

1. Why control grey squirrels?

The grey squirrel (*Sciurus carolinensis*) is a non-native species which was first introduced to the UK from North America in 1876. Populations of grey squirrels grew rapidly following multiple introductions. [Natural England's Joint Publication JP025](#)¹, published in 2018, estimates the grey squirrel population of the UK at circa 2.7 million, against circa 287,000 native red squirrels (*Sciurus vulgaris*). The study however contains a number of caveats about the lack of survey data available to it and the unreliability of the methods used, resulting in a high likelihood that its estimate for the current red squirrel population in Britain is an overestimate. The red squirrel is now classified as endangered on the Red List for Britain's mammals.

i) Impact on the UK treescape

Grey squirrels damage our forests by stripping the protective bark from trees. This damage can happen from the very base of the tree all the way through the canopy. Bark stripping negatively impacts tree growth and vitality. Open wounds are created that can weaken, stress, and kill trees, with subsequent costs of restocking, loss of timber value, reduction in carbon sequestration and impacts on biodiversity. Planted or naturally regenerated trees aged between 10 to 50 years are most vulnerable to bark stripping. The open wounds formed by bark stripping increase the susceptibility of trees to various pests and pathogens, such as fungi, that can be transmitted by squirrels. The resulting damage is a serious problem for the UK when it is working hard to increase its tree and woodland cover for the many essential benefits they provide. A [joint report](#) published in 2021 by the Royal Forestry Society, Forestry Commission, The National Forest, Natural Resources Wales, and Woodland Trust estimate the cost to be at least £1.1 billion over the next 40 years². The UK Squirrel Accord partnership has created a [short film](#) to raise awareness of this issue.

ii) Impact on red squirrels

Grey squirrels are one the main reasons for local extinctions of red squirrels in large areas of the UK. This is due to competition for food and habitat, and the spread of squirrel pox virus, which is almost always deadly to red squirrels but not greys.

iii) Impact on songbirds

Some studies raised the possibility of grey squirrels' predation on eggs and nestlings of songbirds, although the extent and impact of this is still unclear³.

2. How are the grey squirrels controlled?

Grey squirrel management is currently carried out by various methods of culling such as trapping and shooting. The use of warfarin for grey squirrel control has not been permitted since July 2016. Despite extensive culling, the number of grey squirrels continues to grow.

3. Why do we need fertility control when there are culling methods available?

Shooting and trapping can be expensive. For instance, in 2015, 21,000 grey squirrels were culled in the North of England to protect red squirrel populations and tree health. Costs are variable, but the work by Red Squirrels Northern England cost an estimated £60 per squirrel. Culling alone has so far failed to bring the problem under control because the reproductive rate of grey squirrels far exceeds the numbers culled. Oral contraceptives represent an alternative and complementary means of grey squirrel management when used either as a standalone method or in addition to culling.



Fig. 1. Bark stripping by grey squirrels.

4. Who is doing this research?

The National Wildlife Management Centre (NWMC), which is part of the Animal & Plant Health Agency (an executive agency of Defra). The NWMC provides evidence, impartial advice and services, primarily to Defra, to resolve human-wildlife conflicts. Working with international partners, it draws on extensive expertise in wildlife management, invasive non-native species, wildlife disease, animal ecology, population modelling, and animal welfare. As a wildlife management tool, the NWMC has been studying fertility control in different species for around 20 years. The NWMC includes the GB Non-Native Species Secretariat and expertise in all areas of wildlife management.

Two oral contraceptive routes are under research. The first is a vaccine, which is currently being tested for its contraceptive effectiveness on grey squirrels and was originally developed by the National Wildlife Research Center (NWRC), part of the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), in collaboration with NWMC and other European partners. The NWRC provides Federal leadership and expertise to resolve wildlife conflicts that threaten agricultural and natural resources, human health and safety, and property. The second contraceptive being tested is DiazaCon, which is based on a cholesterol-inhibitor drug.

5. How do contraceptives work?

The contraceptive vaccine stimulates the production of antibodies that bind to the Gonadotrophin Releasing Hormone (GnRH), a hormone that is responsible for the production of sex hormones (e.g., testosterone, estrogen, and progesterone). By binding to GnRH, the antibodies reduce the GnRH's ability to stimulate the release of these sex hormones. Animals remain in a non-reproductive state as long as a sufficient concentration of antibodies is present.

The cholesterol-inhibitor DiazaCon decreases the concentration of cholesterol within an animal's body. As cholesterol is needed for the synthesis of sex hormones, inhibition of cholesterol synthesis by DiazaCon indirectly inhibits reproduction.

6. Has this been shown to be effective in other animals?

A similar contraceptive vaccine (GonaCon), developed by the NWRC, is registered in the US as an injectable single-dose contraceptive and has been successful in managing populations of white-tailed deer, horses and donkeys. In addition to these species, GonaCon is also effective on other wildlife, including California ground squirrels, Eastern fox squirrels, prairie dogs, Norway rats, feral cats, goats, cattle, horses, badgers, kangaroos, wild boar, bison and elk.

The NWMC carried out several studies on GonaCon and showed that a single dose caused infertility in 92% of female wild boar for at least 6 to 8 years. Pilot studies of a novel oral contraceptive vaccine, conducted by the NWMC and collaborators, also showed that 60% of laboratory rats were rendered infertile when the agent was delivered directly in the animals' mouth⁴. It is hoped that encapsulating (see below) this vaccine may increase the efficacy and duration of the contraceptive effect.

Trials are ongoing on a new formulation of the oral contraceptive vaccine to determine efficacy and duration. This formulation involves the use of the natural capsule of a pollen or spore grain (known as a SpECs). The SpECs containing the vaccine are added to a food bait. When the animals eat the bait, the 'sticky' SpECs, which protect the vaccine from being broken down too quickly in the gut, attach to the intestine and release the fertility agent into the blood stream. This encapsulation technique is already successfully used to deliver many different types of pharmaceutical chemicals, including vitamins and common painkillers.

7. Do they work on both males and females?

Yes – as the vaccine targets the parent GnRH hormone that makes both female and male sexual hormones, it can render both sexes infertile. DiazaCon also affects cholesterol in males and females.

8. How is the contraceptive delivered to the animals?

The contraceptive will be added to a food bait that is delivered in a grey squirrel-specific feeding hopper (see Q21). The palatability of bait to grey squirrels is being tested in captivity and field trials.



Fig. 2 Hopper used to deliver baits to grey squirrels.

9. Are there any health or welfare effects?

No side effects were observed in the first studies on either of the oral contraceptives being tested. The injectable vaccine may, in some species, cause an injection site reaction similar to that produced by other injectable vaccines, whilst in other species no side effects have been observed.

10. Will non-target species be affected?

The vaccine is mammal-specific, so birds are not at risk. DiazaCon may affect birds and mammals. In order to reduce the possibility of non-target wildlife being exposed, a species-specific delivery system (grey squirrel feeding hopper) is being tested. To mitigate the risk of spillage of bait containing contraceptives, the project will formulate the bait as a paste, such as hazelnut paste, that animals must consume inside the metal hopper. Bait palatability and bait uptake by target and non-target species will be monitored in captivity and in the field using camera traps.

11. What are the risks to the environment or to other animals?

The risks to the environment and to non-target species, including predators and scavengers, will be evaluated as part of the data required for the registration dossier. The hoppers and the bait formulation will ensure that bait uptake by non-target species is minimised.

The fertility of squirrel predators is unlikely to be affected as the contraceptive vaccine is a protein (not a hormone), that will be broken down in the tissues and the stomach of the squirrels. The amount of active product (if any) passed onto predators should be very small, and unlikely to have any biological effect. The breaking down of the vaccine also means that it is unlikely that any

active components will be passed into the environment via excretory products such as faeces or urine. The effects of DiazaCon will be tested in captive trials. Full detailed data on secondary hazards will be collected when registration is considered for these drugs.

12. Are there any risks to humans?

The bait will be delivered in grey squirrel-specific feeding hoppers, clearly labelled with hazard signs and placed on trees so that the risk to non-users would be negligible. In addition, the quantities of the appropriate active ingredient needed for squirrels are very unlikely to have an effect on humans (unlike rodenticides which are known to be highly toxic to humans) either from direct ingestion or from eating squirrels. The final formulation may include adding human taste repellents (such as Bitrex, which is common practice for rodenticides). The registration dossier will include product information and labelling for safe use.

13. Can we target enough animals to reduce the population?

The NWMC developed a mathematical model to compare the relative effort of squirrel population management at a landscape scale using both culling and fertility control, alone and combined, as part of an integrated, sequential, approach⁵. The results suggest that, when applied to low density populations following short-term culling, fertility control could achieve the same effect within the same timescales as continuous culling alone but with substantially lower costs.

In parallel, the project assessed the proportion of the population of squirrels that consume the bait containing the contraceptive at different times in the year (summer or winter). The project is also testing how different densities of hoppers affect grey squirrel bait uptake, to maximise the proportion of squirrels exposed to the contraceptive. These data will be used to assess how we can target enough grey squirrels with fertility control to effectively reduce the number of animals in an area.

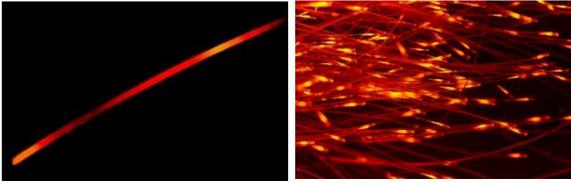


Fig. 3. The marker Rhodamine B (RB), detectable as fluorescent bands in whiskers (left) and hair (right) of animals that ingested RB-treated baits, is used to assess the proportion of grey squirrels that will be affected by bait-delivered contraceptives.

14. By when do you hope to start using the contraceptive in the wild?

Pilot trials will be conducted in the wild as part of the current five-year research project. Further landscape-scale field trials will then be needed to gather the data needed to complete registration of the final products.

15. Will oral contraception be publicly supported?

A recently published UK survey on social acceptability of methods used to manage grey squirrels in the UK found that contraception is considered the most acceptable control method, with 61.5% responders indicating that it is either acceptable or highly acceptable⁶.

16. Has this been tried before in squirrels unsuccessfully?

In 2013, Forest Research carried out a study, in collaboration with NWMC, to test the contraceptive effect of the cholesterol-inhibitor DiazaCon⁷. However, fertility could not be measured because although the treated squirrels did not breed, the control (untreated) animals also did not breed. For this new research project, the NWMC set up a breeding colony of grey squirrels to test the effects of fertility control agents in captivity. Besides litter production, other indicators such as hormone concentration and reproductive physiology parameters are monitored. For the vaccine tests, captivity studies will also quantify the levels of antibodies, routinely measured as infertility indicators in studies of the vaccine.

17. By how much are you hoping to reduce the grey squirrel population, and in which geographical areas?

Based on data collected in the field throughout the project, the mathematical model created will assess the effort and time required to eradicate local populations of grey squirrels at different scales (e.g., local woodland, county, etc.), as well as the proportion of a grey squirrel population that should be targeted by oral contraceptives to achieve a set reduction in the number of animals.

18. How many doses will be needed?

In initial trials of an oral GnRH-based vaccine, 6 doses delivered within a month were sufficient to make 60% of the rats infertile⁴. The original DiazaCon trial saw grey squirrels fed daily for 10 days⁶. The NWMC will test different doses, concentrations, frequency of dosing of these contraceptives, and duration of effects, to maximise the number of animals made infertile. The data collected in the field on patterns of bait consumption by squirrels will be used to design field applications that maximise grey squirrels' uptake of baits containing contraceptives.

19. Could these contraceptives be used on other species?

The GnRH hormone is very similar across all mammal species and indeed the injectable vaccine has successfully reduced fertility in many different wild mammal species. It is expected that an oral GnRH-based contraceptive will be effective on a wide range of mammals, although the dose and the frequency of application may vary between species. The possibility of applying the same vaccine to control other wildlife would scale up field applications, thus increasing the potential commercial return of this drug for investors. DiazaCon might be considered for a wider number of mammal and bird species.

20. How long before there is a contraceptive that can be used in the field?

The aims of the five-year study are to develop an oral contraceptive for grey squirrels and to assess how the contraceptive could be delivered in field applications via a species-specific feeding hopper. In years four and five of the project, the NWMC will work with relevant UK authorities to assemble a registration dossier. Through liaison with the regulatory authorities, and collecting data for the registration dossier in the course of the research, the project will reduce the time and cost of the registration process.

21. Can we use “old” warfarin dispensers to deliver contraceptives in the future?

The NWMC is testing a modified version of the bait hopper originally designed by Forest Research to deliver warfarin. Once it is proven that grey squirrels can feed from these hoppers but other species (including red squirrels) cannot access the bait, we will know whether the “old” dispensers can be modified to deliver contraceptives to grey squirrels.

22. Who is funding the research?

The UK Squirrel Accord (UKSA) partnership and supporters are funding the research. Fundraising is ongoing to secure the final target. More information and updates on the research can be found on the UKSA website: www.squirrelaccord.uk

¹ Natural England 2018. A Review of the Population and Conservation Status of British Mammals: Technical Summary. *Natural England Joint Publication JP025*, 17-18.

² Royal Forestry Society 2021. *An Analysis of the Cost of Grey Squirrel Damage to Woodland*. Available online www.rfs.org.uk

³ Broughton, R.K., 2020. Current and future impacts of nest predation and nest-site competition by invasive eastern grey squirrels *Sciurus carolinensis* on European birds. *Mammal Review*, 50(1), pp.38-51.

⁴ Massei G., Cowan D., Eckery D., Mauldin R., Gomm M., Rochaix P., Hill F., Pinkham R., Miller L. A. 2020. Effect of vaccination with a GnRH-based oral immunocontraceptive on immune responses and fertility in rats. *Heliyon*, 6:e03781.

⁵ Croft S., Aegerter J.N., Beatham S., Coats J., Massei G. 2021. A spatially-explicit population model to compare culling versus fertility control to reduce numbers of grey squirrels. *Ecological Modelling*, 440, 109386.

⁶ Dunn M., Marzano M., & Forster J. 2021. *The red zone: Attitudes towards squirrels and their management where it matters most*. *Biological Conservation*, 253, 108869.

⁷ Mayle B., Ferryman M., Peace A., Yoder C., Miller L., Cowan D. 2013. The use of DiazaCon™ to limit fertility by reducing serum cholesterol in female grey squirrels, *Sciurus carolinensis*. *Pest Management Science*, 69, 414-424.