EDITORIAL

Fertility control of rodent pests: recent developments from lab to field

This special issue of Integrative Zoology (the official journal of the International Society of Zoological Science and the Institute of Zoology, Chinese Academy of Sciences) comprises a series of papers, aspects of which were presented at the 23rd International Congress of Zoology, a virtual meeting for participants between 22-24th November 2021. The symposium topic at the virtual conference was "Fertility control of rodent pests for better agriculture, ecosystems and human health".

Rodents and their management have been an ongoing challenge across the globe for thousands of years. In recent times, particularly in developing countries where smallholder farmers practice subsistence cropping in order to provide food security plus much needed income for their families, rodents can be both a chronic and acute problem for food production. Farmer incomes provide life's essential amenities, including funds for the education of their children and the provision of a healthy family life. Rodents can impact crops at all growth stages, during storage of food after harvest, and throughout the food value chain. The impact of rodents on the health of our livestock and our families through disease transmission is also very substantial. The World Health Organisation has estimated that 400 million human cases of rodent related zoonoses occur every year from diseases such as leptospirosis, typhus, Lassa fever, plague and many other infections (Colombe *et al*. 2019).

Strategies for implementing integrated pest management require a strong focus on the understanding of the biology and ecology of the pest species needing control. In 1999, the term ecologically-based rodent management (EBRM) was defined (Singleton *et al.* 1999), and since then, EBRM has been widely researched, implemented at local scales and widely adopted across regions and countries from Asia to Africa. The benefits of adoption have been far-reaching and impressive (Singleton *et al*. 2021).

EBRM promotes the use of safe, practical, environmentally friendly tools rather than repeated applications of rodenticides, or other unsustainable, poorly targeted techniques that

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may also be environmentally harmful and affect human health. Fertility control has been proposed as one method that could be added to the EBRM toolbox - potentially it has the breadth of requisite characteristics and is promoted as a safe, benign and species-specific method for managing rodent problems. Many approaches, ranging from immunocontraceptives, plant extracts, industrial chemicals to synthetic steroids have been developed and assessed for a wide range of mammals (Massei and Cowan 2014). Some of these techniques, such as injectable immunocontraceptive vaccines and slow-release implants, are unable to be practically delivered to highly fecund, short-lived, small mammals such as rodents (see review by Jacoblinnert *et al*. 2021b). However, an orally deliverable product which is effective for at least one breeding season and meets the requirements of species specificity either directly or in the method of delivery, with good efficacy and environmental safety parameters, could offer a practical solution. Further consideration to develop a commercial product requires a food bait to be presented in an attractive and stable formulation (e.g. Jacoblinnert *et al.* 2021a) that can be consumed by the target pest rodent at the relevant time, such as just before the onset of the breeding season (Jacoblinnert *et al*. 2021b).

Recent research has focussed on orally deliverable products, in particular the use of a combination of synthetic steroids, estrogen and progesterone (EP-1) and the results have provided an impetus for many laboratory and field studies in a range of rodents in China and in Africa. In China, Professor Zhibin Zhang and his colleagues (Zhang *et al.* 2004) were the first to demonstrate in laboratory studies that EP-1 inhibited the fertility of males and females of several rodent species. Since 2004, Professor Zhang has continued to encourage others to undertake research on the compounds, stimulating several other groups across China to test the effects of EP-1 in a wider range of pest rodents, including follow-up field trials to assess broader population impacts (e.g. Liu *et al*. 2012). Professor Zhang has also attracted research funding to support recent collaborative studies in Tanzania, Zambia, Ethiopia and Indonesia. Some of the papers (Selemani *et al*. 2021; Imakando *et al*. 2021; Stuart *et al*. 2021) in this special issue reflect those collaborative efforts, and additional research efforts by other Chinese researchers. One example in this issue is the first laboratory study of the effects of E, P and EP-1 on the subterranean rodent, the plateau zokor *(Eospalax baileyi)*, a key native species competing with livestock on the Qinghai-Tibet plateau (Kang *et al*. 2021). The early field results using EP-1 for management of the multimammate rat in Tanzania (Imakando *et al*. 2021), and the striped field mouse in China (Chen *et al*. 2021), also reported in this special issue, are promising. Larger areas of treatment and more replication

in field situations are required to see if this research can lead to successful broad scale management of various pest rodents.

Nevertheless before major broad-scale field use of EP-1 can be achieved, other assessments such as determining any short or longer term effects of EP-1 in non-target species are essential. In this special issue, He *et al* (2021) describe their assessments of the dose response effects of a single gavage treatment on domestic chickens, reporting minimal short-term effects on reproductive tissues and general bodily organs. Higher doses disrupted egg-laying production for over 120 days after cessation of a single treatment with EP-1. Previous studies examining the environmental fate of quinestrol have shown that it is rapidly degraded in direct sunlight and also in soil and water (Tang *et al*. 2012; Zhang *et al.* 2014).

Where next?

Laboratory research on EP-1 has shown some variability in response among different rodent species and sexes as well as differences in efficacy depending on the ratios of E and P (1:1; 1:2) used. The palatability of different doses presented within contraceptive baits also varies between species (see papers in this special issue). Understanding such species-specific parameters will be key to developing commercially relevant products in different contexts. Existing field assessments in China and Africa suggest that EP-1 could be at least equally effective to current rodenticide use. However, more field assessments at broad scale with appropriate replication and comparative data are essential to increase our understanding on efficacy and non-target effects across a range of relevant pest control contexts. Timing of EP-1 delivery, its potential impact in complex landscapes and the duration of its effects, both positive and negative, require further study.

As many regions continue to restrict the use of anticoagulant rodenticides, with some localities even considering outright bans on their use (Eisemann *et al.* 2018; Jacob and Buckle 2018; Quinn *et al*. 2019; Turcott 2021), the need for new technological innovations for rodent pest management to prevent disease spill-over and crop damage is greater than ever. Due to such restrictions and the development of genetic resistance, the use of other poisons such as cholecalciferol is growing, but there are few other options.

Another orally delivered contraceptive product, which has been registered for rat control in the USA, is ContraPest - a mix of 4-vinylcylohexene diepoxide (VCD) and triptolide. This liquid product has marked effects in males whereby spermatogenesis is disrupted, while in

females there is some depletion of the primordial ovarian follicles, and more marked, short-term effects on secondary and tertiary follicle numbers. Together, there is a short-term disruption in conception in treated females and a longer period of reversible infertility in treated males. A major disadvantage of this product is that it must be presented in a continuous manner over about 50 days in order to inhibit production of litters for around three successive breeding rounds as shown recently in an arena study for Norway rats (Witmer and Whish 2021).

The registration and commercial use of EP-1 could provide a more viable alternative, particularly as research suggests infertility occurs relatively quickly. Currently EP-1 has been given a temporary registration permit in Tanzania. This registration should allow further field research to be carried out at scale to provide essential knowledge on whether EP-1 can be effective in various agricultural and urban contexts without non-target environmental impacts. These outcomes could point the way to broader uptake of EP-1 as an important tool in the implementation of sustainable rodent pest control.

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