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GM ANIMALS

Use of genetically modified (GM) animals in research has increased tenfold in the last decade. This has occurred against a general decline in the overall number of animals used in scientific procedures. This briefing describes recent trends in the use of GM animals, examines the underlying reasons for these trends and looks at possible future developments. Specific welfare issues relating to the production and use of GM animals are also examined.

Genetic modification of animals

Techniques for 'cutting' genes from one organism, and 'pasting' them into another were first developed using simple, single-cell organisms such as bacteria in the 1970s. Adapting such techniques for animals requires inserting the 'novel' gene into every cell in an animal's body. This can be achieved by incorporating genes into animals at a very early stage in their development (see box opposite) although the success rate of such techniques is low (in the region of 1-10% for rodents).

The first genetically modified animals were **transgenic** (i.e. possessed active copies of a gene or genes inserted from another individual) mice, created in 1980. Since this time, further techniques have been developed. As well as inserting genes, it is now possible to 'knock out' specific genes, or to make larger-scale genetic alterations. Such animals are now generally referred to as **GM animals**. This term includes transgenic animals and those genetically altered by other means. But it does not include animals produced by selective breeding nor those with random genetic alterations (mutations) induced via exposure to chemicals or radiation.

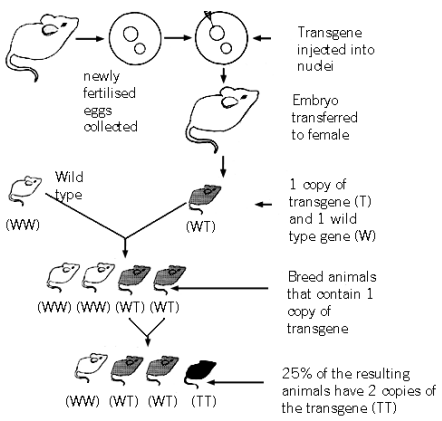
Animals (Scientific Procedures) Act 1986

All scientific procedures on animals are regulated by this Act (see box page 2). It defines what constitutes a scientific procedure and to which animals the Act applies. As outlined in more detail in the box, the Act

Producing GM animals

Most transgenic animals have been produced using microinjection (see figure below). Copies of a gene are injected into a newly fertilised egg with the aim of incorporating the gene into the egg's DNA. If this occurs, it will be copied each time the cell divides, and may be present in every cell in the body. However the cells will contain only one insertion of the genetic material; normally cells carry two copies of genetic sequences (one from the mother and one from the father). GM animals that carry two of the genetic insertions can be obtained through breeding (see figure). Overall, the method is inefficient because insertion into the DNA of the host cell is random – it can occur at any point. If it inserts into another gene then it may disrupt that gene's normal function. Such insertions would probably prove lethal before the animal was born, although in some cases the effect may only become apparent later in the animal's development.

Another approach is the genetic manipulation of (stem) cells isolated from embryos. New genes can be inserted into these cells or targeted genes 'knocked out'. The cells are introduced back into early stage embryos where they will give rise to mosaics – animals where some cells are genetically altered and others are not. Breeding from those animals carrying the alteration in their sex cells will eventually produce GM animals that carry the alteration in all of their cells.



Alternatives to animal use

The 1986 Act requires alternatives to animals to be used where possible. Animal welfare groups promote the concept of alternatives to animal use via the '3 Rs'. In the short-term they see **reduction** (e.g. reducing animal use through better experimental design, improved access to databases, and harmonising regulations) and **refinement** (e.g. to minimise pain and suffering) as the main ways forward. In the longer term, such groups hope that research will develop alternatives to **replace** the use of animals in experiments altogether. Research areas include:

- Use of lower order species (insects, bacteria or plants).
- Development of test-tube (*in vitro*) techniques using cultures of animal or human cells, organs or tissues. Examples include the development of artificial skin for toxicity testing, and the use of embryonic stem cells to test chemicals for effects on embryos.
- Use of computer models to simulate interactions between different body systems.
- Increased use of human volunteer studies.

regulates where scientific procedures take place, what can be done and by whom. At the heart of the Act is a requirement to weigh the potential costs of the proposed research in terms of the adverse effects on the animals against the likely benefits (e.g. to humans, other animals or the environment). The Act also embodies the 3Rs concept of non-animal alternatives (see box above).

Trends in GM animal use

Information on a wide range of different aspects of animal use in scientific procedures is collected each year by the Home Office; the last year for which such data is available is 1999. Since 1990, information has been collected on the genetic status of animals. Categories used by the Home Office include:

- Genetically normal animals.
- Non-GM animals bred to possess genetic defects that are harmful to them ('harmful mutants').
- Transgenic/GM animals. The category of 'transgenic animals' was added in 1990, but was replaced in 1995 with the wider category of 'GM animals'.

Recent trends in procedures involving animals of different genetic status are shown in the figure opposite. Three main trends are apparent since 1990:

- a slow decline in the overall number of animal procedures, due to a fall in the use of genetically normal animals (from just over 3 million in 1990 to slightly under 1.9 million in 1999);
- an overall rise in the use of animals with harmful mutations (from ~143,000 to ~251,000).
- a tenfold rise in procedures using transgenic/GM animals from just under 50,000 to over 500,000; around one in five of all animal procedures in 1999 involved GM animals.

Mice account for the majority (98%) of procedures involving GM animals with the rest comprising rats (1%) and pigs, sheep, domestic fowl, amphibians or fish (1% combined). One reason for this is that the mouse genome has been highly studied and the similarities between it and the human genome are well documented.

Animals (Scientific Procedures) Act 1986

A regulated procedure is defined as being any experimental or other scientific procedure applied to a protected animal which may cause pain, suffering, distress or lasting harm. This includes breeding animals with genetic harmful defects, and using animals to produce blood preparations or tumours, but excludes procedures involved in standard veterinary, agricultural or animal husbandry practices.

A protected animal was originally defined as any non-human living vertebrate, including larval or embryonic forms that have reached a certain stage in development. This definition has since been extended to include an additional (invertebrate) species, *Octopus vulgaris*.

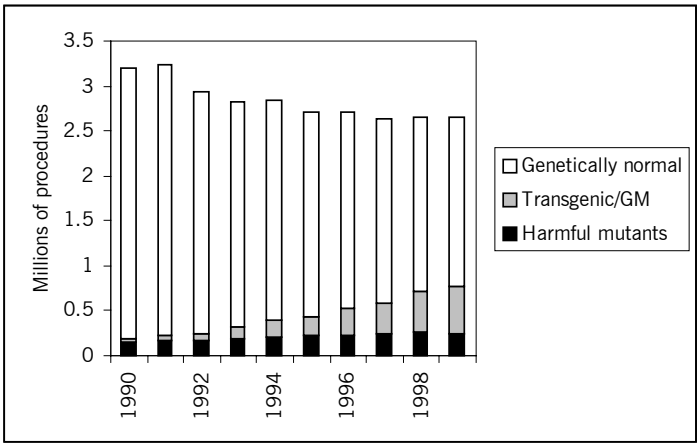
Licensing – all procedures must take place on licensed (designated) premises, form part of a licensed programme of work (for which a project licence has been granted) and be conducted by a researcher with a personal licence.

Designated premises - premises must meet standards of animal housing and care laid down by the Home Office and are subject to regular visits from the Animals (Scientific Procedures) Inspectorate. Establishments that breed certain animals for laboratory use, and those that obtain or supply laboratory animals must also have certificates of designation. In 1999, there were 296 designated premises in the UK.

Project Licences - the Act requires potential costs of proposed research to be weighed against likely benefits. Inspectors are responsible for making such judgements, taking into account the amount and duration of suffering caused, number of animals used, and whether anaesthetics are used or other action is taken to reduce suffering.

Personal licences – are designed to ensure that any person conducting animal procedures is suitable and competent to do so. Applicants must be 18 years or older, must have completed an accredited training course and provide details of education, qualifications and relevant experience. First time applicants must also have endorsement from a qualified sponsor. Licences are reviewed every 5 years and revoked if the researcher is no longer active. In 1999, there were around 13,700 active personal licences in the UK; some 1,791 new licences were granted and 1,862 revoked.

Trends in procedures by genetic status (1990-99)



Of the 511,607 procedures involving GM animals in 1999, around 70% were primarily concerned with breeding (e.g. used to generate and maintain populations with a specific genetic modification). As illustrated in the figure on the first page, not all of the offspring from breeding programmes to produce GM animals actually

carry the genetic modification. Most of the remaining procedures (25% of total) were involved in fundamental biological research (see box, opposite) on studies of gene function and genetic disease, with the rest (5%) used in applied studies (e.g. testing new drugs).

Issues

Current uses and likely future trends

Fundamental research

Current uses of GM animals are outlined in the box opposite. The number used in fundamental research is likely to continue to rise in the coming years. One factor driving this trend is the recent publication of a first draft of the human genome. Researchers now know the sequence of some 30-40,000 human genes, but do not know the function of the vast majority of them. Studies involving GM animals are designed to help identify genes involved in common diseases such as cancer and diabetes. A recent Royal Society working group report [1] on GM animals highlighted the increasing importance of GM animal models to study disease processes and develop better drug treatments.

Use of higher order species

To date, nearly all research applications involving GM animals have used mice or rats. However, because rodent models may not exactly mimic human disease, some researchers[2] see a need to use higher order species to develop better models. A step in this direction came in January 2001, when scientists in the US announced the birth of the first GM monkey (ANDi), containing a gene for a fluorescent protein. While this was hailed as a breakthrough by some, others[3] expressed concerns. Any move to using more GM animals of higher order species – particularly primates – would be opposed by animal welfare groups.

Toxicological testing

Few GM animals are currently used in toxicological tests. This could well change in the near future; as explained in the box opposite, several commercial strains of GM rodents have been created specifically for use in tests to assess whether chemicals cause mutations or cancer. The extent to which GM animals are routinely used for such tests will depend in part on on-going evaluations to determine whether the tests will be acceptable to regulatory bodies around the world. Welfare issues raised by use of such animals are discussed below.

Agriculture and other uses

The recent Royal Society working group called for more research to develop GM agricultural animals, noting that modifying animals to resist conditions such as trypanosomiasis (an insect-borne disease affecting cattle throughout Africa) would help farmers in developing countries. GM animals have also been used in developmental studies and developed for medical purposes such as xenotransplants and the production of therapeutic proteins. In practice it is doubtful whether any of these approaches will have a big impact on the numbers of GM animals used in the near future. Use in agriculture is likely to be limited by lack of public acceptance while the whole area of xenotransplantation is beset by concerns over safety. Several companies are already using GM sheep, goats or cattle to produce therapeutic proteins, but such operations use only relatively small numbers of animals.

Main uses of GM animals

Animal models of human disease - many human diseases have a genetic basis. Some are caused by faults in single genes (e.g. cystic fibrosis), others (e.g. cancer, diabetes and heart disease) by a complex interaction between environmental factors and many different genes. Once research has identified a gene or genes implicated in human disease, genetic modification can be used to try and create an animal model of that disease. Researchers have used such models extensively to investigate disease processes, looking at the effects on all of the organs and systems in the organism. Animal models are also increasingly being used in applied studies to screen potential new drugs. However, there is some debate as to the usefulness of such models because they often do not exactly mimic the human disease.

Studies of gene function – GM animals are likely to be used widely in the race to figure out what each of the 30-40,000 human genes actually does. More often than not, a mouse equivalent to a human gene of interest can be identified, targeted and 'knocked out'. Another approach is to genetically modify animals to over-produce specific gene products. Studying the biological consequences of such approaches may reveal the underlying function of a gene.

Toxicity and other types of testing. Animals have long been used to test whether new products contain chemicals that can damage DNA, thereby causing mutations or cancer. GM animals are **not** widely used in such tests at present, although several strains have been developed for such purposes and are currently being evaluated. GM mice and rats have been developed to be more susceptible to chemicals that cause cancer. Use of GM animals in such tests could reduce the time taken to evaluate chemicals (from ~2 years to 6 months) and require fewer animals.

Safety

The Royal Society identified a number of potential safety concerns arising from use of GM animals – they might harm human health (if eaten), affect the environment /ecosystems (if they escape) or cause adverse effects on other animals – but considered the likelihood of these happening as being "*relatively low*". In practice, the Society was most concerned about the rearing of GM fish in marine pens because of uncertainty over the consequences of inter-breeding between GM and wild fish. It endorsed a call from the Royal Society of Canada for a moratorium on rearing GM fish in marine pens.

Animal welfare

Producing genetic modifications

Welfare concerns about producing GM animals centre on the inefficiency of the techniques; only a small proportion of implanted embryos develop successfully into GM animals. A 1994 study[4] using GM mice found that:

- out of a total of 1,585 embryos, some 1,360 survived implantation into surrogate mothers;
- just under 400 (29%) of these survived to weaning;
- less than 100 (7%) developed into adult GM mice.

While the efficiency of such techniques may have improved since, more recent data on mortality rates and ages of death are hard to find. No figures are available on the overall number of deaths occurring prior to birth during the production of GM animals. Nor is information routinely collected on the stage of foetal development at which failures occur, although most are thought to occur between implantation and birth. The later the stage of development at which failure occurs, the greater the animal welfare implications, both for the foetus and for the surrogate mother.

Harmful genetic modifications
While genetic modification is not necessarily harmful, some types may give rise to greater concerns over animal welfare than others. For instance, knocking genes out to study their function, using GM animals to model human disease or modifying mice to be more susceptible to developing cancer (see box Page 3) all have potential welfare implications. However, replacing normal animals with GM mice in tests to see whether chemicals cause cancer could require fewer animals to yield a statistically valid result. The Animals Procedures Committee (APC[5]) estimates that each test would use ~120 animals, rather than the 400 or so needed with normal mice. In such cases, as with all animal procedures, decisions on whether to licence the project have to weigh welfare costs against potential benefits arising from the research.

Weighing costs and benefits
The Royal Society report considered the welfare costs and potential benefits of GM animals, concluding that:

- **Costs** – the application of GM technology "*is capable of generating special welfare problems*" but "*no qualitative distinction in terms of welfare can be made between genetic modification using modern GM technology and modification produced by artificial selection, chemicals or radiation*".
- **Benefits** –the Royal Society concluded that the development of GM animals has been "*hugely beneficial in many areas, not least on research into the causes and possible treatments of disease*".

As far as costs are concerned, the Royal Society called for publicly-funded research on the extent of any adverse welfare effects involving GM animals (including detailed analyses of the genetic control of muscle growth and physiology) and for the results of such research to be openly available. Animal welfare groups such as FRAME (Fund for the Replacement of Animals in Medical Experiments) suggest[6] that the potential animal welfare costs of GM technology "*can be severe and difficult to predict*". It wishes to see greater emphasis on the development and use of non-animal alternatives (see box on page 2) as "*the best way to eliminate welfare costs and increase the benefits to animals and humans alike*".

FRAME has also claimed that the benefits of research on GM animals have been overstated, suggesting that "*the benefits have been relatively few, considering the enormous numbers of animals that have been used"*. While accepting that research into gene function has obvious benefits to mankind in some cases, animal welfare groups are anxious to avoid a situation where GM animals are used to investigate the function of each of the 30-40,000 human genes systematically. They also question the benefits of GM animals as models of human disease. Debate here focuses on the extent to which results gained in GM animal models can be extrapolated to humans. However, the Royal Society report concluded that there was "*a strong scientific case for using GM animals to understand human disease*".

Alternatives to animal use
As noted previously, procedures are authorised only if there are no scientifically suitable non-animal alternatives available. Groups such as FRAME and the RSPCA[7] promote the development of alternatives to the use of live animals through the 3 Rs approach outlined in the box on page 2. The ultimate aim of this approach is to replace the use of live animals in experiments altogether, although there is debate as to how far this is achievable. A difficulty here is whether it is possible to develop alternatives that allow 'whole organism' interactions (e.g. between different systems and organs) to be studied. Animal welfare groups concerned about increased use of GM animals have formed a joint[8] working group to look at refinements in the generation and management of GM rodents. The development and use of alternatives is also one of the subjects being considered by an *ad hoc* House of Lords Committee on Animals in Scientific Procedures, which will report early in 2002.

Overview

- Use of GM animals in scientific procedures has increased tenfold over the last decade. Continuation of this trend could reverse the decline in the overall number of animal procedures performed.
- GM animals are currently mainly used in studies of gene function and human disease. Publication of the first draft of the human genome means that use in such studies is likely to continue to rise.
- GM technology offers potential benefits but may also have implications for animal welfare. Assessing costs and benefits and weighing one against the other is far from straightforward. The APC recently consulted on the costs and benefits of GM animal use (expected to report in summer 2001).

Endnotes

1 The use of GM animals, May 2001, Royal Society, London
2 Animal research in the post-genome era, Lancet, **357**, 817 (2001)
3 Editorial, Alternatives to Laboratory Animals, **29**, 1-2, (2001)
4 Wight DC & Wagner TE, Mutation Research **307**, 429-440 (1994)
5 The APC is an advisory body established and appointed under the Animals (Scientific Procedures) Act 1986
6 FRAME Press Release, 21 May 2001
7 Royal Society for the Prevention of Cruelty to Animals (RSPCA)
8 The British Veterinary Association Animal Welfare Foundation, FRAME, RSPCA and the University Federation for Animal Welfare

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