The response reproduced below was submitted to the consultation held by the Nuffield Council on Bioethics on the ethics of research involving animals during October-December 2003. The views expressed are solely those of the respondent(s) and not those of the Council.

Genewatch UK

"There is a striking mismatch between the traditional concern of regulators with issues of risk and safety, and that of the public, which centres on questions of moral acceptability."
Biotechnology and the European Public Concerted Action Group[1].

GeneWatch UK is a small not-for-profit policy research group which monitors developments in genetic technologies. The impacts of genetic engineering, cloning and other genetic technologies on animal welfare is one of our areas of interest. We welcome this opportunity to contribute to the Nuffield Council's thinking in this area.

Our comments are focussed on Questions 2, 5 and 6 but clearly involve more general views about the use of animals in experiments. GeneWatch UK published a detailed report on the subject of GM and cloned animals in 2002, 'Genetically modified and cloned animals. All in a good cause?'. We include a copy of this report as part of our submission to the Council.

Introduction

Overall, GeneWatch UK takes the position that fundamental alteration of the genetic code of other species is a new, significant and damaging step in our relationship with them. Furthermore, both genetic modification and cloning of animals are extremely inefficient processes with only 1-3% success rates. Not only may the GM animals created 'successfully' suffer, but many other 'failures' will also. The total impact on animals of both these techniques has to be fully acknowledged and justified.

Our position, the reasons for which are explained in the following sections, is this:

GeneWatch believes that society must establish boundaries for the genetic modification of animals and a framework for their evaluation including, as a minimum, that:

- **the genetic modification or cloning of companion animals (including dogs, cats and horses) is not allowed;**
- **the genetic modification or cloning of farm animals (including for drug production) is not allowed;**
- **experiments intended to reduce the sentience of any species are not allowed;**
- **a presumption against the genetic modification and cloning animals in other situations should only be allowed if it will contribute significantly to the relief of serious human suffering and there is an absence of more acceptable alternatives;**
- **there should be explicit consideration of alternatives, with the onus on the applicant wishing to undertake genetic modification of animals to demonstrate that other approaches could not achieve broadly similar goals.**

Transgenic work is seductive, fashionable – and expensive. It is frequently linked to drug development, which is generally concentrated on those diseases for which there

[1] Wagner W *et al.* Anon. Europe ambivalent on biotechnology. *Nature* 387: 845-847, 1997.

will be adequate financial returns. There is a danger that the glamour associated with genetic modification, the technological possibilities and the potential profits in pharmaceuticals will drive development rather than medical or social need. There has already been a vast increase in the number of animals (mainly mice) genetically modified to have painful and distressing diseases.

Whilst our position includes companion and farm animals, we do not consider these in detail below except to say that research using animals to these ends is clearly unjustifiable in our view.

Our main conclusions on failings in the current regulatory and public information system are that there is:

- a total failure to provide information on applications to use GM animals in research, preventing public scrutiny of decision making;
- an over optimism in the power of genetic modification to produce appropriate animal models of human disease.

GeneWatch also wishes to emphasise that an ethical debate about the production and use of GM animals cannot be separated from a detailed and rigorous assessment of the claimed benefits in the light of alternatives.

Do GM animals raise new or different issues?

For GeneWatch and, we believe, the wider public, the genetic modification of animals arouses grave ethical concerns about species integrity as well as all the questions normally associated with animal experimentation. A Eurobarometer survey showed that the public is primarily concerned with the question of whether animals *should* be genetically modified rather than questions of usefulness or risk. There was effectively a 'moral veto' on the pursuit of this type of biotechnology[2].

Of course the consideration of GM animals cannot be undertaken in isolation from the use of animals in general. 2.2 million cattle, 19 million sheep or lambs, 14.7 million pigs[3] and 803 million chickens and turkeys[4] were slaughtered in the UK in 1999. Most UK farm animals are raised in intensive systems in conditions which allow them little if any quality of life or opportunity for normal behaviour[5]. Harmful genetic effects have been bred into farm animals[6], dogs[7] and laboratory mice using traditional breeding methods. Intensive agricultural practices cause more animal suffering, at least in terms of numbers, than genetic modification. However, existing treatment which denies animals a reasonable quality of life does not justify the creation of a new arena where animals potentially or actually suffer.

The creation of GM animals also represents a significant alteration in our relationship to other species and represents a further step towards seeing them purely as commodities without regard for their inherent worth as sentient beings. This is at

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2 Wagner W *et al.* Anon. Europe ambivalent on biotechnology. *Nature* **387**: 845-847, 1997.

3 DEFRA. *UK Slaughter statistics- monthly*. July 2001. (available from http://www.defra.gov.uk/esg/econfrm.htm)

4 DEFRA. *UK Poultry slaughterings*. July 2001. (available from http://www.defra.gov.uk/esg/econfrm.htm)

5 Turner J. Factory Farming and the Environment. Compassion in World Farming, Hampshire, 1999.

6 Dickman S. Gene mutation provides more meat on the hoof. *Science* **277**: 1922-1923. 1997.

7 Royal Society. *The Use of Genetically Modified Animals*. The Royal Society, London 2001.

odds with current trends in society, which increasingly see animals as having rights[8]. For example, the European Directive of 1986 on animal experimentation forbids the use of an animal if another scientifically acceptable method exists[9]. The 'normalisation' of transgenic animals in laboratories is in opposition to this trend and could indirectly impact on wider attitudes towards animals.

Species integrity and crossing species barriers

The concept of 'telos' originated with Aristotle, who contended that every creature had a goal in life which he designated its telos. It has since been described as the 'dignity and integrity' or 'inherent worth' of a being[10]. Few would dispute that every human has telos and, crucially, many people take for granted that it is also possessed by animals. Many ways in which animals are treated may be seen as assaults on their integrity. For example, the ability to live a normal life is denied by many intensive agricultural systems. This does not, however, justify other infringements.

Germ line genetic modification is a fundamental alteration of the genome, one of the most basic attributes of both individual and species. It continues beyond an individual's lifetime, reaching into future generations of animals. Certainly, genetic codes change over evolutionary time and to a very much lesser degree as a result of breeding programmes. However, the direct, deliberate alteration possible with genetic modification is qualitatively different. The ability to 'engineer' genes unconstrained by species boundaries and the haphazard nature of genetic recombination are entirely new.

There are also fears that these developments could herald a eugenic future with humans also undergoing genetic modification[11,12]. These fears are not unfounded since techniques used on people are generally first used on animals and there is already a group in Italy which has publicly stated its intention to clone human beings[13].

All this has provoked strong reactions, leading to accusations of scientists 'playing god'[14] and references to 'Frankenstein's farmyard'[15]. These reactions are not facile. They stem from a deep unease that genetic modification, especially when it involves crossing species boundaries, is an assault on the sanctity of life and represents a seismic shift in our relationship to the natural world.

The human-animal relationship

The advent of transgenic technology has added an entirely new dimension to this relationship as we now have the power to alter animals, mix species and create a different animal if the existing one does not conform to our requirements. This treats animals as objects for our convenience and is a significant further step towards

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8 Mepham B. 'Wurde der Kreatur' and the common morality. *Journal of Agricultural and Environmental Ethics* **13**: 65-78, 2000.

9 European Commission. *Council Directive of 24 November 1986 on the protection of animals used for experimental and other scientific purposes.* (86/609/EEC)

10 Mepham B. 'Wurde der Kreatur' and the common morality. *Journal of Agricultural and Environmental Ethics* **13**: 65-78, 2000.

11 Guardian, March 29th 2001 Rifkin J, Shopping for humans.

12 Daily Telegraph, January 22nd, 2001. Is ANDi a miracle or a monster?

13 Cohen P. Clone encounters. *New Scientist* 18th August 2001

14 Guardian, January 13th 2001. Handy ANDi. Just what we need: genetically modified monkeys and the revival of unknown species.

15 Daily Mail, 29th September 2000. Tudge, C. Frankenstein's Farmyard.

seeing animals as mere commodities. The intensification of farming has already pushed our relationship with animals in this direction as demonstrated even by the language we use to describe it. 'Factory farming' does not only reflect the conditions in which animals are kept but also their objectification. In the United States, intensively reared animals are now referred to as 'animal units'. An animal unit may equal 1,000 cattle or 100,000 chickens.

The concept of '*ubuntu*' is described by Desmond Tutu in his book about the Truth and Reconciliation process in South Africa following the end of apartheid[16]. *Ubuntu* roughly translates as the essence of being human. It is about the communality of life and maintains that anything which attacks another's humanity not only subverts one's own but also damages the community. *Ubuntu* means that the perpetrator and the victim are inextricably linked.

Although Tutu did not extend the concept of *ubuntu* beyond the human community, there are many parallels with the human-animal relationship. It could be argued that as a society we are deeply affected by our treatment of other species. The lack of respect inherent in our current practices has serious implications for our collective well-being.

Species integrity and our relationship to laboratory mice

Since mice are so widely used in laboratory experiments, it is especially important to question whether the creation of transgenic mice is a significant assault on the species integrity and if it represents a radical change in our relationship to them.

Since the early 1900s - when mice which had developed tumours were used to breed a line particularly susceptible to cancer - mice have been deliberately inbred to develop genetic defects. Mice have also been subjected to regimes (radiation and chemicals) which trigger germ line mutations. This arose from research into radiation and toxicity risk assessment where it was observed that the programme caused mutants. These mice were subsequently selected and used to produce inbred lines[17]. Now there are deliberate mutagenesis programmes where mice are injected with proven mutagens to generate random mutations. Some of these programmes are formally linked to the Human Genome Project [e.g 18] and some are part of the resultant drive to identify the maximum number of genes [19].

The development of transgenic techniques has led to an explosion of mouse disease models as researchers attempt to insert genes to make mice susceptible to human diseases or display symptoms that mimic human diseases. Transgenic mice are also used extensively in basic biological study as genes are selectively knocked out or disrupted to observe the effect this has on phenotype or function[20].

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16 Tutu D. *No future without forgiveness*. Random House, London, 1999.

17 Roths JB *et al.* Spontaneous and engineered mutant mice as models for experimental and comparative pathology: history, comparison and developmental technology. *Laboratory Animal Science* **49**: 12-34. 1999.

18 De Angelis MH *et al.* Genome-wide, large-scale production of mutant mice by ENU mutagenesis. *Nature Genetics* **25**: 444-447, 2000.

19 Nolan PM *et al.* A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse *Nature Genetics* 25: 440-443, 2000

20 Roths JB *et al.* Spontaneous and engineered mutant mice as models for experimental and comparative pathology: history, comparison and developmental technology. *Laboratory Animal Science* **49**: 12-34. 1999.

Selective breeding for harmful genetic defects is a phenomenon restricted to laboratory animals. In no other situation do debilitating or even fatal conditions form the basis for selection. In the case of current mutagenesis programmes and transgenic mice, the initial defect is also deliberately induced. There are currently a large number of 'mutant' strains of mice and rats available through mail order via the Internet. These include both inbred strains and transgenic lines [eg 21].

The crossing of species barriers in mice is certainly an assault on species integrity. The insertion of genes from other species – as has happened countless times to mice – is a fundamental alteration of an animal's genome which could not be achieved except by using GM techniques. However, deliberate mutation by means of chemicals or radiation is also an assault on species integrity although qualitatively different. It could be argued that systematic breeding for harmful defects resulting from spontaneous mutation is likewise an assault.

In answer to the question, 'Does genetic modification radically change our relationship with mice?', the insertion of genes from different species is certainly different from what has been done before. However, even though they do not involve the introduction of foreign genes, mutagenesis programmes also set out to deliberately alter the mouse genome on a massive scale. The alteration was not to be achieved by breeding for desired traits, even if harmful, but by deliberate gene mutation. Mutagenesis programmes have therefore already raised similar ethical issues to those arising from genetic modification.

While the distinction between deliberate mutagenesis and opportunistic breeding for observed mutation may be small for the mouse, the ethical distinction for humans is important. In previous selection, mutation has either been spontaneous or the result of screening work which was thought to be important for human safety. In the mutagenesis programmes, genetically abnormal mice are deliberately created with the full knowledge that they are likely to suffer (as is also the case in transgenic disease models).

There is also an issue of scale, which is certainly relevant to questions of welfare. Literally thousands of mice are being used in the mutagenesis programme - 40,000 were screened in just two studies[22].

It might be claimed that mice have already been subjected to so much interference that species integrity is no longer a valid argument and that concerns should centre on welfare and the three 'Rs'. It has also been argued that the use of transgenic mice could reduce the use of other species and promote animal welfare in that way. Do mice for some reason no longer deserve the attention afforded to other species?

Abandoning the laboratory mouse as a species worthy of moral consideration probably has more to do with mice being small, cheap and easy to work with compared to other species rather than any ethical considerations. Scientists - and to a lesser extent, society - have become habituated to experiments on mice for these practical reasons. However, insults to a species in the past do not morally justify genetic modification as an additional insult. Because the interests of mice can so

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21 Taconic Farms Inc.. Transgenic Models product list. Taconic Farms Inc web site 5/11/01 (http://www.taconic.com/anmodels/transgenic%20model%20list%202001.htm)

22 De Angelis MH *et al*. Genome-wide, large-scale production of mutant mice by ENU mutagenesis. *Nature Genetics* **25**: 444-447, 2000; Nolan PM *et al*. A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse *Nature Genetics* **25:** 440-443, 2000

easily be overridden on grounds of convenience, there should be even more careful examination of the justification for transgressing their species integrity as well as their individual welfare. The watershed in the human relationship with the mouse arguably arose at the start of the deliberate mutagenesis programme. Perhaps the advent of transgenesis, with the ethical issues it raises, should be the trigger to reassess that programme.

GM mice are now business ventures. In the UK, scientists from the Medical Research Council have set up a company, Etiologics, to produce mice genetically engineered to have human diseases[23]. In the USA, Genome Biosciences regularly announces new deals with researchers wishing to use its 'Positive-Positive Selection™ gene targeting technologies' in the production of GM mice[24]. Whilst mice have been laboratory commodities for some while, at the very least some serious assessment of the value of their sacrifice and suffering that the additional insult that GM brings is needed.

'Side effects' and risks of GM of animals

The National Research Council, in its review of genetic modification and cloning of animals, drew attention to the inefficient nature and risks of GM and cloning for both the animals involved and other species (including humans)[25]. The problems include:

- the random insertion of genes and associated positional problems of expression;
- unintended harmful side effects – including the activation or inactivation of other genes both at the site of insertion or more distantly;
- unexpected effects of a modification when an introduced gene operates as desired. For example, the human complement modifying proteins CD46 and CD55 act as receptors for measles and Cocksakie viruses and when introduced into pigs as part of xenotransplantation experiments could open new pathways for these viruses;
- extra DNA inserted especially when using retroviral vectors which can also introduce genetic material from their host cells including viral and viral-like sequences. These may then be involved in recombination events and produce novel viruses. The NRC review refers to one such case in rhesus monkeys involved in gene therapy experiments (p45);
- inadvertent transmission of the introduced gene into other animals when viral vectors are used. For example, the feline leukaemia virus found in cats could acquire genes from a GM cat if these had been introduced using related viral vectors and pass these genes to other cats and possibly other species.

These unintended side effects and risks are important because they raise questions about whether GM animals will behave 'normally' in scientific research if there have been a range of disruptive effects as a result of the modification process. Together with the wider safety questions, these form an important part of the assessment of the ethical justification for GM animals.

How useful are GM animal models?

"The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all."
Alan Oliff, Executive Director Cancer Research, Merck Research Laboratories[26].

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23 MRC commercial spin-off Ananova 07/10/02: http://www.ananova.com
24 See www. GenomeBioSciences.com .
25 National Research Council (2002) Animal Biotechnology. Science-based concerns. National Academy Press: Washington DC. pp 41-50.

'The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades - and it simply didn't work in humans.'
Dr Richard Klausner, Director of the National Cancer Institute, USA[27].

"With the exception of basic genetic mechanisms, the mouse is a relatively poor model for the human" Petters and Sommer, 2000[28].

GeneWatch believes that an unjustified emphasis is being placed on the potential for GM animals to help understand and treat disease. This is driven by a lack of recognition of the complex nature of most diseases and the failings of laboratory research to mimic environmental, social and economic factors in disease.

To justify the creation of a GM animal model of disease it has to represent an genuine advance and result in an accurate representation of a serious disease which would make a considerable advance in treatment. Two major question marks over GM animal models of disease, in addition to the intrinsic uncertainties arising as a result of the GM or cloning technique, are whether:

- genetic modification can overcome intrinsic problems with animals not being humans;
- genes are the most important determinant in the diseases being investigated.

The simplest disorders to detect, model and treat are those caused by disruption of a single gene - for example, cystic fibrosis or Huntington's disease. Yet genetic environment may still have a crucial effect: as the same mutation can show no symptoms at all or trigger a severe condition even in different individuals of the same species. One of the best researched single gene disorders is ß-thalassaemia, where red blood cell production is impaired and patients are anaemic. People carrying the gene may be completely healthy, mildly affected or severely anaemic[29].

Cystic fibrosis (CF) is the most common Caucasian severe single gene disorder, affecting one in two thousand births. Sufferers usually die in their mid twenties. Several transgenic mouse models have been created by insertional mutation and display similar molecular changes to CF patients. However, the disease progress is extremely different. Serious lung disease is the cause of death in 95% of human patients but CF mice develop lung disease infrequently and mildly. CF mice generally die peri-natally from severe intestinal obstruction while only a minority of human CF patients develop serious intestinal problems[30,31].

Lesch Nyan syndrome is another single gene disorder, characterised by mental retardation and distressing behavioural abnormalities such as compulsive self-mutilation. Several mouse models were created with the same genetic defect but the mice did not display abnormal behaviour[31].

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26 Gura T. Systems for identifying new drugs are often faulty. *Science* **273**: 1041-1042. 1997.

27 Los Angeles Times, May 6th 1998. Cancer drugs face long road from mice to men.

28 Petters RM and Wommer JR. Transgenic animals as models for human disease. *Transgenic Research* **9**: 347-351, 2000.

29 Weatherall DJ. Single gene disorders or complex traits: lessons from the thalassaemias and other monogenic diseases. *British Medical Journal* **321**: 1117-1120. 2000.

30 Porteous DJ and Dorin JR. How relevant are mouse models for human diseases to somatic gene therapy? *Trends in Biotechnology* **11**: 173-181, 1993.

31 Bedell MA *et al.* Mouse models of human disease. II. Recent progress and future directions. *Genes and Development* **11**: 11-43, 1997.

These failures of GM mouse models in even relatively 'simple' genetic disorders is unsurprising when the complexity of gene function and its role in disease is considered. GM mouse models of more complex diseases are even more unjustifiable when the genetic basis or lack of it is considered. Some forms of heart disease and cancer are inherited as single-gene diseases and around 5% of cancers are thought to be of this type, although having the faulty gene still does not necessarily mean someone will get the disease[32].

Common, complex diseases in the wider population are not usually inherited. They have many different causes including lifestyle and environment. Despite much research, genetic susceptibility to complex diseases such as heart disease, cancer and obesity has proved difficult to identify, with many poorly reproducible results. Except in a small percentage of cases, genes are poor predictors of future health[33]. Many people with the 'high risk' form of the gene will not get the disease and many people without it will. For complex diseases, there is a real prospect of statistical studies identifying false associations between genes and the risk of future illness. A spurious link between a gene and a disease is often found in the first scientific study published, or the importance of the gene is exaggerated[34].

For both heart disease and cancer, many different genetic mutations in many different genes may each play a minor role, and a single genetic trait may predispose to one disease whilst being protective for another. Multiple environmental factors – particularly smoking, diet and exercise, and often infection and pollution – will also play a role and are usually more important than genetic make-up[35]. A single environmental exposure may contribute to many diseases and eliminating one exposure - such as smoking - can therefore reduce a large proportion of disease.

The use of transgenic techniques is resulting in an explosion in the development of new animal disease models despite concerns over whether mice can in fact accurately model human diseases. Human genes can be inserted into mice but they are still operating in a mouse genetic background, physiology and laboratory environment. Gene interactions will be different to those which take place in humans. On top of these issues are those of unintended effects of the GM or cloning technique which were considered above. There is the worrying prospect that increasing numbers of transgenic animals will be generated, which are bound to suffer and whose impact on human diseases may be marginal. The use of GM animal models of complex diseases including cancer is highly questionable and there should be an urgent investigation into their use.

Access to information and the regulatory system

In many ways it is extremely difficult to engage in a fully informed debate about the use of GM animals in research because of the lack of information available. Information about animal experiment licensing is kept largely secret, only overall numbers and very general statistics being revealed. This does not allow for an examination of the justification for any particular experiments. GeneWatch understands concerns about the safety of researchers who may be subject to attacks

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32 Vineis, P, Schulte, P, McMichael, AJ (2001), Misconceptions about the use of genetic tests in populations, *The Lancet*, **357**, 709-712.

33 Holtzman, NA, Marteau, TM (2000), Will Genetics Revolutionize Medicine?, *New England Journal of Medicine*, **343**, 141-144.

34 Ioannidis, JPA, Ntzani, EE, Trikalinos, TA, Contopoulos-Ioannidis, DG (2001), Replication Validity of Genetic Association Studies, *Nature Genetics*, **29**, 306-309.

35 Baird, P (2001), The Human Genome Project, Genetics and Health, *Community Genetics*, **4**, 77-80.

from animal rights campaigners. GeneWatch deplores such violence, but believes there must be a system where an individual's identity can be withheld but detailed information about research project made available. Much of such research will be publicly funded and it is indefensible that such secrecy remains and hinders well informed debate.

We noted with alarm the comments in the most recent report of the Animal Procedures Committee that, when considering an application for (non-GM) experiments on primates, the APC found it difficult to assess the potential benefits and likely welfare costs from the material provided[36]. This suggests that there may be an underlying problem, which will also apply to GM and cloning experiments, of a lack of serious scrutiny of this balance.

Because of this lack of information, it is not possible to determine or comment upon whether the regulations are working properly **in practice**. While regulations may require cost benefit analyses, how these are undertaken and the outcomes is shrouded in secrecy. Whilst these should always be contingent and subject to re-evaluation whether this happens is not clear.

The Nuffield Council should recommend both that more information is made available and that an independent inquiry into the operation of the regulations should take place.

On the question of whether licenses should be required for the breeding of all GM animals, GeneWatch believes the answer is yes for the following reasons:

- to add confidence that there will not be inadvertent escape or release of GM animals into the environment – licensing of breeders adds an additional safeguard that standards will be maintained;
- because adverse effects of the GM or cloning techniques may not become evident for many generations[25] and, therefore, continued safeguards are needed for the animals' welfare;
- because removing the requirement for licensing of breeding would 'normalise' GM and cloned animals in a manner which is unacceptable.

[36] Report of the Animal Procedures Committee for 2002. The Stationary Office: London. See pages 2 and 39.

*[*GeneWatch UK also submitted to the Council a paper they had written entitled *Genetically Modified and Cloned Animals. All in a Good Cause?*]