RSPCA Response to Genome Editing and Farmed Animals, Nuffield Council for Bioethics Call for Evidence, September 2019

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Summary

1. The RSPCA welcomes the Nuffield Council on Bioethics inquiry into the use of genome editing in farmed animals. We acknowledge that humans have been altering farmed animals for millennia, including via conventional breeding techniques and surgical procedures. However, the increasing use of drugs, hormones and now genome editing (GE) technologies threatens to push farmed animals even further towards - or beyond - their biological limits.

2. We are deeply concerned that:

   - Genome editing techniques can cause unpredictable and unintended changes to the genome - the precision and safety of the technology have yet to be satisfactorily demonstrated
   - GE is being lauded as a solution to myriad problems faced by the livestock industry without exploring - or effectively applying existing - alternative approaches to securing a sustainable food supply
   - Public opinion on the use of GE in animals for food production has not yet been sought in a balanced and unbiased manner; the public perception of GE is currently being manipulated by those with a vested interest in the technology

3. Below, we have answered those questions in the consultation document that specifically address the animal welfare, ethical and regulatory issues that are most relevant to the RSPCA's remit.

4. **6. What are the societal, production, environmental and policy challenges to which genome editing applications in farmed animals might offer a response?**

   As other respondents will no doubt detail, GE has been posited as a viable tool to address challenges such as increasing human demands for: animal protein, meats of specific qualities and animals resistant (or resilient) to infectious disease. It has also been suggested to help ameliorate global heating (e.g. by creating heat tolerant animals). It was disappointing that this question did not include animal welfare challenges, e.g. ways of avoiding mutilations - although the RSPCA believes alternative approaches to GE should be used, as outlined below.

5. Groups with an intellectual, or economic, interest in genome editing are likely to promote the techniques as an appropriate response to these challenges, including those of animal welfare. But the RSPCA believes it is essential to recognise that the technology is just one approach, which should be objectively considered alongside more ethically defensible alternatives, e.g. improved animal husbandry; reduction of food wastage. We also strongly question the necessity of further increasing production in farm animals via any technique, including genetic alteration.

6. **7. How might genome editing technologies help to address these challenges, and what practical benefits and drawbacks would genome editing applications have over existing or envisaged alternative approaches?**

7. The RSPCA is aware of the arguments that genome editing could help to address these challenges[1]. There are, however, significant drawbacks.

8. For example, in the case of disease resistance (or resilience), each pathogen can adapt and change, making benefits short-lived; different strains and serotypes may need addressing; and inherent disease resistance may mask poor practices on-farm. GE for disease resistance would also have to prevent initial infection triggering the disease process, but without harbouring the pathogen (i.e. creating asymptomatic carriers). Failure to address this would create a disease reservoir for non-edited animals or wildlife.

9. Widespread adoption of a limited number of edited genetic lines across the sector would result in further reduction of genetic diversity within populations, making them more susceptible to outbreaks of infectious disease, and less capable of coping with environmental change.

10. Instead, the focus should be on increasing genetic diversity in these highly inbred animals. For example, there are only two Y chromosome lineages in the US dairy Holstein population[2]. A fresh approach to conserving animal genetic resources would support sustainable productivity and food security[3]. This, along with vaccine development and improved biosecurity, will require time, money, changes in husbandry practices, production rate, and changes in policy, but all of these represent a sustainable and less ethically questionable approach that does not involve violating the genome of a sentient being using a technology that carries inherent risks.

11. This is just one example that sets out the drawbacks associated with genome editing animals, and the necessity to give due weighting to alternatives.

12. **8. What groups or organisations are likely to benefit most from the use of genome editing in farmed animals and what groups or organisations might be disadvantaged?**

13. Clearly, those with an interest in the technology, including biotech organisations and the larger breeding companies, will be the immediate beneficiaries. If food products from genome edited animals are brought to the market, consumers who are not concerned about animal welfare and ethical issues may also benefit, for example if food is cheaper. However, people who *are* concerned, and who want to buy products that fit their personal ethics, will be disadvantaged unless labelling is clear and unambiguous.

14. Smaller producers, who are unable to profit from genome editing technologies - or may choose not to do so on ethical grounds - will also be disadvantaged.

15. The animals themselves are the key stakeholders who will be most disadvantaged by genome editing, because of the harms involved and the negative effects on their integrity, as set out in our responses to the questions on ethics.

16. **9. What do you think are the broader social, economic and political drivers that will facilitate, impede or otherwise shape the development and use of genome editing applications in farmed animals, and what effect do you think these will have?**

17. Political drivers, in the form of public concerns about ‘naturalness’ and animal integrity, could either facilitate or impede the development and use of GE applications

in farmed animals. Of course, there are multiple ‘publics’, and different people’s opinions and concerns are likely to vary regarding whether, and how, it is acceptable to use farmed animals as food.

18. For example, governments and many individuals are increasingly acting upon environmental and animal welfare concerns. This is evidenced by changes in people’s dietary habits in the UK and in other countries and cultures, with less reliance on animal protein and/or less food waste. This may reduce the demand for animal products - so GE techniques intended to increase yields may no longer be considered necessary and would be classified as an ‘unjustifiable benefit’.

19. The RSPCA believes that public concerns about GE farmed animals should be properly researched, acknowledged, and acted upon (see **Q11** below).

20. **10. How might differing regional social, economic and political drivers influence the likely development and adoption of genome editing applications in the UK, the EU and the rest of the world?**

21. As the UK prepares to leave the EU, the Government is seeking to procure new trade deals with international partners that may have lower standards of animal welfare and regulation. This could lead to pressure for domestic regulatory standards to be lowered accordingly, which is a real concern.

22. The method of leaving the EU will determine the impact on the UK. Under a ‘no deal’, the UK will lose convergence parity with the EU on regulatory standards. The EU classifies gene editing under the GM regulations, limiting any procedures or products entering the market. The UK may diverge from this position once it leaves, so opening up the possibility of increased development of domestic products derived from genome-edited animals and imports of such products from countries such as the USA where GE is more widespread. The UK Government has stated it would not lower its animal welfare standards in any new trade deals, but increasing divergence from the EU model will increase the pressure for it to do exactly that. This would be unacceptable to the RSPCA - and many others, judging by recent media and public pronouncements.

23. **11. What effect do you think public attitudes will have on innovation in this field (in the UK, the EU and internationally) and how should researchers and policy makers take account of these?**

24. Public attitudes could either favour innovation (if gene edited animal products prove safe and cost-effective), or hamper it, if people are concerned about animal welfare, ‘naturalness’, animal integrity, harms that should not be done, or benefits that cannot be justified.

25. For example, when the Royal Society explored UK public perceptions of genome editing in 2017, participants were ‘not convinced of the need’ to use GE to develop faster growing animals for human consumption[4]. Participants deemed genome editing farm animals to increase efficiency/profitability to be a ‘less acceptable’ use of the technology.

26. Since then, consultations have, in our view, been designed with implicit bias, using non-neutral language, and deliberately excluding subsections of society, and have often been put forward by bodies not independent of the GE industry. For example, a recent survey by the Roslin Institute[5] appeared heavily weighted towards providing ‘evidence’ to help ensure public acceptance of GE animals:

- Gene-edited plants and animals were considered together, with just one question asking whether a distinction should be made between them, but providing no opportunity for participants to explain why.

- Respondents were given no opportunity to express their concerns about animal welfare, ethics, or 'naturalness' with respect to GE animals.
- Respondents were expected to accept that GE will always improve animal health, yet none of the questions related to this. Instead, there were questions about acceptance of products such as meat from chickens edited to produce Omega-3, with no opportunity to explain why one would, or would not, consider purchasing this.
- If respondents indicated that they did not buy meat products, they were excluded from participating further.

27. Similarly, a study of public attitudes in the United States posited the use of GE to create polled cattle as the alternative to the current practice of disbudding/dehorning animals (often with insufficient pain relief). Unsurprisingly, many respondents agreed that GE was a better option when faced with this binary choice. A smaller percentage of participants responded with more nuanced questions around the need to remove horns at all, or the use of appropriate anaesthesia and analgesia at the time of the procedure[6]. Factors such as these should always be included in the information for survey participants, as they are valid alternative approaches which should be given due consideration.

28. Such attempts to manipulate public perception of gene editing animals for human consumption are of grave concern. Those who have a vested interest in the technology also use the term ‘precision breeding’ to refer to GE[7]. We believe this euphemism is chosen to manipulate the public’s perception of the genetic modification of animals, and must be challenged.

29. **The RSPCA believes that it is unacceptable to seek to ‘normalise’ food products from genome-edited animals, and thus normalise the practice of instantly editing animals on demand to suit human needs.**

30. We believe that further appropriately structured and funded public consultation on the acceptability of genome editing farmed animals is essential. This would require resource, which would be justified because of the high level of public concern regarding farm animal welfare. Evidence for this includes the fact that 279,205,000 animals were raised to RSPCA Assured standards in 2017, and year on year there are increasing demands for retailers and supermarkets to stock RSPCA Assured products[8,9].

31. All consultations should include an appropriate level of unbiased information on GE techniques, the (direct and indirect) impacts of these on animals, the challenges they are intended to address and the current or future alternatives to tackling these challenges. The results should be respected and acted upon by researchers and policymakers.

32. Such consultations should be conducted as a matter of urgency, because regardless of the current lack of public acceptance[10], GE has been used in recent years to generate hundreds of edited pigs, cattle, sheep and goats[11]. These will potentially be used to create genetic lines with disease resistance and resilience traits[12,13], or enhanced productivity[14–16]. If the majority of people are not willing to accept GE animal products, then there is no market for them, and research efforts - and animal lives - are wasted. This raises the question of why research into generating GE animals is being funded by the taxpayer, and how the public might feel about being unwittingly complicit in this research.

33. A recent call for connecting informed public opinion to scientists and policy makers suggested a consortium of organisations including the ‘multitude of actors invested in and concerned about gene editing’ animals[17]. The consortium’s role would

include mapping out communities with different levels of engagement in the debate about GE and providing them with appropriate evidence-based information. The consortium would then communicate the range of views to policymakers and scientists, correcting any misconceptions that they may have about people's perspectives on the development of a technology, for example, that they will inevitably reject it or never understand it. The RSPCA would welcome this approach.

Ethics

34. **12. Are there any categorical ethical objections to genome editing farmed animals and if so on what grounds are they based?**

35. Previous considerations about the impact of emerging biotechnology on farm animals are worth revisiting. The Farm Animal Welfare Council (FAWC) *Report on the Implications of Cloning for the Farming of Livestock* lists activities which may be considered categorically ('intrinsically') objectionable:

(i) 'If it inflicts very severe or lasting pain on the animals concerned;
(ii) 'If it involves an unacceptable violation of the integrity of a living being;
(iii) 'If it is associated with the mixing of kinds of animals to an extent which is unacceptable;
(iv) 'If it generates living beings whose sentience has been reduced to the extent that they may be considered mere instruments or artefacts.'

36. The first of these is an absolute wrong: no animal is to be used like this even if there might be a benefit for humans. The last three are less clear cut - some may consider them absolute wrongs, while others may regard them as intrinsically undesirable acts which might still be excused under particular circumstances. In particular, genetic modification methods - including GE - would be considered by many to be an example of (ii) - an unacceptable violation of the integrity of the animal and their dignity, as highlighted by the Nuffield Council on Bioethics Review Of Research On Public Perspectives[18], and others[19,20]. It also reinforces the perception of animals as commodities rather than individual sentient beings.

37. The RSPCA recognises that all animals have their own intrinsic value, entirely distinct from their value to humans (their extrinsic or instrumental value). Genome editing an animal to create an organism of specific instrumental value to humans violates an animal's intrinsic value, without their awareness, before their life even begins. In our view this would be ethically unacceptable to many.

38. A key question is whether GE might be justifiable, if alternative approaches to solving the problem would be worse. But answering this question requires full exploration of available alternatives, and the RSPCA is not satisfied that this has been done in most (if not all) of the potential applications of GE in livestock animals thus far.

39. **In light of this, and the unintended genomic alterations the technology creates (see Q17), the RSPCA believes that genome editing animals for food is an absolute wrong, and not justifiable. Sustainable changes in human consumption of animal products, and alternative approaches to animal husbandry that put animals' needs towards the forefront of farming, should be adopted instead.**

40. **13. What, if any, are the ethical differences between using genome editing and deliberately altering an animal's physiology in other ways, for example, by using hormones, surgical procedures or drugs?**

41. This section asks some critically important questions. Below, we have considered the ethical and welfare implications of GE versus using hormones, surgical procedures or drugs. Although in practice animals who have been genome edited will often undergo other husbandry interventions, we have thought about these two approaches separately and set them out in table 1.

42. It is important to note, however, that there is a third approach not accounted for in **Q13** i.e. that there are - or could be - alternatives to both genome editing and 'other ways' of altering physiology, that could lead to the same ultimate desired outcome. For example, fundamental changes in human behaviour and farm animal husbandry are likely to deliver benefits both to people and to animals, whilst also being by far the most acceptable option ethically.

43. The approaches set out in columns one and two of Table 1 both involve harm and distress to animals, raise ethical issues, and are far from ideal. But using hormones, drugs and surgery to alter animals is established practice, with many of the concerns relating to proximate harms to animals, whereas genome editing raises additional wider ethical issues regarding naturalness, integrity and public consent for these techniques to be applied to animals for food. Thus it is difficult, if not impossible, to directly compare these two approaches and identify consistent 'ethical differences'.

44. In our view this question can only be examined one case at a time. For example, consider the case of removing horns from cattle vs genome editing a line of hornless cows. *If* it is justifiable to remove an animal's horns, then what is the most ethical way to do it? From the individual animal's perspective it would be better to be born without horns, and therefore not have to undergo surgery. If tens of animals were subjected to procedures to create thousands of hornless cattle, then solely on the basis of the numbers of animals whose welfare is affected, and the level of suffering if pain is not adequately relieved during and after horn removal, it would appear that GE would be preferable.

45. However, it is not that simple, due to significant and legitimate concerns about naturalness, animal integrity, and societal consent for animals to be altered and manipulated. Is it right in itself to remove the horns of a horned animal, or does this disrespect the animal's telos[21] and disenfranchise people who would not want animals to be mutilated in this way? Furthermore, GE technology is neither proven nor predictable, and results in other changes to the calf's genome[22] (see **Q17**). If it is deemed acceptable to remove an animal's horns to de-risk husbandry practices, then it should be done in a way that causes the least pain, suffering, distress (i.e. using appropriate anaesthesia and analgesia) and not using a technology that will also introduce unintended changes that confer potential disease risk. It is worth noting that traditional selective breeding using naturally occurring polled breeding stock has been practised for many years, though there can be different inherent risks associated with this approach too (see response to question 14).

Table 1. *Comparison of ethical issues associated with hormones/drugs/surgery vs genome editing*

Hormones/drugs/surgery	**Genome editing**
Involves directly administering substances to, or physically altering, one individual animal	Requires multiple founder animals to create a single 'edited' animal
Harms to individual: stress of capture and restraint, discomfort of injections, distress associated with administration of substances and their side effects, pain of physical alteration if inadequate (or no) analgesia, pain of neuroma formation, distress due to being unable to perform natural behaviours (last two in the case of removal of body parts)	Harms to founders: discomfort and stress of injection with hormones for superovulation, restraint and distress associated with embryo transfer or semen collection, risks to dam from non-viable offspring, risk of dystocia due to oversized offspring
Effects are predictable	Unproven technique with potential for unintended harmful consequences - effects cannot be reliably predicted, leading to wastage
Alteration is not heritable, so procedure has to be done to each animal	Heritable - maybe no need for more procedures
Harms to animal every time	May be no additional welfare implications once established
Germ line not altered, but animal integrity affected	'Naturalness'/integrity issue - germline altered significantly in a single step
Questionable acceptability to public	Likely unacceptable to public

46. **14. What, if any, are the ethical differences between using genome editing and using alternative methods such as traditional selective breeding methods, or marker assisted selection to alter the characteristics of a breed of farmed animals?**

47. As above, we have considered the ethical and welfare implications of GE against traditional selective breeding methods, or marker assisted selection. Although in practice, animals who have been genome edited will still be subject to selective/marker assisted selection to ensure the continuation of the edit through the breeding line, we have considered these two approaches separately as set out in Table 2.

48. Again, as in **Q13**, from the perspective of the animals' experience, and from the importance that the public places on animal welfare, both of these methods are far from ideal. If it is justified to create a population of animals that have a desired trait, then what is the most ethical way to do it? From the individual animal's perspective it would be better to be born with that one desired edit incorporated into the genome, rather than be born from an already inbred line that may also carry other deleterious traits. Editing single genes could therefore be considered the ethical way of introducing this trait to the population - but again, only if the technology was proven, predictable and safe for the animal and their offspring (**Q17**) and could be justified as being an entirely necessary change for which there is no non-invasive alternative.

***Table 2** Comparison of ethical issues associated with genome editing vs traditional selective/marker assisted breeding for a specific trait*

Traditional selective/marker assisted breeding	**Genome editing**
Multiple founder animals required to create single animal	Multiple founder animals required to create single animal
Harms to individuals: capture, restraint, pain of injections/epidural, distress associated with administration of substances, side effects, pain, superovulation, embryo transfer, semen collection	Harms to individuals: capture, restraint, pain of injections/epidural, distress associated with administration of substances, side effects, pain, superovulation, embryo transfer, semen collection; risks to dam from non-viable offspring, dystocia
Selecting for specific traits may also introduce deleterious phenotypes due to genetic linkage	Single genes may be edited individually, (or 'multiplexed' with other desired traits), thereby theoretically avoiding carrying over linked deleterious genes
Desired traits limited to already inbred lines	Desired traits may be introduced to any genetic background
Rare and/or recessive traits will take several generations to establish within a population, resulting in wasted animal lives	Desired traits can be established within a single generation
Predictable	Unproven technique with potential for unintended harmful consequences - effects cannot be reliably predicted, leading to wastage
Germ line altered more gradually, and in a more 'natural' way	'Naturalness'/integrity issue - germline altered significantly in a single step
Acceptable to public	Likely unacceptable to public

50. **15. What, if any, are the ethical differences between using genome editing, which relies on the cell's own repair mechanisms, and using genetic modification techniques that insert transgenes into organisms?**

51. In many cases of GE, the aim is to recreate naturally occurring mutations, for example, in the case of polled cattle. However, this still involves disrupting the integrity of the animal's genome, even if the outcome of this interference is thought to be comparable to a genome that occurs naturally. The insertion of transgenes - genetic material that originates in a different species - into an animal's DNA can be achieved through previous genetic modification (GM) technology, or through the newer GE techniques. Transgenesis carries with it an extra dimension of ethical concern. Creating a transgenic animal means incorporating the DNA of another species, something which could never occur through traditional selective breeding methods. This brings to bear legitimate and fundamental concerns about 'naturalness' and animal integrity. We have set out to compare GM transgenesis with GE in Table 3.

52. We believe that comparing the ethics of GE with that of transgenesis by earlier GM techniques is not a directly binary comparison. GE, like earlier forms of GM, breaks the genome to create desired alterations, and both carry with them known harms to individual founder animals, inherent risks of imprecision, wasted animal lives, unintended genetic alterations that may lead to disease outcomes, unpredictable phenotypic outcomes from a welfare perspective, and both are likely to be unacceptable to the public for use in animals for food production.

53. The added ethical concern of transgenesis - inserting a gene from a different species - can be achieved using GM techniques, but also via the newer GE technology. The incorporation of the DNA of a different species into an animal's genome is another issue in its own right, and is commonly perceived as being more of a violation of 'naturalness' and integrity than the intrinsic activity of genome modification in itself [23,24].

Table 3 *Comparison of ethical issues associated with GM insertion of transgenes vs genome editing*

GM insertion of transgenes	**Genome editing**
Ability to insert genes from other species (but also ability to insert same species, or naturally occurring mutations)	Ability to insert genes from other species (but also ability to insert same species, or naturally occurring mutations)
Transgenesis does not occur naturally, therefore concerns about 'naturalness' and interfering with animals' integrity[20,24].	Recapitulation of naturally occurring mutations (e.g. 'polled' cattle) that arise through natural breeding processes.
Multiple founder animals required to create single animal	Multiple founder animals required to create single animal
Less efficient process requiring greater number of animals	More efficient process requiring few animals
Harms to founders: capture, restraint, pain of injections/epidural, distress associated with administration of substances, side effects, superovulation egg collection, embryo transfer, semen collection, risks to dam from non-viable offspring, dystocia	Harms to founders: capture, restraint, pain of injections/epidural, distress associated with administration of substances, side effects, superovulation egg collection, embryo transfer, semen collection, risks to dam from non-viable offspring, dystocia
Single genes may be edited individually, without carrying over linked deleterious genes	Single genes may be edited individually, or may be multiplexed, without carrying over linked deleterious genes
Awareness of unintended effects, such as incorporation of viral vector DNA, gene duplication, and random insertion throughout genome widespread in literature.	Under-reported unintended effects, such as insertion of template plasmid DNA containing antibiotic resistance genes [22]
Established technique with potential for unintended harmful consequences - effects cannot be reliably predicted, leading to wastage	Unproven technique with potential for harmful consequences, such as cancer risk associated with mechanism of DNA repair[25] - effects cannot be reliably predicted, leading to wastage
Easily identifiable molecular signatures enables detection and therefore traceability	Technically difficult to distinguish GE genomes from naturally occuring mutations therefore traceability a concern
'Naturalness'/integrity issue - germline altered significantly in a single step	'Naturalness'/integrity issue - germline altered significantly in a single step
Unacceptable to public	Unknown acceptability to public

54. **16. Are some but not other applications of genome editing in farmed animals acceptable and, if so, on what does their acceptability depend (for example, improving animal welfare, meeting objectives of importance for animals or humans, etc.)?**

55. The only application that the RSPCA could ever consider acceptable would be for animal welfare, but with the current state of the technology, this is unlikely to be relevant. Even if the technology carried no inherent risk per se, we cannot think of a potential welfare-related application that could or should not be achieved by other means that do not involve painful procedures and tampering with the animal's integrity. All of the benefits that have been described so far in the scientific literature are ultimately for humans, not in the interests of the animals themselves.

56. We do not rule out that some future GE application in farmed animals may result in a real and sustainable improvement in animal welfare that cannot be achieved through other less harmful approaches. However, we remain unconvinced that this will be the case. GE applications posited as improving animal welfare, for example disease resistance, hornless cattle, castration of pigs or sterility in farmed salmon to protect the wild population, have not been properly evidenced or subject to adequate ethical challenge. We believe that there are viable alternative approaches, that do not involve gene editing, which could be implemented and should be seen as part of the economic cost of producing and consuming animal products responsibly.

57. The RSPCA believes that applications of genome editing to farmed animals should receive a thorough ethical appraisal. This should include a harm-benefit analysis which asks fundamental questions regarding whether benefits are justifiable, and how benefits for animals, farmers, companies and consumers should be considered. It should also factor in the inherent unpredictability of GE techniques. Such an assessment should be undertaken by an independent, expert body, including multiple perspectives, such as an Animal Welfare Advisory Council which has been proposed as a requirement of the UK Sentience Bill by a number of animal welfare organisations including the RSPCA[26].

Law, regulation and policy

58. **17. Are there reasons to think that genome editing approaches are inherently more likely than alternative approaches to result in adverse outcomes, or to result in outcomes that are potentially more harmful; what are the major risks or uncertainties that regulation should seek to manage?**

59. The answer to the first part of this question is 'yes'. GE techniques can give rise to adverse outcomes due to the consequences of the desired edit, or from the nature of the cell's DNA repair systems that are exploited by the technology. There have been many claims that the newer gene editing techniques are much more precise, and have few (if any) unintended effects. However, there is increasing evidence that off-target and unintended alterations have been under-reported[27,28]. The GE 'polled' calves[29] have subsequently been revealed to carry multiple antibiotic resistance genes from bacterial plasmid vector found within their genomes[22,30] despite the researchers originally reporting no unexpected alterations[22]. The mechanisms that repair double-stranded breaks in DNA from GE can result in increased risk of cancer[25,31,32], and there are increasing reports of widespread deletions and rearrangements[28].

60. Even simple single base editing methods create previously undetected regions of ‘accidental’ editing. In addition, non-coding regions of DNA are increasingly being found to have important roles in gene function and regulation, so inserting genetic material may disrupt gene expression and negatively affect animal health and welfare. These inadvertent genetic changes caused by GE systems are known to be hampering the technology’s uptake in human medicine[33,34]. Science still has a lot to learn about the way cells repair breaks in their DNA, and the undesired effects that gene editing tools can have, after all they have only been in use for a few years.

61. Although the phenotype of some GE animals may be indistinguishable from their wild-type counterparts, adverse effects may not become apparent unless animals are maintained in a less controlled environment than that of the laboratory or experimental farm, or bred in sufficient generations, or in sufficient numbers to indicate trends and significance.

62. Due to the above risks and uncertainties, it is essential to screen the genome, for each line and for a number of generations[22,35] and report any unintended effects, in both genotype and phenotype. Many in science are now calling for a comprehensive and stringent examination of DNA cleavage sites, but this is neither currently common practice nor perceived to be as innovative and attractive a direction to pursue than other lines of GE research.

63. All projects aimed at editing the genomes of animals for human benefit should continue to be regulated by legislation controlling animal research and testing such as the UK Animals (Scientific Procedures) Act 1986, EU Directive 2010/63, and legislation controlling GMOs such as Genetically Modified Organisms (Contained Use) Regulations 2014.

64. **18. What are the roles of policy and markets in shaping livestock farming practices and what should be the key policy objectives in this area?**

65. Supermarkets often protect their brand reputation by imposing their own set of standards for producers. These standards can greatly sculpt farming practices and have resulted in progression on-farm in various areas, e.g. Johne’s disease control on UK dairy farms is now required by most milk buyers and supermarkets selling dairy products. RSPCA Assured products are now sold by Aldi, Asda, Co-op, Lidl, Sainsbury’s, Marks and Spencer, McDonald’s, Morrisons, Ocado, Wetherspoons etc, all of which are responding to increasing demand for higher welfare on farms.

66. Changes to standards are usually made in response to consumer demand or reputational damage, with policy and legislation lagging behind. For example, increasing public concern about antimicrobial resistance led the livestock industry voluntarily to set up sector-specific groups, under the Responsible Use of Medicines in Agriculture Alliance to consider current practices, set targets and disseminate knowledge to producers and veterinarians ‘on the ground’.

67. The key policy objectives (with respect to marketing) should be openness and honesty with the general public. It should be ensured that any GE application in farmed livestock is transparent, accessible to and acceptable to the public, with clearly labelled products, and therefore has a sufficient market prior to its commercial application. As GE animal products are difficult to distinguish from their naturally occurring counterparts, even at the molecular level, there is an imperative to ensure public trust and facilitate informed purchasing choices.

68. **19. Do you think that the existing EU regulatory framework for the production and sale of GMOs is appropriate for genome editing applications in farmed animals and, if not, what alternatives might be considered?**

69. Yes, we believe the existing EU regulatory framework for the production and sale of GMOs is appropriate for GE farmed animals. The lack of public acceptance of genetically modified animals in food in the UK and EU, the absence of consistency in their regulation across international borders, and the technical difficulty in distinguishing naturally occurring mutations from those deliberately engineered, all raise key questions for concerned consumers. As we discussed in **Q17**, the editing of genomes of animals for human benefit should be restricted to regulation by the Animals (in Scientific Procedures) Act/Directive 2010/93/EU, and subject to legislation controlling GMOs such as Genetically Modified Organisms (Contained Use) Regulations 2014.

70. **21. Is there any important question that you think we should have asked or an area that we ought to have covered, or any other information that you would like to bring to our attention in order to help us with this inquiry?**

71. Other applications of genome editing farmed animals include animals used as sources of organs for transplantation, or of biomolecules as 'bioreactors' or 'pharmed animals'. All of these applications raise animal welfare, and in some cases scientific concerns, plus ethical questions that are different from those discussed above and in our view, are outside the scope of this consultation. The RSPCA has serious ethical and animal welfare concerns about these animals. In our experience, the perception that farm animals are 'there to be used' predisposes the public (as a whole) to accept their further exploitation and manipulation. Also, the fact that farm animals may be better housed and cared for in the laboratory is sometimes used to deflect ethical concerns about their use as organ sources, disease 'models' or bioreactors. However, the welfare needs and intrinsic worth of an animal are constant, regardless of their situation or the purposes for which they are being 'used'.

72. We acknowledge that humans have been altering farmed animals for millennia, including via conventional breeding techniques and surgical procedures. However, the increasing use of drugs, hormones and GE technologies threatens to push farmed animals even further towards - or beyond - their biological limits. Many have already reached or even exceeded those limits, with well-documented consequences for their health and welfare[36–38].

73. The RSPCA is deeply concerned that the drive to use GE techniques is outstripping the public debate regarding acceptable innovations. The technology is unproven and causes unintended changes to the genome. Moreover, alternatives to genome editing farmed animals are not properly explored - or where they already exist, not diligently implemented - and the drivers to alter farmed animals are not adequately balanced to take account of legitimate animal welfare, ethical and public concerns.

74. At a time when human impacts on other animals and the environment are under unprecedented scrutiny, we would like to see a watershed for farmed animals. Rather than obtaining ever more productivity and profit from individual animals, who are sentient and have intrinsic worth, it is time for human behaviour change to drive sustainable agriculture that respects farmed animals and their welfare needs.

References

1. Tait-Burkard, C. *et al.* Livestock 2.0 - genome editing for fitter, healthier, and more productive farmed animals. *Genome Biol.* **19**, 204 (2018).
2. Yue, X.-P., Dechow, C. & Liu, W.-S. A limited number of Y chromosome lineages is present in North American Holsteins. *J. Dairy Sci.* **98**, 2738–2745 (2015).
3. Paiva, S. R., McManus, C. M. & Blackburn, H. Conservation of animal genetic resources – A new tact. *Livest. Sci.* **193**, 32–38 (2016).
4. Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society. https://royalsociety.org/~/media/policy/projects/gene-tech/genetic-technologies-public-dialogue-hvm-full-report.pdf
5. 14 February 2019 - Survey seeks to gauge public opinion on gene-edited meat. (2019). https://bbsrc.ukri.org/news/food-security/2019/190204-pr-survey-seeks-to-gauge-public-opinion-on-gene-edited-meat/
6. McConnachie, E. *et al.* Public attitudes towards genetically modified polled cattle. *PLoS One* **14**, e0216542 (2019).
7. Acceligen – Precision Breeding for Agriculture & Aquaculture. Available at: https://acceligen.com/. (Accessed: 26th July 2019)
8. RSPCA Assured Annual Review 2017: https://www.berspcaassured.org.uk/media/1293/rspca-assured-annual-review-2017.pdf
9. RSPCA Assured Annual Review 2018 https://www.berspcaassured.org.uk/media/1376/rspcaass_annualreview2018.pdf
10. Jordan, W. Many in Britain still sceptical of GM foods. *YouGov: What the world thinks* Available at: https://yougov.co.uk/topics/politics/articles-reports/2014/02/21/many-britain-remain-sceptical-gm-foods (Accessed: 27th January 2017)
11. Tan, W., Proudfoot, C., Lillico, S. G. & Whitelaw, C. B. A. Gene targeting, genome editing: from Dolly to editors. *Transgenic Res.* **25**, 273–287 (2016).
12. Lillico, S. G. *et al.* Live pigs produced from genome edited zygotes. *Sci. Rep.* **3**, 2847 (2013).
13. Wu, H. *et al.* TALE nickase-mediated SP110 knockin endows cattle with increased resistance to tuberculosis. *Proc. Natl. Acad. Sci. U. S. A.* **112**, E1530–9 (2015).
14. Proudfoot, C. *et al.* Genome edited sheep and cattle. *Transgenic Res.* **24**, 147–153 (2015).
15. Yu, B. *et al.* Efficient TALEN-mediated myostatin gene editing in goats. *BMC Dev. Biol.* **16**, 26 (2016).
16. Crispo, M. *et al.* Efficient Generation of Myostatin Knock-Out Sheep Using CRISPR/Cas9 Technology and Microinjection into Zygotes. *PLoS One* **10**, e0136690 (2015).
17. Burall, S. Rethink public engagement for gene editing. *Nature* **555**, 438–439 (2018).
18. Naturalness-review-of-research-on-public-perspectives.pdf. http://nuffieldbioethics.org/wp-content/uploads/Naturalness-review-of-research-on-public-perspectives.pdf
19. Verhoog, H. Morality and the 'Naturalness' of transgenic animals.
20. Ortiz, S. E. G. Beyond Welfare: Animal Integrity, Animal Dignity, and Genetic Engineering. *Ethics Environ.* **9**, 94–120 (2004).
21. Rollin, B. E. Telos, Conservation of Welfare, and Ethical Issues in Genetic Engineering of Animals. in *Ethical Issues in Behavioral Neuroscience* (eds. Lee, G., Illes, J. & Ohl, F.) 99–116 (Springer Berlin Heidelberg, 2015). doi:10.1007/7854_2014_279
22. Norris, A. L. *et al.* Template plasmid integration in germline genome-edited cattle. *bioRxiv* 715482 (2019). doi:10.1101/715482
23. Oaks, T. Animals in Their Nature: A Case Study on Public Attitudes to Animals, Genetic Modification and 'Nature'. doi:10.1177/0038038504043217
24. Ormandy, E. H., Dale, J. & Griffin, G. Genetic engineering of animals: ethical issues, including welfare concerns. *Can. Vet. J.* **52**, 544–550 (2011).

25. Ferrarelli, L. K. CRISPR, cancer, and p53. *Sci. Signal.* **11**, eaau7344 (2018).
26. Written evidence - RSPCA. Available at: http://data.parliament.uk/WrittenEvidence/CommitteeEvidence.svc/EvidenceDocument/Environment,%20Food%20and%20Rural%20Affairs/Draft%20Animal%20Welfare%20Sentencing%20and%20Recognition%20of%20Sentience%20Bill%202017/written/76684.html. (Accessed: 18th September 2019)
27. Thomas, M., Burgio, G., Adams, D. J. & Iyer, V. Collateral damage and CRISPR genome editing. *PLoS Genet.* **15**, e1007994 (2019).
28. Kosicki, M., Tomberg, K. & Bradley, A. Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nat. Biotechnol.* **36**, 765–771 (2018).
29. Carlson, D. F. *et al.* Production of hornless dairy cattle from genome-edited cell lines. *Nat. Biotechnol.* **34**, 479–481 (2016).
30. Latham, by J. FDA Finds Unexpected Antibiotic Resistance Genes in ‘Gene-Edited’ Dehorned Cattle. *Independent Science News | Food, Health and Agriculture Bioscience News* Available at: https://www.independentsciencenews.org/news/fda-finds-unexpected-antibiotic-resistance-genes-in-gene-edited-dehorned-cattle/. (Accessed: 13th August 2019)
31. Ihry, R. J. *et al.* p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells. *Nat. Med.* **24**, 939–946 (2018).
32. Haapaniemi, E., Botla, S., Persson, J., Schmierer, B. & Taipale, J. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. *Nat. Med.* **24**, 927–930 (2018).
33. Keep off-target effects in focus. *Nat. Med.* **24**, 1081 (2018).
34. Wienert, B. *et al.* Unbiased detection of CRISPR off-targets in vivo using DISCOVER-Seq. *Science* **364**, 286–289 (2019).
35. Aryal, N. K., Wasylishen, A. R. & Lozano, G. CRISPR/Cas9 can mediate high-efficiency off-target mutations in mice in vivo. *Cell Death Dis.* **9**, 1099 (2018).
36. de Jong, I., Berg, C. & Butterworth, A. Scientific report updating the EFSA opinions on the welfare of broilers and broiler breeders. *EFSA Supporting* (2012).
37. Hiemstra, S. J. & Napel, J. T. *Study of the Impact of Genetic Selection on the Welfare of Chickens Bred and Kept for Meat Production*. (2013).
38. Oltenacu, P. A. & Broom, D. M. The impact of genetic selection for increased milk yield on the welfare of dairy cows.