Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals'

September 2019

Executive summary

- Novel genetic technologies have the potential to accelerate the pace of genetic improvement of livestock species, particularly through the rational design of novel alleles, and the introgression and promotion of favourable alleles in more efficient ways than through conventional breeding methods. Ongoing research projects in farmed animals are focusing on genes implicated in a variety of traits.

- A framework for deciding on the suitability and sustainability of technological applications, such as genome editing, should encompass different and sometimes competing factors related to the societal, production, environmental and policy challenges involved. Technological interventions, which should be locally adapted to the needs and contexts of human and animal populations and their environments, are only one facet of more complex management strategies. Key policy objectives in shaping livestock farming practices should be: (a) the implementation of the highest possible welfare standards; (b) the protection of biodiversity and the environment; and (c) the production of safe, nutritious and affordable food.

- The existing EU regulatory framework for genetically-modified organisms is stifling innovation and potentially leading to missed opportunities for sustainable development. A desirable regulatory framework should be proportionate to risk and not exclusively focused on the techniques involved in the product development process. Regulatory alignment and common standards at a global level are called for, alongside efficient, effective and accessible routes for knowledge exchange. If applications of the technology are based on research utilising genetic resources, then the benefits derived from the research must be shared to enable fair access to these benefits.

- Researchers and policy makers must continue to engage with the public in discussions surrounding genetic technologies and find ways to communicate useful and trustworthy information. Among the multiplicity of factors influencing the development and use of genome editing in farmed animals, societal acceptance is arguably the most important factor, since public views and attitudes strongly influence the economic relationships between producers, suppliers and consumers.

- CRISPR-based genome editing allows for a wider portfolio and more sophisticated gene targeting applications compared to previous methods based on randomly inserted transgenes. However, there are at present technical limitations and constraints, which will be partly overcome as the techniques mature and our understanding of the relationship between genes and traits improves.

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- There are a number of ethical issues raised specifically by the adoption of novel genetic technologies for livestock improvement. These pertain to: the novelty of the techniques, the purpose for introducing a specific genome modification and the ways in which it is achieved, and our understanding of the potential effects and impact of those changes on the welfare of the animal. Ethical consideration should be also given to: how people see animals in themselves and in their relation to humans (e.g. as sources of food and other commodities), the responsibility of scientists who carry out the research and those in the supply chains who bring the discoveries to market.

- Notwithstanding current incomplete understanding of how genes affect complex traits, and the novelty of genome editing technologies, scientists should be enabled to carry out responsible research and innovation by providing the right checks, balances, and training, which should be informed by a sound ethical framework and implemented through appropriate governance and oversight mechanisms.

Part 1: Current research

1.1 There are several ongoing research projects with the aim of editing the genome of farmed animal species (a sample of published studies is collected in Appendix 1 with a short description of the aims of each project, its driving and limiting factors). In summary, these studies can be classified based on their aims as follows:

- Editing of genetic traits that influence the nutritional profile of animal-derived food products (e.g. reducing milk fat content[1] or removing allergens in goat milk).
- Editing aimed at creating "bioreactors" - animals that produce pharmaceutical and other industrially valuable products (e.g. the generation of transgenic chickens for efficient production of functional human cytokines in the egg white[2]).
- Editing aimed at facilitating xenotransplantation[3].
- Editing of genes that provide resistance or reduce susceptibility to infections and diseases[4].
- Editing for the correction of common genetic disorders in livestock species for the benefit of animal health and welfare (e.g. correction of isoleucyl-tRNA synthetase (IARS) syndrome in Japanese Black cattle using CRISPR[5]).
- Editing of genes that influence body development, growth rates or longevity (e.g. hornless cattle carrying the POLLED allele or growth factors such as the insulin-like growth factor 2 gene (IGF2)[6] or myostatin gene (MST)[7]).
- Editing of genes that influence productivity traits (e.g. rate of egg lay in poultry, or increase of hair fibre lengths in cashmere goats[8]).
- Potential editing of genes that influence behaviour of livestock species (e.g. to reduce aggressive behaviours)[9].

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[1] Martin P. et al. (2017). A genome scan for milk production traits in dairy goats reveals two new mutations in Dgat1 reducing milk fat content. Scientific Reports, 7 (1872). DOI: https://doi.org/10.1038/s41598-017-02052-0

[2] Herron, L.R. et al. (2018). A chicken bioreactor for efficient production of functional cytokines. BMC Biotechnology. 18, Article number: 82. https://doi.org/10.1186/s12896-018-0495-1

[3] Recent coverage about projects underway to develop human organs in livestock: Servick, K. (2019). *Embryo experiments take 'baby steps' toward growing human organs in livestock.* Science magazine, [online] available at doi:10.1126/science.aay5320 and Cohen, J. (2019). *China's CRISPR push in animals promises better meat, novel therapies, and pig organs for people*. Science magazine, [online] available at doi:10.1126/science.aay9194 [both articles accessed on 20 September 2019].

[4] Tait-Burkard, C. et al. (2018). Livestock 2.0 – genome editing for fitter, healthier, and more productive farmed animals. Genome Biology, 19:204. https://doi.org/10.1186/s13059-018-1583-1

[5] Ikeda m et al (2017) Correction of a disease mutation using CRISPR/Cas9-assisted genome editing in Japanese Black cattle. Sci Rep 7 (1) 17827. doi: 10.1038/s41598-017-17968-w.

[6] Xiang, G. et al. (2018). Editing porcine IGF2 regulatory element improved meat production in Chinese Bama pigs. Cellular and Molecular Life Sciences. Volume 75, Issue 24, pp 4619–4628. https://doi.org/10.1007/s00018-018-2917-6.

[7] Wang, X. et al. (2016). Multiplex gene editing via CRISPR/Cas9 exhibits desirable muscle hypertrophy without detectable off-target effects in sheep. Sci. Rep. 6, 32271; doi: 10.1038/srep32271

[8] Wang, X. et al (2016) Disruption of FGF5 in Cashmere Goats using CRISPR/Cas9 results in more secondary hair follicles and longer fibres. PLoS One 11 (10) e0164640. doi: 10.1371/journal.pone.0164640.

[9] For selective breeding of less aggressive behaviours in pigs and underlying genetic traits please see: https://www.ed.ac.uk/roslin/research/isp/improving-animal-production-welfare/genetic-improvement-of-farmed-animals/reducing-aggression-pigs. For genetic selection of maternal behaviour (broodiness) in hens please see:

- Editing of genes that influence sex ratio of the progeny of livestock species or their fertility[10].

1.2 **Novel genetic technologies (genome editing coupled with genomics) have the potential to accelerate the pace of genetic improvement of livestock species**. Significant contributions of novel genetic technologies, such as genome editing, relative to conventional breeding are : (i) the rapid increase of the frequency of favourable trait-associated alleles; (ii) the introgression of favourable alleles from other breeds/species without linkage drag; (iii) creation of de novo favourable alleles[11]. Genetic improvement via traditional breeding programmes is limited by the variation that exists in elite populations and it is difficult to bring in new traits via cross-breeding without diluting the genetic merit of the ensuing progeny, which would require generations of back-crossing to resolve. Genome editing permits precise alteration of single or multiple base pairs in the genome of animals, therefore it allows the introgression of favourable alleles derived from populations for which cross-breeding would be impractical or impossible; it even allows the rational design of novel alleles[12]. This can be achieved in a single generation without dilution of genetic merit. Additionally, current domestic breeding pools often utilise a tiny fraction of the genetic variation available in that species. Wild relatives are a source of key alleles to future-proof agriculture (in the face of changing climatic conditions, for example) and resequencing projects are identifying the function of allelic differences. Beneficial 'wild' alleles can now be incorporated directly into elite germplasm via allele replacement or by recreating mutations using gene editing. This genetic 'rewilding'[13] application could help to reduce genetic erosion and safeguard the genetic diversity of farmed and domesticated animals. It should be noted that, at the herd-level, a general improvement in the health and welfare of domestic species may come alongside an increase in the genetic diversity of domestic livestock populations[14].

1.3 **CRISPR-based genome editing allows for more sophisticated genetic modifications compared to previous methods based on randomly inserted transgenes**. From a technical point of few, CRISPR-Cas9 is a more efficient 'like for like' system for mutagenesis, relative to earlier nuclease-based genome editing tools (e.g. TALENs)[15]. Creation of knock-out (KO) animals, in which gene

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https://www.ed.ac.uk/roslin/research/isp/improving-animal-production-welfare/genetic-improvement-of-farmed-animals/understanding-maternal-poultry

[10] *It was recently reported that "Dr Alison Van Eenennaam (UC Davis) is looking at the use of gene editing in producing all male beef cattle. The aim is to improve efficiencies for beef finishers. The work is trying to duplicate the gene SRY, which is found on the Y chromosome (traditionally, male = XY, female = XX). This will then be introduced to the X chromosome. This would mean that an animal with XX chromosomes will be male, but won't be fertile. To date, the research has produced pregnancies but none have survived."* Available online at https://www.fwi.co.uk/livestock/livestock-breeding/livestock-gene-editing-current-rules-and-potential-benefits

[11] Tait-Burkard, C. et al. (2018). Livestock 2.0 – genome editing for fitter, healthier, and more productive farmed animals. Genome Biology, 19:204. https://doi.org/10.1186/s13059-018-1583-1. See pages 2-3.

[12] Lillico, S. (2019). Agricultural applications of genome editing in farmed animals. Transgenic Res 28(Suppl 2): 57. https://doi.org/10.1007/s11248-019-00134-5

[13] For a discussion about the use of modern biotechnologies for the reintroduction of properties of wild species in the context of crop production and their bearings on organic farming please see Marchman Andersen, M. et al. (2015). Feasibility of new breeding techniques for organic farming. Trends in Plant Science, Vol. 20, No.7. https://doi.org/10.1016/j.tplants.2015.04.011. For the potential introgression of valuable alleles from wild ancestors and extant congeners of farmed animals please see Rexroad, C., et al. (2019). Genome to Phenome: Improving Animal Health, Production, and Well-Being – A New USDA Blueprint for Animal Genome Research 2018–2027. Frontiers in Genetics, 10:327. doi: 10.3389/fgene.2019.00327

[14] Regarding the importance of genetic diversity for the ability of farmed animals to adapt to environmental challenges please see the collections of studies 'Advances in farm animal genomic resources' available online here https://www.frontiersin.org/research-topics/2123/advances-in-farm-animal-genomic-resources

[15] A presentation on the technical advantages brought by CRISPR/Cas9 in the creation of genetically-altered animals was given by Dr Sara Wells at the RSB Animal Science Meeting on 15 February 2018. For more details, please contact alessandro.coatti@rsb.org.uk

function is disrupted by a frameshift mutation or a deletion of a critical exon, has become technically more straightforward. But gene KO animals might not always display a phenotype of interest. A great advantage of CRISPR-Cas9 is the larger portfolio of targeting applications achievable in a more efficient way, such as: small insertion/deletions; point mutations; large deletions.

1.4 **However, there are limitations to the technology:**

- Allelic introgression into elite populations via genome editing requires a clear understanding of phenome/genome relationships, which has been boosted by the availability of high-throughput genotyping and whole-genome sequence data. However these sequencing data have shown that most traits (including those of interest for animal breeding) exhibit "complex inheritance with many genes of small effects, complex epistatic interactions, partly affected by epigenetic mechanisms"[16] so that it is difficult to identify single or few genetic loci[17] with a large enough effect on a trait of interest. The same allelic variant could have different effects if introduced in different breeds because of the effect of different genetic backgrounds. This implies that "while genome editing appears to be a promising breeding tool in cases where relevant variation is caused by known genetic variants, it seems less promising in cases where the trait of interest is genetically complex by nature, being affected by many, mostly unknown genes with complex interactions"[18, 19].
- The reproductive biology of the species under consideration (and our ability to tap into it with the aim of introducing genetic changes in the offspring) also affects the likelihood of realising particular applications in farmed animals. A case in hand is represented by the delay in creating genetically modified chicken with respect to other livestock species. This is due to the fact that it takes about 24 hours from ovulation to lay, during which time the chick embryo develops into approximately 60,000 cells. While in mammalian species one can try and target the fertilised oocyte or the 2-cell stage embryo, in chicken embryos one needs very efficient viral vectors to be able to transduce a sufficient number of cells with the goal to obtain genetically modified chicken in second generation[20]. An alternative and promising method is based on the isolation, culture and editing of the embryonic primordial germ cells (PGCs), which are then returned to the blood stream of surrogate host where they will home in the developing gonads to give rise to edited eggs and sperms[21]. On the other hand, some aquatic species (like salmonids for example) appear particularly tractable to genome editing given that fertilisation is external and one can recover a huge number of eggs for a single donor[22].

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[16] Simianer, H. (2016). Genomic and other revolutions – why some technologies are quickly adopted and others are not. Animal Frontiers, Volume 6, Issue 1, January 2016, Pages 53–58, https://doi.org/10.2527/af.2016-0008

[17] *Also referred to as 'Quantitative Trait Loci' or 'QTL'. These are genetic loci identified through the statistical analysis of complex traits (such as plant height and body weight). These traits are typically affected by more than one gene and also by the environment.*

[18] Simianer, H. (2016). Genomic and other revolutions – why some technologies are quickly adopted and others are not. Animal Frontiers, Volume 6, Issue 1, January 2016, Pages 57, https://doi.org/10.2527/af.2016-0008

[19] Van Eenennaam, A.L. (2019). Application of genome editing in farm animals: cattle. Transgenic Res., 28(Suppl 2): 93. https://doi.org/10.1007/s11248-019-00141-6

[20] McGrew, M.J., et al. (2004). Efficient production of germline transgenic chickens using lentiviral vectors. EMBO Rep, 5, pages: 728-733. https://doi.org/10.1038/sj.embor.7400171

[21] Cooper, C.A. et al. (2018). Innovative approaches to genome editing in avian species. Journal of Animal Science and Biotechnology*,* volume 9, Article number: 15. https://doi.org/10.1186/s40104-018-0231-7

[22] Lillico, S. (2019). Agricultural applications of genome editing in farmed animals. Transgenic Res 28(Suppl 2): 57. https://doi.org/10.1007/s11248-019-00134-5

1.5 **There are also a number of technical constraints that might hold up applications of genome editing in farmed animals**:

- The prevalence of undesired off-target or on-target edits. Despite the fact that CRISPR/Cas 9 made genome editing easier and more accessible, its use can still lead to unwanted artefacts that must be carefully checked for (with the appropriate set of controls). Genotyping and sequencing screens must be implemented in a specific way based on the type of mutagenesis project undertaken[23]. If editing is carried out in embryos, researchers are required to treat F0 animals as potential mosaics and screen them with the appropriate type of assays, before proceeding to generating F1 animals from a subset of selected founders who would carry the desired edits in the germline[24].
- The type of assisted reproductive technologies (ARTs) deployed. Particularly in the case of ruminants, the use of ARTs (e.g. in vitro embryo culture or nuclear transfer) is often associated with major developmental problems, including large offspring syndrome[25]. This raises serious health/welfare issues for both the mother and any live born neonates, which turn out to be abnormal. Different ARTs present different limitations both in terms of their applicability to a given species but also in their impact on the progeny. If genome editing is carried out in embryos through zygotic microinjection, mosaicism could result from the procedure and efficiency of editing is generally lower than with cloning methods[26]. While if adult cells are edited for subsequent somatic cell nuclear transfer, problems with reprogramming of the somatic nucleus could lead to foetal and placental abnormalities, higher than usual pregnancy losses and increased mortality of calves. In both cases, if the number of genome edited founder animals is limited, the risk for increased inbreeding must be carefully managed.

1.6 Further to the above, **there are many processes involved in bringing a genome editing application to market** - laboratory research and proof-of-principle experiments, patenting, technology transfer, licence agreement with commercial partners, trials and validation and regulatory approval. For the generation of genome edited pigs resistant to Porcine Reproductive and Respiratory Virus (PRRV) infections[27] it is estimated that a licenced commercial company will take 5 years to obtain the approval for farming the animals from US regulators.

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[23] Mianné, F. et al. (2017). Analysing the outcome of CRISPR-aided genome editing in embryos: Screening, genotyping and quality control. Methods, 121-122, pp. 68-76.

[24] *"Full characterisation of F1 animals is essential because the outcome of CRISPR induced mutagenesis is variable and cannot be predicted by initial characterisation of F0s" as in footnote reference number 20.*

[25] Hill, J.R. (2014). Incidence of abnormal offspring from cloning and other assisted reproductive technologies. Annu. Rev. Anim. Biosci. 2014. 2:307–21. 10.1146/annurev-animal-022513-114109

[26] Tan, W., et al. (2016). Gene targeting, genome editing: from Dolly to editors. Transgenic Res, 25: 273. https://doi.org/10.1007/s11248-016-9932-x

[27] '*Scientists on brink of overcoming livestock disease through gene editing*'. Guardian, 17 March 2018. https://www.theguardian.com/science/2018/mar/17/scientists-on-brink-of-overcoming-livestock-diseases-through-gene-editing

Part 2: The socioeconomic context

2.1 Genome editing applications in farmed animals might offer a tool with which to respond to the following challenges:

- **Societal**: the need to improve and maintain food safety, to overcome malnutrition, to improve and maintain food security (e.g. in the face of changing climatic conditions), societal calls for increased animal welfare standards.
- **Production**: the need to maintain optimal animal health and welfare (also with implications for protection of public health), to conserve farm animal genomic diversity, to improve animal resilience to environmental challenges, maintain appropriate supply and quality of animal-derived products (in light of changing consumer demand and policy/ regulatory requirements).
- **Environmental**: the need to optimise the sustainability of agricultural practices (including the use of land and other limited resources) to mitigate climate change and environmental degradation, protect and preserve biodiversity in ecosystems, and protect public health (biosafety) e.g. through reducing farm-generated pollution.
- **Policy**: the need to cooperate internationally to meet the sustainable development goals (for example), to enable capacity development and upskill people involved in livestock production internationally, including in low and middle income countries.

A framework for deciding on the suitability and sustainability of technological applications, such as genome editing, should encompass all these different and sometimes competing factors[28]. Sustainability can be understood in relation to three pillars: society, the economy and the environment[29]. If we consider genome editing applications in the context of sustainable food production systems, they should deliver products that consumers want, and that are inherently healthy for them and the environment, while bringing successive balanced improvements in animal welfare outcomes. In terms of economic impact, they should allow farmers to make a profit and provide affordable food, which is as fairly accessible and distributed as possible. Concomitantly, the use of land for farming purposes must not destroy the environment, pollute soil, air and water, or reduce biodiversity, this would otherwise prevent future generations from utilising the benefits we derive from our environment and ecosystems today. Due to the fact that farming encompasses the three pillars mentioned above, decisions that affect the use of genetic technologies in farmed animals must be understood as trade-offs. Complex interdependencies exist between the pillars and there might not always be win-win scenarios.

2.2 Genome editing applied to farmed animals could provide faster and more locally-adapted responses to emerging challenges, at least in some cases. However, we recognise that **technological**

[28] *An analysis of sustainability in farming systems was presented by Prof Michael Lee (University of Bristol and Rothamsted Research) at the RSB Animal Science Meeting in February 2019*. A write-up of the talk is available upon request to alessandro.coatti@rsb.org.uk

[29] The Government Office for Science (2011). Foresight. The Future of Food and Farming. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/288329/11-546-future-of-food-and-farming-report.pdf

interventions are only one facet of more complex management strategies. Additional and alternative approaches, even if less efficient in the short term, must be considered and compared over longer timescales, particularly to avoid apparent "quick fixes" for issues, which may not tackle the often multiple and distinct underlying causes. Certainly, one of the challenges involved in the use of genetic technologies is the detection and tracing of the outputs resulting from their application, particularly if there is a risk of gene edited alleles spreading to wild populations of organisms. The public perception of these technologies, and the needs and opinions of the consumers of products from the livestock farming industry, and of those people affected by the activities of this and related industries, must be taken into consideration when developing *and* deploying management strategies to meet challenges, such as those listed.

2.3 Developing countries could benefit from appropriate uses of genome editing and marker-assisted breeding technologies to improve the nutritional quality of foods derived from livestock, while improving climatic resilience and stacked disease-tolerance mechanisms across livestock populations. However, **to achieve optimal benefit, technological interventions would need to be locally-adapted to the needs and contexts of human and animal populations and environments.** Given the current restrictions on commercial uses of genome editing in food production in Europe, only farmers in other countries such as China, the US or Brazil could farm genome-edited animals. The resultant animal-derived products will also be subjected to an import ban in Europe (at least in the case of food products) but could be traded with other countries with alternative regulatory requirements. The price and accessibility of food and other products derived from genome-edited animals would influence and determine who may or may not benefit from them, thereby requiring careful ethical review of the impact of their application in order to ensure that communities are not disadvantaged indirectly through their use. **If applications of the technology are based on research utilising genetic resources, then the benefits derived from the research must be shared to enable fair access to these benefits, with the aim to prevent exploitation of local communities and unsustainable use of biological resources**[30].

2.4 **A multiplicity of factors (social, economic, political drivers) are shaping the development and use of genome editing applications in farmed animals**. Arguably, it is likely that genome-editing based innovations will be fully and rapidly implemented "if they are suitable for daily use, provide an added breeding benefit, are cost efficient, and society accepts their application in the food chain" - with societal acceptance arguably the most critical factor [31]. This is because societal views and beliefs strongly influence the economic relationships between producers (e.g. farmers), suppliers and consumers. Farmers will only keep livestock if there is a market for their produce. This ranges from local sales (e.g. through farm shops) to much larger scale enterprises and it may also include export as a major outlet for some produce. The latter is therefore influenced by policies from other trading nations. Within the UK, the main purchasers are the supermarket buyers and they have influence over the activities of their suppliers. Supermarkets are both influenced by the perceptions and needs of their consumer clientele (e.g. in relation to food affordability and safety or animal welfare) and in turn influence the customers through directed marketing campaigns (e.g. on grazing or calf housing

[30] The Nagoya Protocol on Access and Benefit-sharing. https://www.cbd.int/abs/

[31] Simianer, H. (2016). Genomic and other revolutions – why some technologies are quickly adopted and others are not. Animal Frontiers, Volume 6, Issue 1, January 2016, Pages 53–58, https://doi.org/10.2527/af.2016-0008

policies)[32]. Such perceptions, and the resultant consumer buying trends, are translated back to the supplier in terms of demand. Thus, one of the drivers of farmers' acceptance of the technology is the perception of how consumers are going to respond to the food derived from genome-edited animals (please see 2.8 below). The perception that consumers might avoid buying meat or dairy derived from genome-edited animals can act to reduce farmers' acceptance of the technology[33].

2.5 As a case study of how political drivers might influence decision-making, the Scottish *Animal health and welfare in the livestock industry: strategy 2016 to 2021* expresses an aspiration to support food production systems that are sustainable and include high standards of animal husbandry and welfare[34]. The policy focus is justified economically given that "the livestock industry alone supports just under 35,000 jobs and contributes £1.6 billion worth of output". The strategy also demonstrates a political commitment to defend the status of Scotland as "a Good Food Nation, and its stewardship of the land, [which] helps maintain Scotland's world-famous landscape". The importance of science and technology in driving development of farming and breeding methods is recognised and reflected where the strategy cites "over £10 million spent on animal science, including research on livestock genetics, product quality, animal health and welfare, and sustainable livestock systems" by the Scottish government. Moreover, the strategy states that "the purpose of these programmes is to reduce the burden of disease, secure a safe supply of high quality food from the livestock industries in Scotland and to improve efficiency while managing environmental impacts and animal welfare". However, the strategy has so far not included genetically-modified organisms (GMOs) and genome editing has valid methods to meet its proposed goals. It has been argued that the reason is mainly political and rests on the perceived detrimental effect that adopting these methods would have on the economic output of the farming sector, driven by the presumed rejection of food derived from genome edited animals by consumers.

2.6 In addition to the aforementioned drivers, the following factors will likely shape the development and use of genome editing applications in farmed animals.

- A global patchwork of regulatory frameworks, which differ significantly across nations, hinders research, product development, trade and creates missed opportunities for sustainable development.
- Trading agreements and international relations can either stimulate or inhibit innovation.
- Political drivers towards more sustainable production systems can alternatively support or prevent the adoption of the technology.

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[32] *To note, we would advise that buyer policies should be based on sound and thorough review of the scientific evidence available*

[33] *In June 2019 the Farmers Weekly reported that "a recent Farmers Weekly poll showed that the farming community is fairly split regarding its use (gene editing in livestock), with 57% of voters in favour of the practice"'. In the same article, farmers interviewed at Oxford Farming Conference in 2019 were quoted to say: "However, I think it's something that needs to be handled quite closely. With my farmer hat on – we're too far removed from the consumer, we have a real challenge to connect with them. With the growing vegan movement – why would we want to alienate our consumers more?" and "My number one issue is, you will need quite a shift in public opinion away from thinking it's Frankenstein food, as any gain we get could be set back by people not buying British pork or beef".* Available online at https://www.fwi.co.uk/livestock/livestock-breeding/livestock-gene-editing-current-rules-and-potential-benefits

[34] The Scottish Government (Riaghaltas na h-Alba). Cabinet Secretary for the Rural Economy. (2016). Animal health and welfare in the livestock industry: strategy 2016 to 2021. Available online at: https://www.gov.scot/publications/animal-health-welfare-livestock-industry-strategy-2016-2021/pages/2/

- Similarly, the influence of multinationals' business choices on the economy and political decisions can act in either direction.
- An appropriate set of IP laws and the use of public domain equivalent licences can enhance the adoption and equity of access of the technique.
- Non-governmental organizations (NGOs) and small and medium sized enterprises (SMEs) could play a role in supporting the adoption of the technique as part of on-the-ground initiatives in low-income countries, where an apparent lack of financial incentives might preclude investment from industry.

2.7 The proposed exit of the UK from the European Union has the potential to greatly influence the development and adoption of genome-editing technologies in farmed animals. However, the present state of political uncertainty makes it very difficult to predict any future outcomes. There is wide recognition that the current EU regulation related to field use of genetic technologies is unsatisfactory[35], not fit for purpose and unjustifiable both from the perspective of risk-assessment and moral/political philosophy[36]. [37]. There is also a risk that the prohibitive European regulatory regime could lead to a 'brain drain' of talented scientists and entrepreneurs, in addition to financial investments, from Europe to countries, such as in South America, where product development and field trials can be more easily conducted.

2.8 Public attitudes and views on a whole host of topics, such as: food systems, markets, profit, party politics, science and technology, can contribute to how people judge the value of technological solutions to societal challenges, including the use of genetic technologies[38]. At a recent meeting of fellows of the Royal Society of Biology, the scientists noted that public acceptability of genome editing varies between sectors, such as where it may be used in medicine versus food production. Some people may see genome editing in medicine as a threat to society beyond safety concerns – potentially risking societal inequality through genetic elitism - while its use in food production may be seen as a personal health risk or as an undefined environmental risk. However, public trust has been forthcoming in cases of therapeutic use of genome editing for serious and immediate health risks more than their potential use in agriculture. It is important for policy makers and scientific institutions[39] to be aware and take into account public attitudes towards the technology and its uses, given that public opinion is a major driver

[35] *The Royal Society of Biology has expressed a view on improvement to regulation, enforcement and inspection for a future UK farming system in paragraphs 56-59 of the response to the 'Health and Harmony' consultation on the future for food, farming and the environment issued by the Department for Environment, Food and Rural Affairs*. Available online at https://www.rsb.org.uk/images/RSB_response_to_Defra_consultation_on_Health_and_Harmony_submitted.pdf

[36] Christiansen, A.T. et al. (2019). Are current EU policies on GMOs justified? Transgenic Res, 28: 267. https://doi.org/10.1007/s11248-019-00120-x

[37] Christiansen, A.T. et al. (2019). Are current EU policies on GMOs justified? Transgenic Res, 28: 267. https://doi.org/10.1007/s11248-019-00120-x

[38] *Given that the adoption of genome editing in farmed animals might bring renewed public interest on the use of biotechnologies in food production, we would like to highlight a study that investigates German consumers' attitudes toward reproductive management practices in dairy cattle. Most people perceived advanced reproductive technologies negatively e.g., the use of sexed semen (53%), embryo transfer (58%), cloning (81%), and hormone treatments to increase fertility (65%). Given the association between genome editing and ARTs it will be worthwhile to consider the two aspects together and provide resources to the public so they better understand reproductive management strategies in farmed animals.* Pieper, L. et al. (2016). Consumers' attitudes about milk quality and fertilization methods in dairy cows in Germany. Journal of Dairy Science Vol. 99 No. 4, 2016. http://dx.doi.org/10.3168/jds.2015-10169

[39] *The Roslin Institute provides a recent example of a research institute engaging with a survey to gauge public opinion on genome edited meat*. https://www.ed.ac.uk/roslin/news-events/latest-news/survey-public-opinion-gene-edited-meat

for political decisions and influences market dynamics. Surveys are one way of collecting quantitative data on public attitudes and a number of them have been devoted to this topic in the last few years[40]. Surveying public attitudes can help to delineate a broad picture but further research should be devoted to understand the justification and basis behind people's views. The Royal Society has recently run a public dialogue, which included a focused group discussion of the issues related to genome editing in animals, and a separate survey of a representative sample of the UK public. The report notes that: "there is more support for the use of genetic technologies in animals to prevent or cure disease than for the production of food" and that "science still needs to engage with poor perceptions of genetic technologies applied to food production in society"[41]. The concerns of the participants, which emerged while considering different applications of genome editing in animals, can be useful to shine some light on the reasons underlying their views. To note, a recent study showed that overconfidence about one's own competence despite an actual lack of scientific literacy and knowledge of relevant facts has been associated with people who have stronger opposing views to GMOs[42]. A different stance is put forward by Couée (2017), who counters that the European public (with strong GM opposition) is "relatively well-informed on scientific discoveries, biotechnological developments, and socio-technological issues" and that some concerns may well be rational. The author concludes that scientists should see the debate as a "stimulating intellectual challenge [...] rather than as a conflict between rationality and irrationality"[43]. Other studies point to the conclusion that "people avoid information to protect an intuitive preference, and they are most likely to do so when the information is most valuable to have"[44]. Clifford and Wendell (2016) argue that "'purity attitudes' [...] are driven by the emotion of disgust"[45]. In their studies they find "that greater sensitivity to disgust is associated with support for organic foods, opposition to genetically modified foods, and anti-vaccination beliefs". In practice, for example "claiming the presence of 'toxic chemicals' in vaccines[46] or GMOs may be an effective way to induce disgust in the listener". The authors further conclude, "whether interest groups choose to frame their causes in terms of purity or alternative motivations could have important implications for the ideological makeup of supporters and the political future of these issues". The media encouraging hype surrounding scientific research and technologies is certainly an issue to be limited where possible, for example through the clear and in-depth communication of scientific concepts and the complexities of the issues involved. A recent survey indicates that the UK public seems much more in line with scientific opinions

[40] *Please find in Appendix 2 a short summary of views of the UK, EU and US public on the use of genetic technologies*.

[41] The Royal Society (2018). Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society. Please see page 77. Available at https://royalsociety.org/-/media/policy/projects/gene-tech/genetic-technologies-public-dialogue-hvm-full-report.pdf.

[42] Sample, I. (2018). Strongest opponents of GM foods know the least but think they know the most. Guardian, [online]. Available at: https://www.theguardian.com/environment/2019/jan/14/gm-foods-scientific-ignorance-fuels-extremist-views-study

[43] Couée, I. (2016). Hidden Attraction. Empirical Rationality in GMO Opposition. Trends in Plant Science 21 (2), p. 91. DOI: 10.1016/j.tplants.2015.12.002.

[44] Woolley, K., Risen, J. L. (2018). Closing your eyes to follow your heart. Avoiding information to protect a strong intuitive preference. Journal of personality and social psychology 114 (2), pp. 230–245. DOI: 10.1037/pspa0000100.

[45] Clifford, Scott; Wendell, Dane G. (2016): How Disgust Influences Health Purity Attitudes. In Polit Behav 38 (1), pp. 155–178. DOI: 10.1007/s11109-015-9310-z.

[46] *Amin et al. (2017) look into vaccines based on the respective 'moral foundations theory.' They find that vaccine hesitancy is associated with foundations [values] of 'purity' and 'liberty,' but not 'harm' and 'fairness.' They further found 'purity' tied to beliefs like "vaccines contain poisons and toxins, while diseases like measles are natural" and 'liberty' tied to beliefs like "vaccine mandates violate civil liberties and are excessive government control."* See Amin, A. B. et al. (2017). Association of moral values with vaccine hesitancy. Nature Human Behaviour 1 (12), pp. 873–880. DOI: 10.1038/s41562-017-0256-5.

on GMOs, than many politicians or media outlets. Proponents hope they could "help feed the work and save the environment," whereas "opponents are most concerned about possible impacts on health"[47].

2.9 **Researchers and policy makers must continue to engage with the public in discussions surrounding genetic technologies**, considering that the adoption of such technological interventions should be based on the evidence of risk, areas of uncertainty and expected long-term effects of the technology, but also societal, needs, views, values and expectations. Work is needed on methods to enable more effective dialogue on, and broad societal comprehension of, the potential for change, and the challenges and opportunities, arising from genetic technologies. People should be involved in discussions around changing personal behaviours in combination with the adoption of technological solutions. There is the need to carefully consider the language used; for example, we should 'educate' children and provide 'tools' for adults, so that all can take part in a broader, transparent conversation. The use of jargon is unhelpful. Rather than using the traditional method of stating the 'pros and cons' of using genome editing, the scientific community must start conversations and discuss potential 'trade-offs' of genome editing. Blancke et al. (2017) propose educational approaches to GM opposition, focusing on the message that "genome editing is only a genetic improvement method, or rather a set of methods – nothing more, nothing less." Furthermore, the authors "make clear that many of their concerns [of the public] are legitimate, but that [scientists] need to decouple these concerns from the technology." Finally, the authors clarify that their message is not that scientists need to steer clear of discussing the social, political, and economic issues relating to genome editing. On the contrary, they invite colleagues to become "better informed on such topics so that they can engage with the public in discussions on, for instance, the problems and needs of farmers, the place of agriculture in modern society, the involvement of industry in science and technology, and so on", emphasizing that genome editing should not be at the focus of the discussions[48].

2.10 **An important aspect to consider is how the scientific community can provide useful information to a non-specialist public, which is also deemed trustworthy by them**. What mechanisms generate trust in the public? Rutjens et al. (2018) conducted experiments on moral foundations theory and scientists themselves as trusted actors, the authors conclude that "people believe that scientists place relatively more value on knowledge gain and satisfying their curiosity than on acting morally. They [scientists] were also seen as potentially dangerous. At the same time, scientists were found to be relatively well-liked and trusted". Thus, they concluded that "scientists are perceived as capable of immoral behaviour, but not as immoral per se." The authors also conclude that it helps communication if science is presented as providing order and structure to the world, ideally accompanied by "a sense of social moral progress"[49].

2.11 One of the key items raised by the fellows of the Royal Society of Biology at our recent workshop on genetic technologies (across areas of application) was the importance of presenting and communicating full, trustworthy and unvarnished evidence, avoiding hype, managing expectations, and

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[47] Lawton, G. (2018). Revealed: What the UK public really thinks about the future of science. New Scientist, 9/18/2018. Available online at https://www.newscientist.com/article/2179920-revealed-what-the-uk-public-really-thinks-about-the-future-of-science/.
[48] Blancke, S. et al. (2017). De-Problematizing 'GMOs'. Suggestions for Communicating about Genetic Engineering. Trends in biotechnology 35 (3), pp. 185–186. DOI: 10.1016/j.tibtech.2016.12.004.
[49] Rutjens, B.T., et al. (2018). Attitudes Towards Science. Advances in Experimental Social Psychology, Volume 57, pages: 125-165. https://doi.org/10.1016/bs.aesp.2017.08.001

actively identifying and explaining risks and uncertainties to support decision-making that reflects the true state of knowledge. This must be communicated in relation to assessment of the balance of benefits (i.e. trade-offs are as clear as possible) and in an open and transparent manner.

Part 3: Ethics

3.1 The adoption of genome editing for the purpose of farming animals may call into question the ways, conditions and limits of how human seek to improve animals bred and raised for the purpose of providing food and other commodities. **The provision of food[50] and the present challenges associated with it[51] form the necessary backdrop against which we should evaluate how ethical our choices are**. Alternatives to animal-based diets and products must be explored and fairly judged in light of the widest body of scientific evidence available from a variety of disciplines. Exploration of the variety of options available, and the trade-offs associated with their application in different social and environmental contexts, should focus on understanding and addressing the challenges of sustainability, food security, human health, animal health and welfare, climate change, and the preservation of biodiversity and ecosystems. **That said, the act of breeding an animal for a purpose puts the animal under direct human responsibility and the concept of animal welfare then becomes of paramount ethical importance**. In a response to Defra's recent consultation on the Draft Animal Welfare Bill[52], the Royal Society of Biology referred to the concept of a 'life worth living'[53], which should inform the assessment of the use of genome editing in farmed animals: "the value of this approach is to put the animals at the centre and build policies based on evidence from animal welfare studies. In order to achieve a 'life worth living', it is not enough to simply avoid unnecessary suffering and provide for the basic needs of the animals, but also to enhance, whenever possible, the positive experiences for which corroborating evidence exists - e.g. through [meeting] certain wants"[54].

3.2 **There are a number of ethical issues raised when comparing techniques (here, genome editing versus traditional breeding methods) for livestock improvement, and the different types of potential applications:**

- Technical unknowns. Genome editors (e.g. TALENs or CRISPR) have only recently been widely adopted in laboratories and represent a technique that is still maturing. Therefore, one must be aware that this novelty and associated uncertainties have ethical implications, which may require enhanced context awareness, reflection, considerate decision-making[55] and an appropriate

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[50] Food and Agriculture Organisation of the United Nations, (2019). The State of Food Security and Nutrition in the World. Available online at http://www.fao.org/state-of-food-security-nutrition/en/

[51] Godfray, H.C.J., et al. (2010). Food Security: The Challenge of Feeding 9 Billion People.

[52] The Royal Society of Biology (2018). Response from the Royal Society of Biology to the Department for Environment, Food and Rural Affairs' consultation on the draft Animal Welfare (Sentencing and Recognition of Sentience) Bill. Available at https://www.rsb.org.uk/images/RSB_response_Defra_draft_Animal_Welfare_Sentencing_and_Recognition_of_Sentience_Bill.pdf

[53] *The concept of a 'good life for the animal' is a key staple of the Farm Animal Welfare Committee (FAWC) 2009 report* 'Farm Animal Welfare in Great Britain: Past, Present and Future'. Available at https://www.gov.uk/government/publications/fawc-report-on-farm-animal-welfare-in-great-britain-past-present-and-future

[54] The Royal Society of Biology (2018). Response from the Royal Society of Biology to the Department for Environment, Food and Rural Affairs' consultation on the draft Animal Welfare (Sentencing and Recognition of Sentience) Bill. See appendix 3, page 15. Available at https://www.rsb.org.uk/images/RSB_response_Defra_draft_Animal_Welfare_Sentencing_and_Recognition_of_Sentience_Bill.pdf

[55] Eriksson, E., et al. (2018). Breeding and ethical perspectives on genetically modified and genome edited cattle. Journal of Dairy Science, Volume 101, Issue 1, January 2018, Pages 1-17. https://doi.org/10.3168/jds.2017-12962

pathway for translation of research on genome edited animals into production of food and other commodities.

- Present limits in our understanding of the genome-phenome relationship[56] (e.g. genetic control of complex traits; identification of functional mutations; pleiotropic effects and epistasis; epigenetic control of traits; influence of genetic background, environmental factors and sex). The complexity of biological processes involved must not be downplayed and it is ethically relevant that we acknowledge that more basic and applied research needs to be carried out if these applications are to be taken forward. The degree of uncertainty would have to be considered for each project on a case-by-case basis but in a way that does not automatically stifle innovation (more in Part 4 on law, regulation and policy). Even in the case of genome editing to effect change in monogenetic traits (e.g. change to a cellular receptor to prevent infection) the overall impact of using genome editing on the welfare of the animals affected must be considered. A recent high-profile case in humans highlighted how unethical the underlying scientific rational was, because it neglected that altering a gene may help protect against one disease, while making the organism more vulnerable to others[57].
- Types and purpose of mutations. Undoubtedly genome editing methods represent an improvement on previous technological methods of altering the DNA of organisms (e.g. random mutagenesis or methods based on random integration of viral vectors) and allows for a wider portfolio of targeting applications. The reason to introduce a change (e.g. to correct a gene defect for the exclusive benefit of the animal[58] versus to produce a molecule in animal-derived food that will only benefit humans[59]) or the types of change introduced (e.g. editing based on alleles derived from another breed or from a whole different species) have ethical importance, which must be considered.
- Refinement and reduction in breeding programmes. It has been suggested that genome editing could improve rapidity and efficiency in current breeding programmes by avoiding generations of selection within breed, or the need for backcrossing to regain genetic merit after introgression of genes derived from inferior breeds[60]. If this resulted in an overall reduction of animals involved in breeding programmes, and more refined ways to obtain equal level of genetic gain than current methods, the decision to refuse to use the technology would be ethically questionable.
- Assisted-reproduction techniques. A pre-requisite for current and novel breeding methods is the types of ARTs employed (e.g. cloning through somatic cell nuclear transfer and embryo microinjections)[61]. These are not ethically neutral and must be considered in this context. The main factors to take into account are: the burden on females for oocytes production and surrogacy; the use and manipulation of foetal forms[62]; and the risk of increased inbreeding rate and thus

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[56] Mackay, T.F.C., et al. (2009). The genetics of quantitative traits: challenges and prospects. Nature Reviews Genetics, volume 10, pages: 565-577. https://doi.org/10.1038/nrg2612
[57] Cyranoski, D. (2018). Baby gene edits could affect a range of traits. Nature (news). doi: 10.1038/d41586-018-07713-2
[58] see Appendix 1 project 4
[59] see Appendix 1 project 3 or 7
[60] Eriksson, E., et al. (2018). Breeding and ethical perspectives on genetically modified and genome edited cattle. Journal of Dairy Science, Volume 101, Issue 1, January 2018, Pages 1-17. https://doi.org/10.3168/jds.2017-12962. See page 6
[61] Tan, W., et al. (2016). Gene targeting, genome editing: from Dolly to editors. Transgenic Research, 25, 3, pages: 273-87. doi: 10.1007/s11248-016-9932-x.
[62] *We considered ethical problems related to the sentience of foetal forms in Appendix 2 of the Royal Society of Biology response to the Department for Environment, Food and Rural Affairs' consultation on the draft Animal Welfare (Sentencing and Recognition*

inbreeding related problems in the population[63].

- Hereditability and reversibility of the change. The fact that germline genome editing aims at introducing changes that are hereditable and can spread through the progeny of a species is of ethical relevance. Hereditability of the changes and our ability to ensure that genetic lines of animals are preserved/not edited or that the process could be reversed[64] is an additional reason for caution for some.
- Animals containing human material[65]. The generation of human-animal chimeras[66] raises additional ethical questions, for example about the moral status of the hybrid animals.

A utilitarian harm-benefit analysis centred on the costs and benefits to human and other animal populations may be necessary to tackle some of these ethical considerations - but may not be sufficient to resolve them all.

3.3 **There are ethically relevant considerations beyond animal welfare and the aforementioned methodological aspects**:

- The focus of some ethicists on the "wholeness and intactness" of animals (their dignity and integrity)[67]: at least for some of these ethical aspects, e.g. the reference to an animal *telos*[68] or an animal's genetically encoded "nature", the science of animal welfare can inform the way we frame this concept based on our knowledge of the animals' biology and adaptations, in order to guide our ethical decision-making process[69].
- The perceived naturalness of the technology or its uses[70]: this may be of relevance when considering the type of mutations introduced by genome editing.
- The ethical and cultural value of human-animal bonds[71] and their shared histories[72]. This may

of Sentience) Bill. Available at: https://www.rsb.org.uk/images/RSB_response_Defra_draft_Animal_Welfare_Sentencing_and_Recognition_of_Sentience_Bill.pdf

[63] Eriksson, E., et al. (2018). https://doi.org/10.3168/jds.2017-12962

[64] Eriksson, E., et al. (2018). https://doi.org/10.3168/jds.2017-12962

[65] The Academy of Medical Sciences (2011). Animals containing human material. London. Available online at https://acmedsci.ac.uk/file-download/35228-Animalsc.pdf

[66] Hughes, J. (2016). *Human-pig 'chimeras' may provide vital transplant organs, but they raise ethical dilemmas*. The Conversation UK. Available online at https://theconversation.com/human-pig-chimeras-may-provide-vital-transplant-organs-but-they-raise-ethical-dilemmas-60648

[67] *Rutgers, B. and Heeger, R. (1999). Inherent worth and respect for animal integrity. In M. Dol, M. van Vlissingen, S. Kasanmoentalib, T. Visser, H. Zwart (Eds.), Recognizing the Intrinsic Value of Nature, Van Gorcum, Assen, the Netherlands (1999), pp. 41-53. Cited by Eriksson, E. et al. (2018) (*https://doi.org/10.3168/jds.2017-12962*) who report that "Rutgers and Heeger (1999) defined animal integrity as the "wholeness and intactness of the animal and its species-specific balance, as well as the capacity to sustain itself in an environment suitable to the species." This view is an influential branch of animal ethics, pointing at aspects beyond animal welfare, concerning the overall respect for another being. Hence, it advocates limits set for acceptable treatment of animals other than utilitarian calculations. Where these limits are set cannot be answered by scientific facts; rather, each answer is embedded in a person's set of values, choice of ethical theory, and worldview."*

[68] Rollin, B.E. (1993). Animal welfare, science, and value. Journal of Agricultural and Environmental Ethics, volume 6 (supplement 2), pages: 44-50.

[69] Fraser, D. (1999). Animal ethics and animal welfare science: bridging the two cultures. Applied Animal Behaviour Science, 65(3), 171-189. Available online at: https://doi.org/10.1016/S0168-1591(99)00090-8

.[70] Verhoog, H. (2003). Naturalness and the genetic modification of animals. Trends in Biotechnology, Vol.21, No.7. doi:10.1016/S0167-7799(03)00142-2

[71] See section on "Communitarian and care-base ethics" in Fraser, D. (1999). Animal Ethics and Animal Welfare Science: Bridging the Two Cultures. Applied Animal Behaviour Science, 65(3), 171-189. https://doi.org/10.1016/S0168-1591(99)00090-8

[72] Berger, J. (2009). Why Look at Animals? London: Penguin, pages 12-37.

guide decisions about the adoption of novel versus traditional breeding methods, and will have an effect on the choices made by consumers of animal products.

- The (factual or perceived) control of food production, supply and demand by multi-national companies, which may affect the choices made by, for example, producers (such as farmers), and consumers (this is a recurrent economic argument for criticizing the use of gene technologies)[73].
- The right of consumers to choose the source of their food and the available standards of traceability and labelling schemes.
- The moral (and in some countries, regulatory) obligation to ensure equity of access to the technology and benefits derived from its use. This should take in to account the impact of applications of genetic technologies on the economy and way of living of local and global communities.
- It is important to include here the responsibility of scientists towards society. Scientists and scientific bodies that engage in public discourse must accept responsibility for factual accuracy and completeness of information. They must also be prepared to continue the conversation ensuring that it is appropriately interpreted by others.

With regards to ethical questions hinging-off the socio-economic and cultural context, an understanding of societal views, values, their motives and underpinnings becomes of paramount importance in guiding decisions.

3.4 Another important ethical aspect for consideration is that **the acceptability of genome editing applications, particularly in the context of global cooperation, will depend on ethical standards of research conduct, which must be culturally appropriate and avoid cross-border exploitation of resources[74]**. As reported recently in *The Biologist*[75], "ethics dumping[76] is a practice that has become more pronounced with globalisation and as the mobility of researchers has increased. It can even occur inadvertently when well-meaning researchers from high-income countries (HICs), who believe they are solving problems in low and middle income countries (LMICs), disrupt local communities in an unethical manner"[77].

[73] Lassen, J. & Jamison, A. (2006). Genetic technologies meet the public—The discourses of concern. Sci. Technol. Human Values, 31, pp. 8-28. https://doi.org/10.1177/0162243905280021

[74] The Global Code of Conduct for Research in Resource-Poor Settings. Available at: http://www.globalcodeofconduct.org/

[75] Schroeder, D. (2019). What is ethics dumping? The Biologist 66(3) p22-25. Available at https://thebiologist.rsb.org.uk/biologist/158-biologist/features/2160-what-is-ethics-dumping

[76] Schroeder, D., et al. (2018). Ethics Dumping - Case Studies from North-South Research Collaborations. 1st ed, Springer International Publishing. Available at: https://www.springer.com/de/book/9783319647302

[77] *The article reports that "in [a] study funded in the US, researchers developed a transgenic banana with enhanced beta-carotene content with the aim of resolving Vitamin A deficiencies in Uganda. Uganda is home to banana varieties that are, in fact, higher in beta-carotene content than the transgenic variety. On a mild reading of this case, one can speak of a waste of resources, but critics noted that this inappropriate and ad hoc overseas solution risked undermining local food and cultural systems. The study was eventually stopped because of research ethics concerns in the US. Hence, the banana was never introduced in Uganda. Other examples of dubious ethical practice when working abroad include researchers conducting research without ethics approval and then trying to obtain it retrospectively (when they realise they need approval to publish); research participants being refused compensation for harm incurred during a study; commercialisation of genetic samples without benefit sharing with local communities; and undertaking high-risk research in a setting that will not benefit from the research results."* Available at https://thebiologist.rsb.org.uk/biologist/158-biologist/features/2160-what-is-ethics-dumping

Part 4: Law, regulation and policy

4.1 In addition to the material of relevance provided in previous parts of this response, we would like to restate here **the need to acknowledge our current limited (though growing) understanding of how genes affect complex traits, and the potential risk of off-target modifications or unwanted side effects due to complex genetic interrelationships.** It may be difficult, therefore, to predict the full effect of certain modifications in large-scale breeding programs. It is also important to add that genome edited alleles may spread by mistake (e.g., genetically modified fish escaping from sea cages) and mitigation in planning is therefore important. **Notwithstanding these difficulties, scientists should be enabled to carry out research in this field and to define pathways for translation of their discoveries, provided the right checks and balances, a sound ethical framework, appropriate governance and oversight mechanisms (regulatory and otherwise) are in place**. Proposals for product development using genome editing must be backed by sound, verified research evidence and clear hypotheses. Financial drivers and stakeholders should be made obvious. Translation pathways must be clearly delineated and appropriately tested. Relevant expert and lay scrutiny must assess the research, translation and impact of proposed developments from the point of view of science, ethics, social acceptability and economics – through sound and thorough review processes and with consideration and involvement given to all affected communities. The overall balance should be sustainable and progressive for society, animal welfare and the environment (including ecosystems).

4.2 **Key policy objectives in shaping livestock farming practices should be: the implementation of the highest possible welfare standards; the protection of biodiversity and the environment; and the production of safe, nutritious and affordable food.** Improved and appropriate registration of individual animal identity (e.g. including registration of the trait introduced by genome editing), traceability (e.g. through current livestock tag and trace systems, or expanding technologies such as blockchain) and monitoring of the impact of application of the technology (e.g. at the level of the individual animal, through linked recording of results of animal health and welfare assessment) must be considered as part of effective and efficient policy and regulatory frameworks. Certification schemes indicating the priority of one or more of the above policy objectives (such as the LEAF Marque[78]), if based on sound evidence and clear, appropriate communication of complete, accurate and trustworthy information, could enable consumers to make more informed choices on some criteria, when buying products. The establishment of independent ethical advisory boards, or committees, to advise organizations directly involved in livestock production, product development and supply chain, as they are regularly in place at research institutions, has been suggested as a governance development which could enable continuity of practice across livestock improvement and production while ensuring that ethical standards and policy objectives are met and kept to[79].

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[78] https://leafuk.org/eating-and-living/leaf-marque

[79] Eriksson, E., et al. (2018). Breeding and ethical perspectives on genetically modified and genome edited cattle. Journal of Dairy Science, Volume 101, Issue 1, January 2018, Pages 1-17. https://doi.org/10.3168/jds.2017-12962. *On pages 13-14 the authors* ***state that:*** *"such advisory boards would ideally act as a resource for breeding organizations in internal discussions and decision-making rather than creating additional regulations or external control. The implementation needs to be made with care, taking each organization's topical ethical issues as point of departure to ensure that it is not imposed from outside. Such boards are already in place in some countries. For example, the Dutch/Flemish cattle improvement co-operative CRV (Arnhem, the Netherlands) has had*

4.3 As described previously in this response, **the existing EU regulatory framework[80] is prohibitive for innovation in genetic technologies**, with significant risks that investment in this area will focus on other parts of the world where regulations are less restrictive. However, food and animal welfare standards are of great importance, and should not be watered down with the goal of encouraging investment in a race to the bottom. The EU regulatory framework makes the approval for all uses of genetic technologies - irrespective of the specific application, the type of change introduced in the genome or the proposed aims of the project – a very difficult, expensive and uncertain process. An alternative regulatory approach, which acts on product development when it reaches its 'proof of concept' stage, considers benefits and hazards of the marketed product and not the techniques involved in the development process, and makes greater use of standards, has been suggested as more favourable approach[81].

4.4 **Regulatory alignment and common standards at a global level are called for. A desirable regulatory framework should be proportionate to risk.** At the recent workshop for fellows and members of our community held by the Royal Society of Biology, with a focus on genetic technologies, several examples of how to account for novel products or traits were considered, and some participants considered a pragmatic approach for short-term improvements to the EU Directive 2001/18/EC[82] while others considered the need for more drastic changes, which could only be effected long-term[83]. The proposed exit of the UK from the EU might open up opportunities to develop a new regulatory system for the UK with respect to genetic technologies: one which supports disruptive innovation with promise for societal and environmental benefit (and while maintaining high standards of animal welfare) and facilitates global knowledge transfer and trade. The UK has a history of international leadership in the development of effective and progressive regulations and guidelines and should be at the forefront of this process, so we must not be left out of the conversation.

4.5 **There is an important need for ongoing development of efficient, effective and accessible routes for knowledge exchange** in relation to genetic technologies and their application. This conversation must include members of society from all backgrounds, including people living and working in low- and

an ethical committee in place since 2002. The committee advises the executive board on ethical issues, such as the application of new technologies (CRV, 2012). The committee consists of an ethicist from a university, farmers, an expert from CRV, and representatives from society. Topics such as in vitro reproduction, embryo cloning, and genome editing have been discussed in the committee. Ethical discussions start internally in CRV; thereafter, the ethical committee is consulted and, when needed, the approval or opinion of the member council of CRV is sought. A dialog with the most important stakeholder is then often initiated[79]. Another active internal ethical committee can be found in the farmer-owned international pig breeding company Topigs Norsvin (Helvoirt, the Netherlands). The committee was introduced in 2005 with the task to review and evaluate various new technologies. It is seen as a necessity by the company, considering today's critical oversight from society (Coöperatie Topigs, 2015)."

[80] The European Commission. Genetically-modified organisms legislation. Available at: https://ec.europa.eu/food/plant/gmo/legislation_en

[81] Tait, J., et al. (2017). Proportionate And Adaptive Governance Of Innovative Technologies (PAGIT): A Framework To Guide Policy And Regulatory Decision Making. University of Edinburgh (Innogen Institute). Available online at http://www.synbio.ed.ac.uk/synbio/sites/sbsweb2.bio.ed.ac.uk.synbio/files/FrameworkReport-Final_170717.pdf

[82] The European Parliament and the European Council, (2001). Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms. Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0018&from=EN

[83] Bratlie, S., et al. (2019). A novel governance framework for GMO. EMBO Rep, 20, e47812. https://doi.org/10.15252/embr.201947812

middle-income countries[84]. As part of this, it is important to make sure that genome editing and genetic technologies in general are not perceived as solely a ‘Western’ technology, or utilized as such. NGOs may have an important role to play in facilitating this conversation in low-income countries, where an apparent lack of financial incentive might preclude investment from industry and other bodies. There are ongoing internationally-led programmes (e.g. under the auspices of the Food and Agricultural Organization of the United Nations) that involve SMEs and on-the-ground initiatives **aiming to ensure access to the benefits to be derived from these and other technologies in agriculture**. Inclusive support and communication frameworks may help to serve unmet needs for locally-adapted research programmes and applications, which could bring incremental positive impact for people and the environment.

[84] Adenle, A.A. et al. (2018). Rationalizing governance of genetically modified products in developing countries. Nature Biotechnology, 36, 137-139. DOI https://doi.org/10.1038/nbt.4069

Appendix 1

Summarised below is published research on genome editing in livestock species targeting genes involved in a variety of traits.

	Aim/objectives	Driving factors	Limiting factors	References
Project 1 **Improving the nutritional profile of goat milk**	Genome scans have identified naturally-occurring variants in the DGAT1 gene that are associated with a reduction in the fat content of milk from two continental dairy goat breeds [1]. The use of CRISPR would greatly accelerate the introgression of the low-fat allele into other breeds, including indigenous breeds better adapted to local environments, compared to conventional breeding.	• Increasing knowledge about the genetic basis of useful traits resulting from functional genomics studies of livestock species • Improvement of the nutritional profile of animal-derived food • Market expansion for goat milk given its desirable characteristics (easily digestible, less allergenic, great nutritional profile) • Genome editing-assisted breeding programmes would speed up the process of genetic improvement[2], reduce inbreeding and maintain or boost genetic gain	• technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of food derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes • barriers to trade due to international relations	[1] Martin P. et al. (2017). A genome scan for milk production traits in dairy goats reveals two new mutations in Dgat1 reducing milk fat content. Scientific Reports, 7 (1872). DOI: https://doi.org/10.1038/s41598-017-02052-0 [2] genetic improvement explained with an example from sheep breeding programmes
Project 2 **Improved meat production in Chinese Bama pigs**	Insulin-like growth factor 2 (IGF2) is an important foetal and postnatal developmental growth factor. Using CRISPR, mutant IGF2 alleles have been produced [3]. These mutants cannot interact with the ZBED6 repressor (the main IGF2 regulator) [4]. The resulting pigs show accelerated growth while maintaining meat quality [3]	• Increased understanding of IGF2 regulation of growth and the importance of the ZBED6 repressor [3] • Improvement of production of porcine meat without reduced quality [3]	• The number of repeats is low throughout and the statistics are weak (particularly the use of SEM)- repeated experiments using larger numbers is essential • public acceptance of food derived from a genetically-modified animal • Analysis of the impact of ZBED6 repression on cardiac muscle and quality of life for life stock is needed.	[3] Xiang, G et al. (2018) Editing porcine IGF2 regulator element improved meat production in Chinese Bama pigs. Cell Mol Life Sci. 75 (24): 4619-4628. • [4] Markljung E et al (2009) ZBED6, a novel transcription factor derived from a domesticated DNA transposon regulates IGF2 expression and muscle growth. PLoS Biology. https://doi.org/10.1371/journal.pbio.1000256
Project 3 **Production of human**	Human interferon beta (IFN-beta) is a Type I interferon that is a front-line therapy for several inflammatory and autoimmune disorders [5] Using CRISPR technology, the authors have produced	• Expanded understanding of CRIPSR technology • Alternative production process for a clinically essential human cytokine that could be	• Clinical viability of the hIFN isolated has not been tested • Experiments are limited to laboratory animals, but could be expanded to live stock- quality of the modified chicken meat would need to be assessed.	[5] Oishi I et al (2018) Efficient production of human interferon beta in the white of eggs from ovalbumin gene-targeted hens. Sci Rep. 8 (1) 10203.

interferon beta from genetically altered hens	hIFN-beta knock-in hens, which express high levels of egg-white hIFN-beta in the eggs [5].	used to treat multiple sclerosis.		doi: 10.1038/s41598-018-28438-2.
Project 4 **Correction of IARS in Japanese Black cattle using CRISPR**	Japanese Black cattle are bred to produce high quality meat. 95% are bred by artificial insemination using with semen from a restricted number of superior bulls. This results in a high prevalence of genetic disorders, including isoleucyl-tRNA synthetase (IARS) syndrome [6]. Using CRISPR, the authors have corrected the main inherited mutation (c.235G>C) The aim is to improve quality of life for Japanese Black cattle while maintaining the quality of the meat they are bred for.	• Expanded understanding of CRISPR technology • Correction of a common genetic disorder associated with a sort after beef breed. • Increase the quality of life of the cattle without impacting the quality of the produced beef	• Long term impact on the welfare of the cattle has not been established • Impact on the quality of the beef has not been established • technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of food derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes • barriers to trade due to international relations	[6] Ikeda m et al (2017) Correction of a disease mutation using CRISPR/Cas9-assisted genome editing in Japanese Black cattle. Sci Rep 7 (1) 17827. doi: 10.1038/s41598-017-17968-w.
Project 5 **Increase hair fibre lengths in cashmere goats using CRISPR**	Cashmere goats produce cashmere wool that is sort after commodity in the fashion industry FGF5 has been shown to be a crucial regulator hair length in humans [7] CRIPSR has been used to modify MSTN and FGF5 genes in goat embryos [8]. The aim is to improve the quality and quantity of the cashmere wool that the goats produce.	• Expanded understanding of the use of CRISPR in embryos. • FGF5 alterations increase the number of secondary hair follicles and the length of hair fibres • The technology could increase the yield of cashmere wool in live stock	• Quality of the resulting wool has not been confirmed • technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of wool derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes • barriers to trade due to international relations •	[7] Higgins CA et al (2014) FGF5 is a crucial regulator of hair length in humans. PNAS 111 (29) 10648-10653. [8] Wang X et al (2016) Disruption of FGF5 in Cashmere Goats using CRISPR/Cas9 results in more secondary hair follicles and longer fibres. PLoS One 11 (10) e0164640. doi: 10.1371/journal.pone.0164640. eCollection 2016.
Project 6 **Increase muscle mass in sheep using CRISPR to modify MSTN**	MSTN (Myostatin) is a muscle growth factor that can be used to increase muscle mass in live stock [9]. Using CRISPR, the authors have altered MSTN in sheep to increase muscle mass [10]. The aim is to increase the quantity of meat produced from sheep.	• The authors used CRISPR to alter three target genes (MSTN, ASIP and BCO2) [10]. • Alterations to the MSTN gene caused muscle hypertrophy, with enlarged muscle fibres • Cell line analysis identified no off target following the introduction of the sgRNAs	• The authors claim that there are no "off target" effects is restricted to tissue culture analysis. • These studies need to be expanded to include a detailed analysis of the modified animals (RNA and protein expression profiles). • Quality of the increase hypertrophic meat needs to be confirmed	[9] Deng B et al (2017) The function of myostatin in the regulation of fat mass in mammals. Nutrition and Metabolism 29: 10.1186/s12986-017-0179-1 [10] Wang X et al. (2016) Multiplex gene editing via CRISPR/Cas9

			• technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of meat derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes	exhibits desirable muscle hypertrophy without detectable off-target effects in sheep. Sci Rep. 26;6:32271. doi: 10.1038/srep32271
Project 7 **Genetic modification of goat milk to replace beta-lactoglobulin with human lactoferrin**	beta-lactoglobulin (BLG) is a major allergen in goat milk that is absent from human milk. The study aimed to use TALEN technology to BLG knock out livestock. These KO goats were then genetically modified to express human lactoferrin (hLF) [11]. The aim is to produce nutritional goat milk without the major allergen.	• Improve our understanding of the technical applications of TALEN technology. • Improved production of goat milk that (potential) has a reduced clinical impact on allergic individuals.	• There is no evidence that the modification will not alter the taste of the produced goat milk • technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of food derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes • barriers to trade due to international relations	[11] Cui C et al (2015) Gene targeting by TALEN-induced homologous recombination in goats directs production of BLG-free, high hLF milk. Sci Rep. 5:10482. doi: 10.1038/srep10482.
Project 8 **Genome editing of livestock species (pigs and cows) to increase content on n-3 PUFA in milk and meat**	1. Generation of cloned pigs that express the cbr-fat-1 gene from Caenorhabditis briggsae, encoding an n-3 fatty acid desaturase. Analysis of fatty acids demonstrated that the cbr-fat-1 transgenic pigs produced high levels of n-3 fatty acids from n-6 analogs. 2. Generation of a mfat-1 transgenic cattle expressed a Caenorhabditis elegans gene, mfat-1, encoding an n-3 fatty acid desaturase. Fatty acids analysis of tissue and milk showed that all of the examined n-3 PUAFs were greatly increased and simultaneously the n-6 PUAFs decreased in the	• Livestock meat is generally low in n-3 polyunsaturated fatty acids (PUFAs), which are beneficial to human health. • Transgenic animals for meat/milk production could supplement higher level of PUFAs to human diets. • This is potentially good for consumers and might also reduce need for fish consumption, with possible environmental benefit.		[12] Transgenic Res. 2014 Feb;23(1):89-97. doi: 10.1007/s11248-013-9752-1. The high-level accumulation of n-3 polyunsaturated fatty acids in transgenic pigs harboring the n-3 fatty acid desaturase gene from Caenorhabditis briggsae. Zhou Y(1), Lin Y, Wu X, Feng C, Long C, Xiong F, Wang N, Pan D, Chen H. [13] Transgenic Res. 2012 Jun;21(3):537-43. doi: 10.1007/s11248-011-9554-2. Production of cloned

	transgenic cow. A significantly reduction of n-6/n-3 ratios (P<0.05) in both tissue and milk were observed. 3. The generation of cloned pigs that express a humanized Caenorhabditis elegans gene, fat-1, encoding an n-3 fatty acid desaturase. The hfat-1 transgenic pigs produce high levels of n-3 fatty acids from n-6 analogs, and their tissues have a significantly reduced ratio of n-6/n-3 fatty acids (P < 0.001)			transgenic cow expressing omega-3 fatty acids. Wu X(1), Ouyang H, Duan B, Pang D, Zhang L, Yuan T, Xue L, Ni D, Cheng L, Dong S, Wei Z, Li L, Yu M, Sun QY, Chen DY, Lai L, Dai Y, Li GP. [14] Nat Biotechnol. 2006 Apr;24(4):435-6. Generation of cloned transgenic pigs rich in omega-3 fatty acids. Lai L(1), Kang JX, Li R, Wang J, Witt WT, Yong HY, Hao Y, Wax DM, Murphy CN, Rieke A, Samuel M, Linville ML, Korte SW, Evans RW, Starzl TE, Prather RS, Dai Y.
Project 9 **TALEN mediated SP110 knock-in increases resistance to tuberculosis in cattle**	SP110 is a nuclear protein that is involved in gene regulation and transcription in mice. SP110 has been shown to control growth of *M. bovis* in macrophages and induce apoptosis in infected cells [12] The aim of this study was to introduce SP110 into cattle to determine if it increased resistance [13].	• Improve our understanding of the technical applications of TALEN technology. • To increase the resistance to tuberculosis in live stock • To improve the quality of life to live stock	• The resistance experiments were performed in culture cell lines- these studies need to be repeated in the transgenic animals to determine if the expression of SP110 does confer resistance. • As SP110 is a gene regulator, off target effects and alterations in the RNA and protein profiles of transgenic animals needs to be analysed. • technical factors: consideration of off-target effects and quality control of the genome-edited allele • public acceptance of food derived from a genetically-modified animal • prohibitive EU approval processes for commercial uses • different regulatory systems in different countries imply country-by-country variation in assessment and approval processes • barriers to trade due to international relations	[15] Pan H et al (2005) Ipr1 gene mediates innate immunity to tuberculosis. Nature. 434 (7034). 767-772. [16] Wu H et al (2015) TALE nickase-mediated SP110 knockin endows cattle with increased resistance to tuberculosis. PNAS 112 (13) E1530-E1539

Appendix 2 – Public views on genome editing

Below are some sources that document how the UK, US and EU public view various applications of genetic technologies:

- The Royal Society commissioned a public dialogue to explore the views of the UK public on the use of genetic technologies in humans, plants and animals (summary report with main conclusions). The headline was that the UK public is cautiously optimistic about the uses of genetic technologies and academics and researchers are the most trusted source of information for the public. The appendix to the report contains a description of case studies discussed with the dialogue participants (page 35), including genome edited pigs as organ donors for human transplants and genome edited salmon that can grow faster and require less wild-caught fish feed to be produced. The public views on these animal applications are described at pages 71-80 of the report.
- The Pew Research Centre survey concluded that most Americans accept genetic engineering of animals that benefits human health, but many oppose other uses. Pew asked questions on the following applications: gene drives, animals for xenotransplantation, livestock production, de-extinction and enhancement of pet animals. The 2017 Gallup survey on values and beliefs noted a new high of moral acceptability of animal cloning.
- The most recent 2019 Eurobarometer survey on food safety in the EU included questions about genetically modified ingredients in food and drinks. Respondents were asked which food safety topics concerned them most by choosing among the topics that they had previously said they had heard about. There is no single food safety concern that prevails in all countries. In broad terms, topics that are better known tend to register the highest levels of concern. Respondents who have heard about at least one food safety topic are most likely to be concerned about antibiotic, hormone or steroid residues in meat (44%), followed by pesticide residues in food (39%), environmental pollutants in fish, meat or dairy (37%) and additives like colours, preservatives or flavourings used in food or drinks (36%). More than a quarter are concerned about food hygiene (32%), food poisoning from bacteria (30%), diseases found in animals (28%) and genetically modified ingredients in food or drinks (27%). Around a fifth say that they are concerned about microplastics found in food (21%) and allergic reactions to food or drinks (20%). Other topics register lower levels of concern: traces of materials that come into contact with food (16%), poisonous moulds in food and feed crops (11%), plant diseases in crops (9%), nanoparticles found in food (8%) and genome editing (4%). The Special Eurobarometer survey in 2010 (SP354) asked a similar question. Although the comparison of these results should be taken with caution, as the question wording and response categories were different, respondents' main concerns were similar in 2010 as in the current survey. Specifically, in the 2010 survey, respondents were most likely to be very or fairly worried about pesticide residues; residues like antibiotics or hormones in meat; and pollutants like mercury in fish and dioxins in pork. These are very similar to the top three answers in the current survey at EU level. 'Genetically modified ingredients in food or drinks', which was the fourth issue respondents were most worried about in the 2010 survey, has been identified as a concern by 27% of respondents in this survey.

Statement

The Royal Society of Biology (RSB) is a single unified voice, representing a diverse membership of individuals, learned societies and other organisations. We are committed to ensuring that we provide Government and other policymakers, including funders of biological education and research, with a distinct point of access to authoritative, independent, and evidence-based opinion, representative of the widest range of bioscience disciplines.

We are pleased to provide this response, which has been informed by input from RSB Member Organisations and individual members across the biological disciplines.

Member Organisations of the Royal Society of Biology

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British Society for Matrix Biology
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British Society of Plant Breeders
British Society for Plant Pathology
British Society for Proteome Research
British Society for Research on Ageing
British Society of Animal Science
British Society of Soil Science
British Society of Toxicological Pathology
British Toxicology Society
Daphne Jackson Trust
Drug Metabolism Discussion Group
The Field Studies Council
Fisheries Society of the British Isles
Fondazione Guido Bernardini
GARNet
Gatsby Plant Science Education Programme (incl. Science and Plants for Schools)
Genetics Society
Heads of University Centres of Biomedical Science
Institute of Animal Technology
Laboratory Animal Science Association
Linnean Society of London
Marine Biological Association
Microbiology Society
MONOGRAM – Cereal and Grasses Research Community
Network of Researchers on the Chemical Evolution of Life
Nutrition Society
Quekett Microscopical Club
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