Eurogroup for Animal Welfare submission to the European Commission Biotechnology for Europe Study "Consequences, opportunities and challenges of biotechnology for Europe"

Impact of Modern Biotechnology on Animal Welfare

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1 Introduction

Eurogroup for Animal Welfare is a pan European animal welfare organisation. They represent all 25 Member States through their Member Organisations and Observers. They thus represent a significant proportion of EU public opinion.

This submission summarises Eurogroup's concerns about the impact that modern biotechnology has, or is likely to have, on animal welfare throughout Europe. It focuses on biotechnology applications in human and animal health and agriculture, and the effects of such applications on the lives and welfare of laboratory, farm, companion and wild animals. These concerns should be seen in the context of Eurogroup policies on these areas (see appendix I).

Our concerns are based on the fact that some of the developments and applications of 'modern biotechnology' (as defined in the '*Guidance for Submissions from Stakeholders*'):

- involve procedures that may cause animals pain, suffering or distress;
- use a very large number of animals;
- encourage a wider variety of applications leading to increased animal use;
- increase the perception of animals as commodities for human use and/or gain, such as research tools or units of production;
- are progressing at a rate that is outstripping public understanding and ethical and public debate.

2 Concerns relating to human and animal health

The main applications of biotechnology in the fields of human and animal health that are of concern to Eurogroup at the present time are:

- the creation of genetically manipulated (GM) and cloned animals;
- the subsequent use of these animals:
  - as disease models;
  - in fundamental research e.g. to understand gene function;
  - in toxicity testing;
  - as bioreactors to produce biologically active compounds for experimental and/or medical purposes;
  - as sources of cells, tissues and organs for xenotransplantation;
  - in the creation of cloned pets, sports animals and 'living art'.

However, any new biotechnology, or new application of existing technology, that is developed and/or tested in animal models, or that causes the animals pain, suffering, distress or lasting harm is of serious concern to Eurogroup. Examples include tissue engineering, the development of nanotechnology generally, and stem cell research.

2.1 Production of GM and cloned animals

General ethical and animal welfare concerns

- *Numbers of animals used*

Use of animals in experiments is a matter of serious public concern and pressure to reduce numbers has contributed to a downward trend in some countries. Creation and use of GM animals is reversing this trend and there has been an exponential rise in the number of GM animals used in scientific procedures each year in some EU member states. For example, in the UK, the number of GM animals has risen from around 50,000 in 1990 to 900,000 in 2004 (Home Office Statistics 1990-2004). In Germany, Ireland, Finland, Sweden and the Netherlands, there is also increasing creation and use of GM animals (EU Stats 1999, 2002).

GM animals can be produced by a number of different techniques, all of which are inherently wasteful with respect to the number of embryos that are manipulated relative to the number of GM offspring subsequently produced. Current estimates suggest only a 3-5% success rate when generating new GM animals (Nuffield Council on Bioethics, 2005). The remaining offspring are surplus to requirements and are killed. A large number of animals are therefore used to provide sufficient eggs or embryos for genetic manipulation, and to act as recipients and foster mothers for the manipulated embryos. These animals will usually be killed, either before harvesting the eggs or embryos, or, in the case of recipients, once their young are weaned. Thus GM technology is wasteful of animal life and the ethical implications of such wastage are important and need to be acknowledged.

- *Potential for pain, suffering or distress during creation of GM or cloned animals*

The procedures used to produce GM and/or nuclear transfer cloned animals involve hormonal and surgical interventions that can cause pain, suffering and distress. These include; superovulation, vasectomy, semen and embryo collection and embryo transfer (JWGR, 2003; Pew Initiative, 2002).

Many of the manipulated embryos die during gestation. This may also cause suffering, although this depends on the stage of development at which death occurs and the species involved.

- *Adverse effects as a consequence of genetic modification and cloning*

Where GM animals are created as models of specific diseases, they can experience a range of adverse effects associated with the condition in question, which can have profound effects on their health and welfare. However, being genetically modified does not necessarily compromise the welfare of individual animals, and indeed some GM animals are indistinguishable from their non-GM siblings. It also needs to be acknowledged that adverse effects may only become apparent when animals are subsequently maintained in a less well defined or controlled, environment than that of the laboratory or experimental farm. Nevertheless, in many cases, genetic modification can have a deleterious effect on animal welfare and the harms caused depend on a number of factors.

Studies have shown that some *in vitro* culture procedures carried out during genetic manipulation or cloning protocols can lead to unpredictable complications in the animals subsequently produced (ECVAM, 1998). An example of this is Large Offspring Syndrome (LOS), which affects sheep, mice and cows following nuclear transfer. As well as causing complications for the mother during birth, LOS encompasses a range of debilitating pathologies for the offspring including

malformations in the liver, brain and urogenital tract, immune dysfunction, placental abnormalities, stillbirth, fetal overgrowth, respiratory failure and circulatory problems (Vajta and Gjerris, 2006).

A further concern is that there is currently no mechanism to ensure consistency in the training of personnel in specific GM technologies and procedures, or to ensure that experimental and other refinements are disseminated throughout the biotechnology community. This can have a profound influence on the levels of pain, suffering and distress experienced by animals undergoing these procedures. It can also have a negative impact on the success rates achieved and levels of animal wastage.

Concerns regarding mutagenesis programmes

Mutagenesis (using chemicals such as ENU, or physical mutagens such as radiation, to increase the natural mutation rate of DNA) is the quickest method for producing large numbers of GM mice. This technique is being widely applied both in Europe and beyond, with mutagenesis programmes aiming to explore the function of every gene in the mouse genome. This project presents a number of animal welfare concerns:

- the number of animals involved in mutagenesis programmes is vast; e.g. around 35-36,000 for a 3 year project, or around 50 animals per mutant line established (Mammalian Genetics Unit, Harwell, 2006);
- the process of mutagenising animals has significant animal welfare implications for the animals involved, for example males require 12-14 weeks to recover their fertility following treatment with a mutagen. Furthermore, only around 50% of mutagenised males are able to go on to sire offspring with the remainder being culled (Goldwitz et al, 2004);
- the mutations induced are by their very nature unpredictable and the scientific usefulness of mutagenised animals cannot therefore be predicted, nor can the effect of any mutation on the health and welfare of the animals. This makes the justification for producing GM mice in this way highly questionable.

Concerns regarding knockin and knockout technology

A more targeted approach to the production of GM animals uses DNA constructs inserted into the animals genome to either completely remove a gene of interest (knock-out), or to replace a given gene with an altered version (knock-in). This is done either in the whole animal, or within specific tissues of an animal (conditional). The animal welfare concerns include:

- at the current level of efficiency, the numbers of animals used is high - at least 200 animals will be used in the production of a single GM animal (Mammalian Genetics Unit, Harwell, 2006);
- the site of insertion into the host genome and the number of copies of the DNA construct inserted cannot always be controlled unless ES cell manipulation is used. This can be a problem because the incorporation of the construct DNA at an incorrect location can result in the random inactivation of other genes or alterations in the expression of surrounding genes, both of which can impact on the health and welfare of the animals produced;
- when a knockout animal is generated the level, or pattern of expression observed for other genes can be altered to compensate for the lost gene (Okkenhaug, 2003). Thus any effects observed in the GM animal may not only reflect the loss of the gene of interest, which means that investigation of the effects is not always

straightforward. The use of knock-out as an alternative to knock-in or conditional technology, therefore needs careful consideration and justification.

Special concerns for non-human primates

This submission relates to all animals used in biotechnologies, but Eurogroup has particular concerns about the application of such technologies to non-human primates. Macaques have already been produced by nuclear transfer cloning in the USA (Chan et al, 2001), and recent technical advances mean that the production of GM primates is a realistic possibility in the foreseeable future. Eurogroup firmly believes that the genetic modification of non-human primates should not be allowed for any purpose, given the ethical issues raised by such developments, the large number of animals required to produce each GM animal, and the associated potential for harms.

2.2 Animal models of disease

A common justification for the creation of GM animals is that they will provide, or contribute to, 'improved', more predictive models of disease. This is an oversimplification because a) this is not necessarily always true, and b) even where a new GM model is more appropriate, it may be used alongside other, older models by different researchers. There is no mechanism for ensuring only the most relevant are used and that newer models are available to all researchers. In such cases the GM animal is not the new *definitive* model but just an *additional* one.

The motivation for the research may merely be an interest in the model for its own sake, but a medical application may be used to justify the work since this is likely to be more acceptable publicly and politically. Basic, fundamental research carried out within academic research establishments is not regulated under Directive 86/609, so it may not undergo an ethical review with appropriate assessment and weighing of harms and benefits.

There is also currently no requirement for GM animals to be cryopreserved and stored within central archive facilities or depositories. Such methods can reduce repetition and duplication of work by providing a central resource for use by the wider scientific community and protect against adverse events such as environmental disasters or genetic drift. They also reduce the need for live transportation of GM animals, with associated welfare problems, because frozen gametes or embryos could be sent instead.

2.3 GM animals in toxicity testing

GM mice and rats are increasingly used in genotoxicity and carcinogenicity testing, within studies that are done to fulfil regulatory requirements for the marketing of chemicals and pharmaceuticals. Such animals are likely to suffer equivalent (or even more severe) levels of pain and distress to those experienced by animals in traditional tests, but it has been claimed that fewer animals will be needed.

Eurogroup believes that reducing the numbers of animals used in research and testing is an important goal, provided that this can be done without increasing the level of suffering experienced by individual animals. However, relatively severe adverse effects have been reported in some GM strains used in toxicity testing (ECVAM, 1998). For example, mortality rates are higher in *c-neu* and *c-myc* mice used in carcinogenicity testing than in conventional mice used in the same type of test. Many GM mice used in carcinogenicity tests are more susceptible to developing

cancer and so will develop tumours more rapidly, which could make it more difficult to implement humane endpoints. Reducing numbers is thus not automatically a positive outcome for animals - the impact on individuals must be taken into account and it may be justifiable to use more animals who will suffer less.

In any case, the contribution that biotechnologies can make to reducing animal numbers in carcinogenicity and genotoxicity is not consistent, largely due to actual or potential regulatory requirements. In carcinogenicity testing, GM mice were introduced to try to reduce animal numbers and the time taken to obtain test results. However, there are proposals to add additional control groups (a positive control and treated and untreated controls using non-GM mice) that would decrease the magnitude of the reduction if they are adopted (OECD, 2005). It is also uncertain whether testing on one GM strain will be regarded as sufficient by regulators, in which case the reductions will be further diminished by requirements for results obtained using other strains.

For genotoxicity testing, GM models have distinct scientific advantages over existing *in vivo* assays when used as second tier tests for *in vitro* genotoxins. The reduction in numbers of animals used would be fairly substantial, perhaps from 50 to 20 per substance tested, but again it is not certain that a test on one GM model would be regarded as sufficient. There are potentially much greater savings in animals if GM tests can be used in place of very large tests of heritable mutation which are currently used, albeit rarely, for chemicals of high concern.

Conversely, using GM animal models in toxicity testing could increase the use of animals by making some tests more practical, or by increasing the amount of information they produce. For example, the use of GM animals could make investigations feasible that would otherwise require very large and impractical numbers of non-GM animals. Regulators might be inclined to ask for the GM test in cases where the conventional test would not have been requested (and could therefore presumably have been done without) because it was regarded as too cumbersome and possibly uninformative.

Eurogroup believes that, in toxicity testing as in the other research fields discussed in this document, the focus should be on developing *in vitro* alternatives to replace animals and not on developing different animal models.

2.4 Animals as ‘bioreactors’

This category of GM animal use includes:

- “pharmed” animals who produce therapeutic substances e.g. pigs who express the blood protein Factor IX in milk, and goats that express the anti-clotting agent Atryn in their milk (Van Cott et al, 1996; Lindsay et al, 2004; GTC Therapeutics);
- animals producing specialist materials e.g. goats who produce spiders’ silk proteins in their milk for use to make ‘biosteel’. This has both medical and non-medical applications (e.g. in sutures and bullet-proof vests respectively) (Nexia Biotechnologies, Quebec);

The substance produced may have an adverse effect on the animal, either at the point of expression, or if it can enter the animal’s bloodstream. For example, a strain of rabbits genetically engineered to express human erythropoietin (EPO) in the mammary glands also expresses the protein at low levels in other organs, resulting in greatly elevated numbers of red blood cells, infertility and premature death (Massoud et al, 1996).

Using animals in this way, and referring to them as 'bioreactors', reinforces the perception of animals as units of production and/or biological tools, rather than as sentient beings with the ability to experience pain, suffering and distress.

2.5 Xenotransplantation

The use of GM animals to supply organs, tissues or cells for transplantation into humans is a highly controversial issue which has been the subject of a great deal of debate. There are many legal, scientific, human health, animal welfare and ethical concerns, which have been described in a number of documents (Nuffield Council on Bioethics, 1996; Kennedy Report, 1997; Council of Europe, 2002). Only the ethical and welfare issues relating to animals are addressed here. These include:

- the ethics of genetically modifying animals of any species as a source of cells, tissues and organs for human transplantation;
- the harms associated with the initial creation of GM animals as source animals (see section 2.1);
- the suffering and/or distress associated with production and maintenance systems for high health status source herds. This includes hysterotomy-derivation, early weaning practices, and barren husbandry environments, which have a serious negative impact on animal welfare because they prevent animals from satisfying their physical, social and behavioural needs.

Furthermore, development of xeno technology to a point where it can be used still requires a great deal of pre-clinical research. To date, such research has included studies of efficacy, physiology, immunology, and infection risks in a range of species including primates, goats and dogs. This research, by its very nature, causes considerable suffering. Experiments involving organ transplantation require major surgery, which in itself causes suffering that is exacerbated by tissue rejection and immunosuppressive treatment.

Xenotransplantation is also an example of a biotechnology where over-optimistic claims are made to justify the approach, the funding and the use of animals. For example, in September 1995, the UK company Imutran *"envisaged the first xenotransplants of transgenic pig hearts into human patients taking place in 1996"* (Nuffield Council on Bioethics, 1996). Yet despite some progress, particularly with cell transplants, the transplant of whole organs is no closer and xenografts still rarely survive for more than a few months (Chapman, 2004).

2.6 Cloning companion animals, sports animals and 'animals as living art'

Eurogroup believes that, without doubt, some applications of modern biotechnology are trivial, scientifically unnecessary and ethically unjustifiable. Examples include;

- the cloning of champion racing and show jumping horses for sport (Galli et al, 2003; Cryozootech);
- the generation of a green fluorescent rabbit 'GFP Bunny' as transgenic "art" (Eduardo Kac, 2000);
- the cloning of companion animals for example cats, purely to satisfy humans' emotional requirements (Shin et al, 2002; Genetic Savings and Clone Inc).

3 Concerns relating to agricultural production

Gene mapping is the modern biotechnology application most widely used in agriculture to enhance selective breeding schemes. Examples of agricultural applications of gene mapping and other genetic engineering techniques that have given rise to ethical and animal welfare concerns include:

- *Increasing productivity or changing body composition*

Gene mapping has been used primarily to increase productivity i.e. growth rates, litter sizes and production traits such as egg laying, milk volume and meat quality including the proportion of lean meat to fat.

Farmed species have also been genetically manipulated to alter the composition of meat and milk. For example, pigs and cows respectively have been genetically altered to have higher levels of Omega 3 in their muscle (Lai et al, 2006), and to express higher levels of casein in their milk (Brophy et al, 2003).

- *Increasing disease resistance*

Animals are genetically manipulated to be resistant to disease, for example, cattle have been engineered to express the antibiotic lysostaphin in their milk, which results in increased resistance to mastitis (Wall et al, 2005). Animals (including pigs, sheep, mice and rabbits) have also been modified to express antibodies providing immunity to specific diseases (Lo et al, 1991; Weidle et al, 1991), for example mice have been generated with protection against prion disease (Heppner et al, 2001).

- *Making animals more 'environmentally friendly'*

An example of this application is the 'Enviropig™', which has been engineered to contain the enzyme phytase in the pigs' saliva so that they can digest sources of dietary phosphorus. This results in faeces with a lower phosphorus content, which in turn reduces the pollution of surface and ground water with phosphorus (Golovan et al, 2001).

<u>Ethical and animal welfare concerns</u>

The selective breeding of farm animals has been conducted for thousands of years, and has given rise to a number of welfare concerns. However, Eurogroup believes that the use of biotechnologies to speed this process, or to introduce genes that could never be incorporated into the genomes of farm animals by any natural process, is a serious ethical and welfare issue. Directly altering an animal's genome is viewed by many as an unacceptable assault on the integrity of the animal that is incompatible with the concept of respecting farmed animals, and minimising the harms that are caused to them for human benefit. These views are important and should be respected as a legitimate part of the debate on biotechnology and farmed animal welfare.

Eurogroup also questions the necessity of further increasing production in farm animals. In many cases, productivity is already pushing animals to their physical and metabolic limits, so with any further increase there is an enhanced likelihood of animal welfare problems. Enhancing selective breeding, by gene mapping or genetic modification, can also cause suffering if the trait that is selected for has a negative impact on the rest of the animals' physiology. For example, hens who produce high numbers of eggs suffer from osteoporosis because the majority of the calcium they ingest is used in eggshell production (J. Mench, Pew Initiative, 2002).

There can also be less direct effects on welfare, in that some GM animals may receive lower standards of husbandry than conventional animals. For example, clinical mastitis is a major welfare problem in dairy systems with sub-optimal standards of hygiene, and early detection is reliant on routine inspections by parlour staff at milking. The creation of cattle resistant to mastitis may encourage the perception that mastitis is no longer a problem. This could not only compromise standards of parlour hygiene, but may reduce the level of attention paid to each animal at milking. This would increase the potential for other clinical or welfare problems to go undetected.

"High productivity" animals may also be at risk if their husbandry is not appropriate. It may be possible for them to be properly managed and cared for in the controlled environment of a breeding company or experimental farm, but there are serious concerns regarding the welfare of such animals once they are released into commercial agriculture.

4 Concerns relating to industrial processes, energy and the environment

Eurogroup has limited experience in this field, but one ethical and welfare issue of which we are aware is the impact of GM crops on birds and other wildlife. The potential effect on biodiversity is a serious concern. However, the health and welfare of wildlife is also important and can be adversely affected. For example, GM crops (like other aspects of modern intensive farming methods) are associated with a reduction in weed density in arable fields. This has an adverse effect on the health and welfare of farmland birds for two reasons:

- highly efficient weed control programmes are strongly associated with low bird breeding success, since weed seeds are an important component of the diet of farmland birds such as skylarks and linnets (JNCC, 2003; DEFRA, 2006);
- invertebrate density (e.g. bees and butterflies) falls when the number of weeds is reduced and bird chicks fail to thrive when invertebrate densities are low (JNCC, 2003).

5 Concluding remarks

Modern biotechnologies have had, and will continue to have, a serious adverse impact on animals, particularly with regard to their use in scientific research and agriculture. This adverse impact relates to the numbers of animals used and the nature of the harms caused to them. In addition, directly altering an animal's genome, as occurs in many applications of biotechnology, is viewed by many as altering the integrity of the animal in a way that is incompatible with the concept of respecting animals, and minimising the harms that are caused to them for human benefit. Lastly, the technology is progressing at a rate that is outstripping public understanding and ethical and public debate.

The development and application of novel biotechnologies therefore poses new challenges for existing regulatory regimes in a number of fields of science, medicine, agriculture and the environment. Eurogroup believes that the broader issues surrounding the ethical and social acceptability of such uses of animals, as set out in this submission, cannot be effectively addressed within the current regulatory systems. The following principles are fundamental to ensuring that the lives and welfare of animals involved in all modern and future biotechnologies are awarded due priority.

- It is critically important that all relevant regulatory systems are updated to take into account the animal welfare, ethical and social implications of the development and intended use of all modern biotechnologies.

- Biotechnology is applied in many different fields so there needs to be effective liaison, co-ordination and definition of responsibilities within and between all the relevant legislative and regulatory bodies concerned with a particular issue. This includes, for example, the different bodies regulating use of animals in experiments and those setting requirements for product regulation.

- The regulatory framework for each technology must encompass a process which enables a critical scrutiny of the potential harms to animals and the intended benefits, and a careful and fair weighing of these. This applies to broad research directions as well as individual projects and the further application of new technologies that result from these. Critical assessment of justification needs to be done prior to the development and/or application of a technology and must then be reviewed regularly to check whether the harms and benefits are as expected so that appropriate action can be taken if necessary.

- A mechanism should be set in place to ensure that the justification and clinical relevance of all research involving the production and use of GM animals is critically scrutinised, such that animals are not used simply because the technology is available. This also needs to ensure that animal models of disease are regularly reviewed, so that redundant models are no longer routinely used for research purposes.

- There needs to be greater transparency with regard to the use of animals in biotechnology throughout Europe. Clearer information on the numbers of animals, and nature and level of any suffering that they experience, is essential in order to be able to identify issues of concern and assess trends. It is also vital that the public is well informed and therefore able to engage in constructive debate on the associated ethical issues.

- Restrictions should be placed on the species of animal that it is permissible to genetically modify. Non-human primates should not be genetically modified or cloned for any purpose, nor used as source animals for cells, tissues or organs.

- The production of GM livestock where the intention is to modify traits such as increased lean to fat ratio, growth rate, or litter size should not be allowed, as levels of productivity are already causing serious welfare problems.

- There should be far greater effort devoted to developing and validating alternatives to animal use in all fields. There should be greater commitment to, and endorsement of, the principles of the Three Rs of reduction, refinement and replacement in animal experiments. Examples especially relevant to modern biotechnology are:

  – the development of GM germ cells for *in vitro* testing;
  – the production of drugs, proteins, or material by bacteria rather than ‘bioreactor’ animals;
  – generating cells, tissues and organs for treatment or transplantation using a patients own cells, eg human bladders (Atala et al, 2006).

Nikki Osborne BSc PhD, Maggy Jennings BSc PhD, Penny Hawkins BSc PhD, on behalf of Eurogroup for Animal Welfare
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References

- **Atala et al (2006)** Tissue engineered autologous bladders for patients needing cystoplasty. *The Lancet* 367 1241-46
- **Beattie et al (1996)** An investigation of the effect of environmental enrichment and space allowance on the behaviour and production of growing pigs. *App.Animal Behavioural Sci.* 48 (3-4) 151-58
- **Brophy et al (2003)** Cloned transgenic cattle produce milk with higher levels of β-casein and κ-casein. *Nature Biotechnology* 21 157-62
- **Chan et al (2001)** Transgenic monkeys produced by retroviral gene transfer into mature oocytes. *Science* 5502 309-12
- **Chapman LE (2004)** Emerging biotechnology: Xenotransplantation, public health and public policy. *Research Practitioner* 5 48-55
- **Council of Europe (2002)** The state of the art in the field of xenotransplantation http://www.coe.int/T/E/Legal_Affairs/Legal_co-operation/Bioethics/Activities/Xenotransplantation/XENO(2003)1_SAR.pdf
- **Cryozootech** http://www.cryozootech.com/?l=en
- **DEFRA (2006)** Advisory committee on releases to the environment annual report number 12 http://www.defra.gov.uk/environment/acre/pubs.htm#annrpt.
- **ECVAM (1998)** The use of Transgenic Animals in the European Union.*ATLA* 26 21-43
- **Eduardo Kac (2000)** 'GFP Bunny' http://www.ekac.org/transgenicindex.html
- **EU Stats (1999)** Third report on the statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union, 1999
- **EU Stats (2002)** Fourth Report on the statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union, 2002.
- **Galli et al (2003)** Pregnancy: a cloned horse is born to its dam twin. *Nature* 424 635
- **Genetic Savings and Clone Inc.** http://www.savingsandclone.com/
- **Goldowitz et al (2004)** Large-scale mutagenesis of the mouse to understand the genetic basis of nervous system structure and function. *Mol.Brain Research* 132 105-115
- **Golovan et al (2001)** Pigs expressing salivary phytase produce low-phosphorus manure. *Nature Biotechnology* 19(8) 741-5
- **Heppner et al (2001)** Prevention of scrapie pathogenesis by transgenic expression of anti-prion protein antibodies. *Science* 294 178-82
- **Home Office Statistics** of Scientific Procedures on Living Animals Great Britain (1990-2004) http://scienceandresearch.homeoffice.gov.uk/animal-research/publications/statistics/
- **Kennedy Report (1997)** Animal tissue into humans - A Report by the advisory group on the ethics of xenotransplantation.
- **JNCC (2003)** Position statement on genetically modified organisms in the environment – update 15th October 2003. http://www.jncc.gov.uk/page-2992
- **JWGR (2003)** Refinement and reduction in production of genetically modified mice. *Laboratory Animals* 37 Suppl.1 1-51
- **Lai et al (2006)** Generation of cloned transgenic pigs rich in omega-3 fatty acids. *Nature Biotechnology* 24 435-36

- **Lindsay et al (2004)** Purification of recombinant DNA-derived factor IX produced in transgenic pig milk and fractionation of active and inactive subpopulations. *J.Chromatog.A* 1026 (1-2) 149-57.
- **Lo et al (1991)** Expression of mouse IgA by transgenic mice, pigs and sheep. *Eur. J. Immunol* 21 1001-6
- **Mammalian Genetics Unit, Harwell, (2006)** Animal Welfare Mutagenesis Questions http://www.mgu.har.mrc.ac.uk/aboutus/animal%20welfare/mutagenesisQA.html (accessed 19/04/06)
- **Massoud et al (1996)** The deleterious effects of human erythropoietin gene driven by the rabbit whey acidic protein gene promoter in transgenic rabbits. *Reprod.Nutr.Dev* 36 (5) 555-63
- **May et al (2005)** Management of genetically modified herbicide-tolorant sugar beet for spring and autumn environmental benefit. *Proc.Biol.Sci* 272 111-119
- **Nuffield Council on Bioethics (1996)** Animal-to-Human Transplants, the ethics of xenotranplantation.
- **Nuffield Council on Bioethics (2005)** The Ethics of Research Involving Animals Report.
- **OECD (2005)** Draft Detailed Review Paper on Transgenic Rodent Mutation Assays (February 2005 version - http://www.oecd.org/dataoecd/39/26/34446783.pdf)
- **Okkenhaug (2003)** PI3K-signalling in B- and T-cells: Insights from gene-targeted mice. *Biochem. Soc. Trans* 31 270-74
- **Pew Initiative (2002)** Biotech in the Barnyard: Implications of Genetically Engineered Animals.
- **Shin et al (2002)** A cat cloned by nuclear transplantation. *Nature* 415(6874) 859
- **Vajta & Gjerris (2006)** Science and technology of farm animal cloning: State of the art. *Ani.Reprod.Sci* 92 211-230
- **Van Cott et al (1996)** Transgenic pigs as bioreactors: a comparison of gamma-carboxylation of glutamic acid in recombinant human protein C and factor IX by the mammary gland. 15 (3-5) 155-60
- **Wall et al (2005)** Genetically enhanced cows resist intramammary Staphylococcus aureus infection. *Nature Biotechnology* 23 (4) 445-51
- **Weidel et al (1991)** Genes encoding mouse monoclonal antibody are expressed in transgenic mice, rabbits and pigs. *Gene* 98 185-91

Appendix I - Eurogroup Policies on Animal Experimentation

Key points of relevance to this submission are set out below, with the policy statements available in full from: Eurogroup for Animal Welfare, 6 rue des Patriotes, 1000 Brussels, Belgium.

Eurogroup for Animal Welfare:

- is opposed in principle to all experiments and scientific procedures which cause pain, distress or suffering to living animals.
- is opposed in principle to the genetic engineering of living animals
- recognises that there are moral and practical objections to the concept of genetic engineering.
- recognises that research into genetically engineered animals has been going on for many years and appears likely to increase rather than decrease in the foreseeable future.
- is aware that genetic engineering can have unpredicatable consequences which will have an adverse effect on animal welfare
- is aware that it is often difficult, if not impossible, to properly control this technique during research and to monitor and control the release of some genetically modified organisms into the environment.
- believes all regulation concerning genetic engineering should be cross-referenced to the regulations concerning animal experimentation and welfare
- believes products resulting from genetic engineering techniques must be clearly identified as such.