

This response was submitted to the Call for Evidence held by the Nuffield Council on Bioethics on *Genome editing* between 27 November 2015 and 1 February 2016. The views expressed are solely those of the respondent(s) and not those of the Council.

Genome Editing: Animal Impact

Dear Nuffield Council on Bioethics – Genome Editing working group members,

I am sorry that I was not able to attend the re-scheduled meeting in January but please find below the thoughts that I would have hoped to express.

For me it is important when considering the impact on animals of the development of genome editing tools to do so in the context of existing animal welfare, societal, ethical and 3Rs (Replacement, Reduction, Refinement) concerns. Having acknowledged these, it is then useful to consider whether genome editing technologies enhance or reduce these existing concerns, or indeed give rise to new ones. Before I go on to discuss these concerns I would like to make one further point... It is my opinion that genome editing and other genetic modification technologies are being developed and applied solely for human benefit, and we should not kid ourselves that there is any other purpose. Yes there are examples whereby the technology has been applied with the intention of improving the health or welfare of certain animals, but this is not being done for an altruistic purpose. The benefits of such applications for humans are numerous: to reduce spending on veterinary medicines; reduce the cost of animal housing, husbandry or care; increase yields of animal derived products; reduce the spread of disease; ensure animals remain as a source of food, comfort, commercial workforce/tools and environmental enrichment for humankind.

Public Opinions

Since 1991 the European Commission has conducted 7 [Eurobarometer surveys](#) that have had a focus on the opinions of Europeans on Biotechnology (1991, 1993, 1996, 1999, 2002, 2005, 2010). Each of these has asked questions about whether respondents support genetic modification of animals for various different purposes including medical research, human health, food production and environmental impact. The last of these special reports on Biotechnology was published in 2010 and can be access [here](#) alongside an analysis of how public opinion has changed regarding Biotechnology 1991-2010 (see Winds of Change report). The 2010 special report on biotechnology may be of interest to the group because it asks specific questions about horizontal and vertical gene transfer defined as ⁹ *Horizontal gene transfer is a process in which an organism incorporates genetic material from another organism without being the offspring of that organism.* ¹⁰ *Vertical gene transfer where an organism receives genetic material from its ancestor for example a parent or the species from which it was evolved.* It also includes public opinions on “*whose doing a good job*” in terms of all the relevant stakeholder groups, and “*the role of governments*”.

I will leave the group to review these references yourselves but what is clear in my mind is that there has never been particularly strong public support expressed for biotechnology and genetic engineering during any of the years of these surveys. This then begs the question, well if animals are being genetically altered/edited for human benefit, but there is no real demonstrable public desire or demand for such technology then why is this work continuing? In my opinion the application of gene altering/editing technologies is progressing at a rate that far outstrips public understanding regarding whether there is a genuine need for the technology and what other options exist for the various issues the technology is seeking to resolve. I think that there is an unsatisfied need for genuine public engagement regarding all genetic alteration/editing technologies. I am not talking about influencing the public to a specific viewpoint such that they consider technologies and their

applications in a positive light, but rather being open and honest so that whatever opinion an individual holds is an informed one. This means being transparent about all the costs (financial, physical, societal and ethical) associated with developing such technologies, being realistic about timescales and what can/can't be achieved, as well as listening to, considering and addressing public concerns.

Ethical Issues

It is no small task to try and understand what underlies societal views and concerns relating to genome altering/editing technologies. However my experience within Europe is that despite cultural differences and a range of opinions there would appear to be two main ethical concerns. To express these in my own words they are:

1. just because it is technically possible to genetically alter an animals does not mean that there is good reason to do so or that anyone should.....

This first concern relates directly to the human benefit side of the ethical harm/benefit scales. A good example of this discussion is the genetic alteration of animals to improve yields of animal derived products such as meat, milk and wool. Supporters of this application of the technology say that there are environmental benefits to reducing the number of animals required to supply consumer demand. At the same time the public are being told about food mountains and cheaper food prices bankrupting farmers, so the question arises can the same benefits not be achieved by tackling food waste and changing human behaviour? Similar arguments abound when discussing the genetic alteration of animals that humans eat to improve their nutritional content. The potential benefit for humans, especially those in third world and poorer countries is well made, but for all countries alternative approaches such as education and training to drive behavioural change are also possible. These kinds of unresolved questions are what I believe gives rise to 'consumer choice' concerns resulting in public pressure for governments and their regulatory bodies to ensure that any genetically altered products are clearly labelled so that consumers can choose whether to buy them or not. Companies are reluctant to do this because they need to recover their research and development costs and fear that labelling will only reinforce public concerns. Legally governments are in a difficult position to enforce labelling because there would be costs associated with the monitoring and traceability of labelling schemes and there is not always a great deal of data regarding safety, environmental impact or animal welfare concerns to support this. I personally think the 'precautionary principle' that is commonly applied is appropriate but I recognise that it does often lead to a build-up of anger and frustration, rather than provide a timescale for discussion, resolution and clarity.

2. animals are sentient beings with an intrinsic value and we should be mindful that they are not simply 'tool's for humans to use for their own benefit.

This second concern can manifest itself as the 'yuk/frankenstein' factor, but also encompasses the 'its not natural/man should not tamper with what god has given us', and the straightforward 'its' new, its novel, I don't understand it so I don't want it' argument. Each of these will have a different root cause associated with them, but underlying each are fundamental ethical concerns that do not arise using traditional breeding techniques and deserve consideration.

In the context of producing genetically altered animals for research purposes, I am sure the group has already received some very clear arguments in support of gene altering and indeed genome editing technologies. As is often the case when such technologies are developed this will involve some animal use at some stage, especially during pre-clinical studies, but this animal use is very rarely acknowledged. Whether intentional or not, a consequence of this is that the intrinsic value

attributed to the life of a research animal becomes diminished, and so a cycle develops whereby the responsibility for and ethical costs of each animal's life lost becomes meaningless, until it reaches a point at which it becomes forgotten entirely. To my mind this is not acceptable and I believe that more can and should be done to ensure that the use of animals in all fields of research is acknowledged.

In terms of research involving specific animal models, there is a growing body of evidence highlighting problems with the reproducibility and translatability of animal models, much of which I believe is applicable to but I accept not restricted to genetically altered animals (for examples of this see [Mogil et al., 2009](#); [Pouladi et al., 2013](#)). I personally think that the 'transgenic/biotechnology' community is being particularly slow, or quiet about what it as a community can, or is doing to acknowledge and address these concerns. This is just one of a number of reasons why there is growing interest and awareness of the number of genetically altered animals being created, or bred, and herein lies another ethical issue. The number of genetically altered and now genome edited animals is increasing however they do not become the new 'best' model, they do not replace existing models, they are simply a new addition to the list of animal models available. It would appear that the research community is happy that there is continued scientific justification for creating genetically altered or genome edited animals, but I do not believe that the same can be said in terms of the ethical justification. Faced with an ever increasing number of genetically different animals available to use for research purposes, many of which have no specific research purpose and are of limited use or are now redundant, I think that the ethical justification must receive greater scrutiny. Who, if anyone is responsible for conducting a retrospective review of the actual harms and actual benefits associated with the projects producing genetically altered or genome edited animals, and what lessons are there that can be learnt?

Animal Welfare

In terms of the animal welfare concerns relating to the genetic alteration of animals these need to be considered on a case by case basis because the impact of procedural harms will vary between species. For example embryo transfer will require surgery in some species (e.g. rodents), but be a non-surgical invasive procedure for others (e.g. livestock species and horses). Opinions on whether invasive procedures are considered 'uncomfortable' or 'painful' will also vary between veterinary professionals, and in part be influenced by the experience and competency of the individual carrying out the procedure. Another example is the collection of eggs or ES cells for genetic alteration. For many species this is a terminal procedure (e.g. rodents, rabbits), for some it will be considered a routine husbandry practice (e.g. in some fish species), and for others it is another invasive procedure (e.g. livestock species).

In addition to procedural harms associated with the gene alteration protocol, there are also well documented welfare concerns for the surrogate mothers and genetically altered offspring. The incidence of natural abortion/miscarriage of genetically altered fetuses and impact on the health and welfare of the dam will vary between species. For those genetically altered offspring that do survive to birth there is commonly a higher incidence of assisted births reported. This may be due to the value/importance attributed to the survival of the offspring, or because of associated conditions such as 'large offspring syndrome' in livestock species. There is also a number of genetically altered offspring that will die within the first 2-3 weeks after birth due to unforeseen developmental defects or complications. When these deaths are counted all together it is not uncommon for a very small number (2-4%) of genetically altered offspring to survive to adulthood. This means that a significant number of animals will have undergone potentially painful procedures or lost their lives to produce a single founder animal however exact figures will vary between methods and species. For those genetically altered animals that do survive and appear 'healthy' there are also some documented health and welfare concerns that require monitoring and treatment.

For references please read:

[APC Report on Biotechnology - 2001](#)

[FAWC Report on the welfare implications of animal breeding and breeding technologies in commercial agriculture - 2004](#)

[Genetic engineering of animals: ethical issues including welfare concerns - 2011](#)

Gene editing technology

So what does the future hold? Well, the more targeted and specific nature of genome editing tools means that it should be possible to reduce the incidence of unexpected adverse animal health and welfare effects in offspring caused by unwanted genetic alterations. It does not automatically follow that the survival rates of genome edited offspring will be any better, nor does it necessarily follow that there will be any improvement in long-term health and welfare of genome edited animals, but improvements in both are possible. Any improvement in the efficiency of creating and subsequent breeding of novel genetically altered animals would be welcome if it reduced the number of animals used to create a novel GA line. However, I think that improved efficiencies along with a reduction in associated costs and technical challenges of producing novel genome edited animals will drive increased demand for the application of such technology. This would result in any potential reduction in the number of animals required to produce each founder animal being cancelled out by a growth in demand for novel genome edited animals. I also think that every research group will have their own 'favourite' genome editing sequence/tool that they will use and so rather than using GA models that already exist, or sharing genome edited animals to maximise the benefits accrued from each animal, research groups will simply generate their own. It is this that I think presents the biggest risk at present and something that needs to be kept under close scrutiny and review.

The fact that there is known conservation between species with regard to genome editing sequences means that the genomes of a broader range of species is already being edited and novel animal models being created. Put simply this technology can be used to edit the genomes of species that it was either impossible, or more technically difficult to alter before this advance in scientific knowledge. The creation of any novel genome edited animal has ethical concerns associated with it, but in terms of public opinion the ethical concerns are more strongly held for specific species including non-human primates, dogs, cats and equidae. The creation of genome edited non-human primates has for example already been published and so public concerns in this area will need to be managed and addressed. I believe that the development of such technologies increases the urgency with which there is a need to discuss and debate how such technologies will be responsibly used.

I am aware that there are also a number of concerns associated with the potential environmental impact of releasing genome edited animals/organisms outside the controlled environment of the laboratory. These relate to the risk of 'uncontrolled' genome editing happening within subsequent generations, or following breeding with 'wild populations', and all of these I believe will need to be acknowledged, discussed and addressed.

Summary

- all genetic alteration and gene editing technology is being developed for human benefit either directly or indirectly;
- there are two main ethical concerns - 1) is there a 'good/valid' reason for using/developing the technology? 2) animals are sentient beings with an intrinsic value and should not be viewed merely as 'tool' for humans to use for their own benefit;
- there are four main societal concerns – 1) is it safe to edit genes? 2) what will the environmental impact be once the technology is released from the laboratory setting? 3) consumers want the

right to choose to whether to accept gene editing or not, 4) what is the impact on animal welfare?

- genome editing tools could be good news in the short term because of immediate gains that they may bring in terms of potential refinement and reduction gains, but it is far from certain as to what the longer term future holds and whether the technology will be responsibly used.