Williams *et al.* (2019) showed that the best formulation to deliver a vaccine against bovine tuberculosis to European badgers (*Meles meles*) was based on peanut butter, cereal, and sugars. This formulation allowed long-term storage of viable vaccine, especially when the latter was encapsulated within a lipid carrier to overcome the inactivation due to gastric secretions and to enhance its uptake through the intestinal wall.

1d. Longevity: What is the duration of the contraceptive effect?

Once a compound is found both effective as a contraceptive and safe in terms of causing acceptable side effects, the next step toward practical applications is to establish the duration of effect for the target species. This depends on the nature of the compound, its dose, dose frequency, and on the reproductive status of the species at the time of contraceptive consumption in relation to the reproductive season (Jacoblinnert *et al.* 2022b). In rodent species which breed most of the year, preferably the contraceptive would be delivered in baits and become effective before breeding starts, ideally inhibiting reproduction for at least one full breeding season to have an impact at the population level (Jacoblinnert *et al.* 2022b). In species such as the eastern grey squirrels that show two distinct peaks of reproduction per year (Mayle *et al.* 2013), a contraceptive which affects reproduction for a few months should be administered twice per year. Oral contraceptives generally require multiple doses to be effective for at least a few months, with extremes that range from 3 to 7 days of treatment for synthetic steroids such as quinestrol and EP-1 in striped field mice (Chen *et al.* 2022) through to >50 days required for VCD and triptolide to inhibit the production of litters for three consecutive breeding rounds in Norway rats (Witmer & Raymond-Whish 2021).

1e. Palatability: Is the contraceptive palatable?

The taste of the contraceptive compound may affect the palatability of the bait used for its delivery. For instance, 4-vinylcylcohexene diepoxide (VCD) tested in wild house mice (*Mus domesticus*) was unpalatable at relatively high concentrations, and the consumption of emulsions containing VCD was found to be dose-related (Hinds *et al.* 2014). Similarly, Norway rats treated with a combination of VCD and triptolide consumed significantly less bait than control rats, indicating that these contraceptive formulations were less palatable (Witmer & Raymond-Whish 2021). The bitter taste of the cholesterol inhibitor DiazaCon^{TM} also affected grey squirrels' consumption of treated bait (Mayle *et al.* 2013). Similarly, quinestrol and EP-1 are unpalatable at their required effective doses for some rodent species including black rats (Selemani *et al.* 2022), ricefield rats (*R. argentiventer*) (Stuart *et al.* 2022), and multimammate mice (*M. natalensis*) (Massawe *et al.* 2018) but not for Brandt's voles (Wang *et al.* 2011) or

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plateau pikas (*Ochotona curzoniae*) (Liu *et al.* 2012b). Unpalatable baits result in animals consuming insufficient quantities of the compound intended to inhibit their reproduction. Several methods are available for improving palatability, ranging from adding sugar or fats through to encapsulation and use of taste-masking agents routinely employed by the pharmaceutical industry (Mayle *et al.* 2013; Zheng *et al.* 2018; Kang *et al.* 2022; Stuart *et al.* 2022).

1f. Effects on the food chain: Could the contraceptive affect fertility of predators and scavengers and persist in the environment?

Data on the effect of a contraceptive on the food chain and on its persistence in the environment are required for comprehensive assessment of environmental risk and for the registration dossier. Contraceptives may enter the food chain either through direct consumption of treated baits by non-target species, or when predators or scavengers feed on animals that have been treated with contraceptives. Direct consumption of treated baits can be reduced by using bait boxes that allow access only to the target species, such as those that are routinely used to deliver rodenticides. Captive studies can determine whether the target species can access the bait in these containers and also whether dominant animals limit bait consumption by subordinates. For instance, passive integrated transponder (PIT) tags, coupled with bait dispensers equipped with a PIT tag reader and bait-weighing device, have been used to record bait uptake by individual eastern grey squirrels (Beatham *et al.* 2021).

The effect on predators or scavengers depends on the type of contraceptive and its mechanism of effect. For instance, injectable immunocontraceptives, if ingested as part of an item of prey, will be destroyed in the gastric tract and will not affect reproduction of predators or scavengers (Fagerstone *et al.* 2006). Oral contraceptives should be tested for their potential effects on the food chain. For instance, the synthetic estrogen homolog quinestrol, which after ingestion is stored in adipose tissue and released slowly into the circulation (Zhao *et al.* 2007), has the potential to affect mammalian and avian predators. A recent study of the impacts on domestic chickens (*Gallus gallus*) of oral consumption of EP-1 showed egg production was reduced in a dose-dependent manner for about 120 days (He *et al.* 2022), but in the field, EP-1 had minimal effects on bird abundance and diversity in the Qinghai−Tibet Plateau (Qu *et al.* 2015). Some assessments of the environmental fate of quinestrol and levonorgestrel have shown a short half-life in soil (1–2 weeks) and water (a few hours) (Tang *et al.* 2012a,b). Quinestrol is decomposed rapidly by microbes in soil and by ultraviolet, visible light, and acids in water (Zhang *et al.* 2014a).

This is an area surprisingly underreported among studies on oral contraceptives, despite the fact that these data must be produced as part of the registration dossier for a new contraceptive.

1g. Environmental stability: Does the contraceptive formulation remain effective in different weather conditions?

Oral delivery of most contraceptives, and particularly of immunocontraceptive vaccines, also depends on the stability of both these compounds and on the baits used to deliver them under various environmental conditions (Jacoblinnert *et al.* 2022b). Vaccines are susceptible to changes in temperature, oxidizing reagents, salts, pH, light, and enzymes. Several methods and formulations are known to reduce the detrimental effects of these factors, such as freeze-drying, melt-extruding, or hot-molding to improve the stability of vaccine formulations (Ballesteros *et al.* 2007; van Oosterwijk 2021). With broad-scale delivery, bait in natural environments can be exposed to diurnal changes in temperature, humidity, rainfall, and sunlight that can cause degradation of the bioactive due to hydrolysis and oxidation leading to reduced bait stability and efficacy. Environmental conditions, as well as the length of bait exposure to these conditions, may alter the chemical properties of contraceptives and should be tested in controlled environments prior to field studies (McDowell 2022).

1h. Bait marker: Which bait marker can be used for this species?

Bait markers can be added to oral contraceptives to identify individuals that consume the baits to evaluate and optimize the cost-effectiveness of fertility control at the population level. In addition, information about optimal bait placement, competition etc., can be derived. Bait markers tested on rodents include Rhodamine B, tetracyclines, ethyl-iophenoxic acid, and its analogs methyl- and propyl-iophenoxic acid (e.g. Jacob *et al.* 2002; Ballesteros *et al.* 2013; Jacoblinnert *et al.* 2022a). However, the variable persistence of some markers, such as iophenoxic acid analogs in wildlife species highlights the need for calibration testing of each compound as a marker for each species and for each proposed use before starting a bait delivery trial (Ballesteros *et al.* 2013). If marker residues are stable for a reasonable period,

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quantitative data about individual bait uptake can be collected. The detection of distinct bands of Rhodamine B in hair and whiskers of animals that have consumed Rhodamine B-treated bait and the time required to detect the first band depend on the rate of growth of hair and whiskers (Fisher 1999). As this rate varies between species, ideally this marker should first be tested in captive studies using the target species. In addition, some markers, such as Rhodamine B, can affect bait palatability. For instance, black rats offered baits containing different concentrations of Rhodamine B preferred those with the lowest concentrations (Weerakoon & Banks 2011).

2. Field studies

Field studies should start with tests to assess whether the results of captive trials, in terms of effectiveness and duration of effects of a contraceptive on individuals of the target species, can be replicated under natural conditions. These will be followed by field tests on the effects of fertility control at the population level. As one of the main questions for field trials is to assess what proportion of the population can be targeted using contraceptives, initial trials can be run in parallel to captive studies, using bait markers instead of the final formulation of the contraceptive. Once the contraceptive is available for field testing, field trials must be carried out to establish the actual effect of the fertility control at population level, whether the contraceptive can be delivered to a sufficient proportion of the target species and whether non-target species can be prevented from consuming contraceptives (Fig. 2-2b).

2a. Effectiveness and population dynamics: Does the contraceptive achieve management goals?

In most captive studies, the effect of the contraceptive is evaluated at the individual level, while field studies mainly focus on the effects on populations and on the reduction of impacts. Field studies may assume that the efficacy of a contraceptive is the same as found in captive studies, although this is not necessarily the case. For instance, in several wildlife species, the efficacy and duration of effect of a contraceptive on reproduction are more pronounced in captive animals than in free-living conspecifics (see review in Massei & Cowan 2014).

In free-living rodents, the effects of contraceptives at an individual level are assessed by monitoring reproductive activity of males and females, as well as body weight and body condition. At the population level, the effects of fertility control are evaluated by estimating changes in local population densities and recruitment before, during, and after treatment with contraceptives in well replicated and controlled studies at the management scale. In some instances, although the contraceptive remains effective on individual animals, local abundance might not change due to processes such as compensatory natality and immigration (see below).

Presently, most information about the efficacy of fertility control in rodent populations is based on laboratory experiments and enclosure trials. The latter suggest that in a closed population successful contraception in about two thirds of females results in considerable population reduction (Chambers *et al.* 1999b; Singleton *et al.* 2002; Hinds *et al.* 2003; Jacob *et al.* 2004a) and in a decrease in rodent damage (Jacob *et al.* 2004a). For instance, in a series of enclosure and field studies conducted on rice field rats (Jacob *et al.* 2006) and house mice (*M. domesticus*) (Chambers *et al.* 1999b), the effect of fertility control (simulated by tubal ligation, ovariectomy, or progesterone treatment) on population size was assessed. The results suggested that a once-off sterilization of 50% to 75% of founders (rice-field rats), or of 67% of female founders and their first offspring (house mice) respectively, significantly reduced reproductive output in these populations until the end of the reproductive period (Jacob *et al.* 2008). However, in free-living rice field rats, the surgical sterilization of about two thirds of adult females did not lead to a decrease in population growth, breeding performance, or crop damage nor in numeric or reproductive compensation at population level, probably due to immigration by fertile rats (Jacob *et al.* 2006). Similarly, castration of dominant male black-tailed prairie dogs (*C. ludovicianus*) was not found to reduce colony expansion and damage because there was no effect on population composition (Witmer 2019).

Systematic field studies using orally delivered contraceptives are rare and mostly related to testing EP-1 in several Asian rodent species (Zhang 2015) and in multimammate mice in Africa (Imakando *et al.* 2022). EP-1 reduced pregnancy rates and litter size in field populations of Mongolian gerbils (*Meriones unguiculatus*) (Fu *et al.* 2013), Djungarian hamsters (*Phodopus campbelli*) (Xinrong *et al.* 2006), and Plateau pikas (Liu *et al.* 2012b). EP-1 treatment in field trials reduced reproduction and abundance and altered population structure in Mongolian gerbils (Yanjing *et al.* 2013) and Roborovski hamsters (*Phodopus roborovskii*) (Zhang *et al.* 2014b). This contraceptive decreased abundance

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in striped field mice (Chen *et al.* 2022) and reproductive activity and output in Maximowicz's vole (*Microtus maximowiczii*) populations (Zou *et al.* 2014). However, in field studies of multimammate mice baited with EP-1, this compound had little effect on abundance and did not reduce recruitment (Imakando *et al.* 2022).

Triptolide has been used in combination with rodenticides (zinc phosphide and bromadiolone) for management of *B. bengalensis* with the results suggesting some advantage in using such a combination to control rodents in a sugar cane cropping system (Kaur & Singla 2022).

In the United States, the field efficacy of ContraPest© cannot be assessed from the published literature because only information on bait uptake is presented (Pyzyna *et al.* 2014), while the efficacy of ContraPest in combination with the rodenticide bromethalin was measured indirectly using tracking tunnels (Pyzyna *et al.* 2018).

Another study carried out with bait containing DiazaCon, placed daily in small piles on the ground near burrow entrances of black-tailed prairie dogs for 10 days, considerably reduced the proportion of young over a 3-month period (Nash *et al.* 2007).

Field tests of efficacy require trials at an appropriate management scale that are methodical, replicated, and yield robust results. They should be spatially and temporally adequate to assess population effects with sufficient statistical power. The effect sizes aimed for are likely to differ for different goals such as reduction of disease transmission or decreased crop or forestry damage. Therefore, the desired effect sizes should be defined *a priori* for the management goal(s) in question, then the management trials should be designed accordingly and the (substantial) resources to conduct such trials secured.

2b. Side effects: Does the contraceptive affect behavior and physiology?

Contraceptives have the potential to affect survival as well as social and spatial behavior (reviewed in Gray & Cameron 2010). For instance, if infertile animals abandon their territories, fertile individuals may immigrate and compromise the effects of fertility control (Jacob *et al.* 2004a). Where the sterilization of a single dominant female releases subordinates from breeding suppression, sterilization may enhance the overall productivity of the population (Caughley *et al.* 1992). This emphasizes the need to sterilize individuals without compromising their social position (Chambers *et al.* 1997). The possible effects of fertility control should be studied in species like African striped mice (*Rhabdomys pumilio*) for which the size and mass of litters produced are influenced by the dominance status of a female and of her neighbors (Kinahan & Pillay 2008).

Among the few studies conducted in this area, the importance of maintaining hormonal competence was examined in surgically sterilized female mice housed in outdoor enclosures. Comparing reproductive output of populations that had 67% of mice either ovariectomized (hormonally incompetent) or tubally ligated (hormonally competent), Chambers *et al.* (1999b) found no significant difference between the two methods of sterilization in terms of effect on population size. Thus, for this species, the maintenance of hormonal competence in sterilized females is not important when fertility control is applied to reduce population size. However, compensation occurred through improved breeding performance of unsterilized mice (Chambers *et al.* 1999b).

Jacob *et al.* (2004a) showed that surgically sterilized rice field rats had home ranges about twice the size of those of both hormonally sterilized and fertile rats and that hormonally sterilized rats tended to lose their territories, although hormonally sterilized, surgically sterilized, and fertile rats did not leave the rice field systems. This suggested that sterilization was unlikely to negatively affect the success of fertility control in this species as sterilized rats remained in the ricefield system throughout the breeding period (Jacob *et al.* 2004a).

A similar study on rabbits (*O. cuniculus*) following the surgical sterilization of 40%, 60%, and 80% of females found that productivity decreased with increasing sterility, but that a greater proportion of offspring was recruited into populations with higher levels of sterility and that sterile females survived longer in the high sterility treatment (Williams *et al.* 2007). This demonstrated that two density-dependent processes affected rabbit populations, one acting on juvenile survival and the other on the survival of infertile adult rabbits, although these mechanisms were insufficient to overcome the effect of fertility control in the high sterility populations (Twigg & Williams 1999; Twigg *et al.* 2000; Williams *et al.* 2007). In terms of social effects of fertility control, Zhang (2000) proposed a contraceptive model in which sterile males competitively interfered with fertile males, as sterile males continued to attack competitors and participate in mating. If this mechanism was proven, the behavior of sterilized animals may contribute to reduce population growth.

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2c. Delivery: Can the contraceptive be delivered to a sufficient proportion of animals in a free-living population?

Assuming an effective and safe contraceptive that can be delivered via a bait is identified for a particular rodent species, an equally important step toward practical applications of fertility control is to establish how to maximize bait uptake by the target species.

The choice of an optimal bait is not unique to orally delivered anti-fertility compounds but an inherent aspect for trapping rodents using lures (Hansen *et al.* 2017), presenting rodenticides (Buckle & Eason 2015) and delivering other actives such as insecticides or acaricides (Leirs *et al.* 2001; Poché *et al.* 2017, 2018; Hinds *et al.* 2021; Jacob *et al.* 2021) as well as antibiotics to rodents (Dolan *et al.* 2017). Therefore, there is ample scientific general knowledge about bait preferences in several rodent species.

Nutritive drivers of consumption indicate that fat-based caloric value is the most important determinant of bait consumption by Norway rats (Jackson *et al.* 2015). Bait acceptance can sometimes be improved using particular bait substrates (Leung *et al.* 2007), adjusted carbohydrate profile (Johnston *et al.* 2005), and/or bait additives depending on species and setting (Shumake & Hakim 2000; Mushtaq *et al.* 2013; Jackson *et al.* 2015; Takács *et al.* 2017; Schlötelburg *et al.* 2018). Factors affecting bait uptake include extrinsic variables (availability of natural food, density of bait versus density of rodents, methods of bait distribution) (Jacob *et al.* 2003) and intrinsic variables (sex, age, personality, social and reproductive status) (Horak *et al.* 2018). Pre-baiting may increase the success of baiting campaigns when using rodenticides (Buckle & Eason 2015) where there is no social information transfer but rather a time dependent pattern—the longer the bait is available, the greater the likelihood of encounter and the larger is the proportion of individuals consuming bait (Bytheway *et al.* 2021).

Optimal bait placement is required to ensure sufficient bait uptake (Ramsey & Wilson 2000; Endepols *et al.* 2003; Endepols & Klemann 2004; Murphy *et al.* 2014; Pepin *et al.* 2020). Compared to liquid anti-fertility bait (such as ContraPest©) that depends on using containers, solid bait offers more options for delivery. These include subsurface baiting (Khan 1998; Arjo & Nolte 2004), surface broadcast (Dunlevy *et al.* 2000), and the use of bait boxes (Spurr *et al.* 2005; Phillips *et al.* 2007; Buckle & Prescott 2011)—all associated with pros and cons regarding uptake, cost, and protection of non-target species. To improve baiting success, local knowledge and the expertise of pest control specialists can be used (Buckle & Smith 2015).

Given all the factors affecting patterns of bait uptake, the variation in the percentage of a rodent population consuming bait is not surprising. For example, 51% of Norway rats consume anti-fertility bait in an urban situation (Pyzyna *et al.* 2014), and 78% of house mice eat pellet bait in grain fields (Jacob *et al.* 2003). Modeling studies (Krause *et al.* 2014) and enclosure trials suggest that about 33–67% of females need to be infertile to achieve population effects (Chambers *et al.* 1997; Davis *et al.* 2003; Hinds *et al.* 2003; Jacob *et al.* 2004a) and a decrease in rodent damage (Jacob *et al.* 2004a). This percentage is likely to differ depending on the target species and management goal(s) and needs to be estimated and aimed for in field application.

Assessing patterns of bait uptake can be carried out in parallel with captive and modeling studies and, as noted above (section *1h. Bait marker: Which bait marker can be used for this species?*), without using the actual contraceptive but simply employing bait markers (Johnston *et al.* 2003; Jacoblinnert *et al.* 2022a), camera traps, and PIT tag readers. Such studies allow identifying individual and population level patterns of bait uptake in target and non-target species, revealing the reasons for over/under dosing and then adjusting baiting strategies accordingly (e.g. Quy *et al.* 2003; Beatham *et al.* 2021). While prior knowledge of bait uptake related to rodenticides can be used for optimizing uptake of baits containing contraceptives, it is important to remember that the taste or smell of anti-fertility compound can affect bait uptake (see section *1e. Palatability: Is the contraceptive palatable?* above). This can be tested initially in captive trials, but it must also be evaluated in field trials as bait acceptance in natural conditions is likely to be more variable than in captivity.

2d. Non-target species: Can access to the contraceptive by non-target species be minimized?

The majority of oral contraceptives developed so far are likely to affect other species that might ingest the bait containing the contraceptive. This aspect is important because in the environmental assessment of contraceptive products a non-reproducing non-target individual is deemed as “lost” for sustaining population size even though the effect is non-lethal. However, field data are scarce and currently restricted to very few studies. For instance, Qu *et al.* (2015) found that EP-1 did not affect avian biodiversity but caused some changes in the abundance of some bird species, and He *et al.* (2022) demonstrated that increasing doses of quinestrol affected egg production by domestic chickens for approximately 120 days. Since there are no rodent-specific

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contraceptives available, specificity could be achieved via the method(s) of delivery of baits. These include tailored bait dispensers, burrow baiting, and bait box designs which preclude entry as already tested to deliver rodenticides (Erickson *et al.* 1990; Kenward *et al.* 2005; Beatham *et al.* 2021) as well as using temporal and spatial features of bait distribution that minimize access for non-target species.

Using liquid bait rather than solid bait prevents rodents from taking the bait outside the dispensers and into the environment. This is the principle adopted by ContraPest© to minimize the impact of this contraceptive on the environment and on non-target species (Pyzyna *et al.* 2016). The impact of oral contraceptives on non-target species can also be tested by limiting bait availability to relatively short periods at key times (e.g. before the onset of the breeding season) and by using remote monitoring such as camera traps to identify bait uptake by non-target species. Baiting regimes should also evaluate short-term versus long-term baiting requirements in relation to the contraceptive employed and to the desired effects on population size and/or impacts. This area of research has received very little attention, but it is crucial for assessing the overall environmental impact of fertility control agents (Jacoblinnert *et al.* 2022b).

Field trials at landscape scale (e.g. Imakando *et al.* 2022) should be carried out to compare the suitability of different baiting strategies (bait stations, burrow baiting, broadcast) for the target species while minimizing impacts on non-target species.

2e. Outcomes: Is the impact of the contraceptive on the management goals compatible with expectations of reduced impacts?

Reduced reproduction and associated reduction in population size are important but represent only the first steps to achieving the ultimate goals of rodent management. The latter include increasing pre-harvest crop yields, decreasing post-harvest losses, decreasing damage to infrastructure, lowering human infection risk for rodent-borne disease, and minimizing unwanted effects of rodents on native fauna and flora. Therefore, when testing the efficacy of fertility control, depending on the setting and goals to be achieved, future fieldwork needs to address these aspects as a priority.

Factors affecting the outcome of management based on fertility control are especially relevant to understand whether and when the desired effect size can be achieved. The spatial, temporal, and social effects of contraceptives in field conditions are often unknown or poorly understood, as are the effects on immigration, emigration, natality, and survival. For instance, immigration of fertile individuals and emigration of infertile individuals will dilute the proportion of infertile individuals of the target species, when remaining fertile individuals increase their reproductive output. Such was the case in ricefield rats (Jacob *et al.* 2004a,b), where there was a compensatory response to the intervention and in brushtail possums where sterilized females survive longer (Ramsey 2005). Compensation may also occur when survival of young is increased because of decreased intra-specific competition (Chambers *et al.* 1999b; Williams *et al.* 2007) or when the onset of reproduction is early due to decreased breeding suppression by dominant fertile females (Wasser & Barash 1983).

From a management point of view, this is highly important information because both the size (or the proportion) of an area to be treated and the period of and between treatments will affect the success of management based on fertility control. Depending on the compound used, the duration of treatment necessary can range from a single baiting episode for EP-1 (Zhang 2015) to >12 weeks continuous application for ContraPest© + bromethalin (Pyzyna *et al.* 2018). The duration of a treatment effect in the field is also highly variable ranging from 3 months (Nash *et al.* 2007) to about 1 year (Zhang 2015). In rodent species that breed for most of the year, it would be ideal that a contraceptive, delivered before breeding starts, affected reproduction for at least one full breeding season. An example is the single baiting administration of quinestrol in plateau pikas, which led to male infertility for the whole breeding season, (about 2 months), with some residual impact found into the next breeding season 1 year later (Liu *et al.* 2012b). Similarly, single baiting administration of EP-1 at the beginning of the breeding season appeared to affect striped field mice for the whole breeding period, lasting several months (Chen *et al.* 2022).

2f. Cost and sustainability: Is the use of this contraceptive cost-effective and sustainable?

The monetary costs of implementing fertility control for rodents, alone or compared with other population control methods, have received very little attention. Costs can be expressed as a combination of cost of the contraceptive, of the delivery system (if used), and of the number of person-hours required to treat a certain area. In parallel, a cost benefit analysis can be conducted to estimate the benefits of reducing population size or impact of rodents versus the cost of the method applied.

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Among the non-monetary costs that need to be taken into account when considering rodent population management are public attitudes and potentially reduced effects on predators and scavengers of fertility control compared to lethal methods. Fertility control is generally well accepted or even preferred to other methods even if it is predicted to be less effective (Dunn *et al.* 2018; Quinn *et al.* 2019; Hunold & Mazuchowski 2020). For instance, control strategies consisting solely of immunocontraceptive vaccines to eradicate the non-native grey squirrel from Ireland, often preferred by public interest groups, were predicted to be less effective than culling (Goldstein *et al.* 2016). Naturally, the fertility control method needs to be sufficiently effective to achieve the management goal.

Comparing the costs of different population management options and identifying who should bear these costs might raise stakeholders' awareness of the economics of current management practices and assist with decision-making (Massei & Cowan 2014). This awareness will be further enhanced if the full costs, including negative environmental and welfare consequences, associated with each option were included, as well as the feasibility and expected outcomes (Massei 2023).

Another key aspect is to consider how cost and sustainability could be enhanced by integrating fertility control methods with other management actions (see next section below).

Further, legal requirements should be considered for field applications of fertility control as oral contraceptives for rodents are at present registered in very few countries (Massei 2023).

3. Modeling studies

3a. Can the use of this contraceptive achieve the management goal within a set timeframe?

As almost all rodents are characterized by high reproductive rates, managing populations via fertility control requires a relatively high proportion of the population to be made infertile. Mathematical modeling allows simulations of the effects of treating different proportions of a population with contraceptives within a set timeframe and at different scales (Fig. 2-2c). For instance, modeling suggests that 33–80% of house mice females in eruptive populations (Chambers *et al.* 1997; Davis *et al.* 2003) and >50% of females of non-eruptive ricefield rats (Jacob *et al.* 2004a) should be made infertile to reduce population size (Jacob *et al.* 2008). However, these simulations do not include compensatory effects such as social factors that might lead infertile animals to lose their territories or their status (Caughley *et al.* 1992) and increase either the immigration of fertile animals or the reproduction of subordinate individuals (Chambers *et al.* 1999a; Jacob *et al.* 2004a). Other compensatory processes include enhanced survival, increased fecundity of fertile females, and larger litter sizes (Chambers *et al.* 1999a; Twigg *et al.* 2000; Hinds *et al.* 2003; Williams *et al.* 2007).

Achieving very high proportions of infertility in rodent populations appears challenging but experiments with rodenticides or with individually identifiable animals show that large proportions can be targeted (Beatham *et al.* 2021). For instance, a field study on 51 eastern grey squirrels equipped with PIT-tags found that, following a 5-day pre-baiting, between 90% and 93% of the tagged animals fed on baits from the dispensers within the 4 days baits were made available (Beatham *et al.* 2021). However, whether all individuals would have consumed sufficient bait to lead to infertility remains to be tested with a specific contraceptive bait formulation or a quantitative bait marker.

3b. Can the effort to implement fertility control offset the costs?

For some species and contexts, even when infertility can be imposed on a relatively high proportion of a population, this does not mean that fertility control could achieve management goals, nor that it would be the most cost-effective method (e.g. European rabbits; Twigg *et al.* 2000; Williams *et al.* 2007); European fox (McLeod & Saunders 2014); wild boar, (Croft *et al.* 2021a). Croft *et al.* (2021b) used an individual-based model operating in woodlands to compare the relative effort of eastern grey squirrel population management at a landscape scale, employing both culling and fertility control, alone and combined, as part of an integrated, sequential approach. The results suggested that, at least for the assumed initial squirrel densities, fertility control alone was unlikely to achieve rapid enough reduction to prove a viable cost-effective alternative to culling. However, when fertility control was applied to the low-density populations following short-term culling, eradication could be achieved within the same timescales as continuous culling alone but with substantially lower costs.

3c. Can fertility control integrated with other management methods achieve the management goal within set timeframe?

Ideally, the use of fertility control, alone or integrated with other methods of population control, should be

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compared with alternative rodent management options to assess the effects on population size or on the impact of each method alone or combined, but also to assess feasibility and costs of different options. There is surprisingly very little research in this area.

Modeling can also be used to assess whether the goal of population management can be achieved via coordinated control at the regional scale, for instance over relatively large areas and across land owned by several different stakeholders and to analyze the factors that may affect the desired outcome. For example, modeling can be employed to estimate the proportion of an area where fertility control must be applied to achieve management goals. In all instances, predictions made through modeling will be stronger if based on empirically collected biological data, and these predictions could guide statistically robust, replicated field trials.

DISCUSSION

The renewed interest in the use of fertility control to manage rodents and their impacts stems from a variety of factors including: (1) advances in the understanding of rodent social and spatial behavior when managed using fertility control; (2) availability of new technologies, such as camera traps, that allow researchers to monitor patterns of bait uptake by target and non-target species; (3) availability of new oral contraceptives for rodents that make practical applications plausible; (4) stakeholder interest in developing alternatives to rodenticides; (5) increasing knowledge of economic and environmental impacts of rodents; (6) advances in analytical techniques used in population modeling studies; and (7) internet-associated information exchange raising public awareness of alternative methods to rodenticides.

We have proposed an overarching framework to guide those considering fertility control for rodents. This framework presents a series of logical steps aimed at progressing the testing of a contraceptive from laboratory trials through to field applications. The framework was designed to guide stakeholders as they define a work plan which comprises the key elements to be considered when evaluating the use of fertility control for a rodent species in a specific context.

Fertility control to manage wildlife is often advocated by stakeholders who sometimes fail to appreciate the difficulty of putting this method into practice: the framework highlights the complexities and the potential costs of assessing whether fertility control is the correct choice for managing local populations of rodents or their impacts.

Conducting captive studies, field studies, and modeling in parallel, so that the outcomes of each element can feed into the overall assessment of the impact fertility control on rodents, requires significant funding and multi-year commitment. For instance, a 5-year project on developing and delivering oral contraceptives for eastern grey squirrels, recently started, costs £1 million and employs ecologists, modelers, fieldworkers, and technical staff with expertise in immunology, drug formulation, animal reproductive physiology, and behavior (https://squirrelaccord.uk/squirrels/fertility_control/). This cost becomes relatively minor when placed in the context of the impact of this species: For instance, the sole cost of grey squirrel damage to trees in England and Wales is estimated to be between 2.5 and 45 US$ million per year in lost timber value, reduced carbon capture, damage mitigation, and trees to replace those that died due to grey squirrel bark stripping (Richardson *et al.* 2021). Monetary losses are even higher and influence on human livelihoods more dramatic in other rodent species that are widespread in agro-ecosystems where they cause dramatic losses and pose a health risk to people and livestock (Jacob & Buckle 2018; Singleton *et al.* 2021).

The framework suggests parallel lines of research that can be pursued simultaneously when considering the practical aspects of using fertility control to manage rodent populations and highlights that some of the data are required for the registration of a contraceptive product in a country. Registration is an expensive multi-year endeavor and its requirements vary significantly between countries, with little harmonization across countries (Humphrys & Lapidge 2008). For instance, immunocontraceptives for wildlife in the United States, such as GonaCon$^{\text{TM}}$, are registered as “Restricted Use Pesticide,” which means their use is restricted to USDA APHIS Wildlife Services or state wildlife management personnel or persons working under their authority. In Europe, a similar GnRH-based vaccine named Improvac, used in pre-pubertal male pigs to reduce “boar taint” in the meat of these animals by the time of slaughter, is registered a veterinary medicine. Similarly, in Europe, an oral contraceptive for pigeons, based on a molecule called nicarbazin, is registered as a veterinary medicine, whilet an oral contraceptive for the same species and based on the same active principle in the United States is registered as a general-use pesticide and does not require any special permits or license.

This means that while contraceptives not registered in a particular country can still be tested in that country using experimental research permits, they cannot be routinely used until fully assessed and registered by the relevant regulatory authorities.

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The framework also emphasizes that several knowledge gaps still exist in this field. These include the costs and benefits, including welfare costs, of fertility control and other population-management methods as well as the efficacy of fertility control, particularly leading to measurable reductions in crop damage caused by rodents, at the management level. Defining costs and benefits, for instance by following guidelines for assessing the relative humaneness of different population control options or their social acceptance is challenging (Sharp & Saunders 2011). Very little research on oral contraceptives has been conducted on the potential effects of these compounds on the food chain, but this information is essential because it is a legal requirement for inclusion in a registration dossier. Furthermore, stakeholders' increasing awareness of the potential environmental impacts of contraceptives means that these aspects should be addressed before fertility control is considered for routine field application.

The growing value of crops worldwide, coupled with trends for increased intensification of production, is likely to magnify the impacts of rodents on crop yields. Moreover, increased impacts of cereal invertebrates associated with climate change, with extreme climate events or with disease transmission, might result in unexpected interactions between insect, plant, and rodents and also crop diseases (Singleton *et al.* 2021). Against this background, the major requirement for controlling rodents and their impacts in the near future is to develop and adopt ecologically based population management focused on effective, humane, and sustainable methods. Using the framework proposed will assist decisions on whether fertility control, alone or combined with other population management methods, could be one of the tools to achieve defined management goals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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