European Commission

#EthicsGroup_EU

Ethics of Genome Editing

European Group on Ethics in Science and New Technologies

ege

Research and Innovation

European Group on Ethics in Science and New Technologies
Ethics of Genome Editing

European Commission
Directorate-General for Research and Innovation
Unit 03

Contact Jim DRATWA
Email EC-ETHICS-GROUP@ec.europa.eu
RTD-PUBLICATIONS@ec.europa.eu
European Commission
B-1049 Brussels

Manuscript completed in March 2021.

The European Commission is not liable for any consequence stemming from the reuse of this publication.
The contents of this opinion are the sole responsibility of the European Group on Ethics in Science and New Technologies (EGE). The views expressed in this document reflect the collective view of the EGE and may not in any circumstances be regarded as stating an official position of the European Commission.

More information on the European Union is available on the internet (http://europa.eu).

Print	ISBN 978-92-76-30141-7	doi:10.2777/763	KI-01-21-062-EN-C
PDF	ISBN 978-92-76-30140-0	doi:10.2777/659034	KI-01-21-062-EN-N

Luxembourg: Publications Office of the European Union, 2021

© European Union, 2021

The reuse policy of European Commission documents is implemented based on Commission Decision 2011/833/EU of 12 December 2011 on the reuse of Commission documents (OJ L 330, 14.12.2011, p. 39). Except otherwise noted, the reuse of this document is authorised under a Creative Commons Attribution 4.0 International (CC-BY 4.0) licence (https://creativecommons.org/licenses/by/4.0/). This means that reuse is allowed provided appropriate credit is given and any changes are indicated.

For any use or reproduction of elements that are not owned by the European Union, permission may need to be sought directly from the respective rightholders. The European Union does not own the copyright in relation to the following elements:
Image credits:
Cover: © Sergey Nivens, #109431940; © mas0380, #262515783; © Fotomay, #269866045; 2021. Source: stock.adobe.com

EUROPEAN COMMISSION

European Group on Ethics
in Science and New Technologies

Opinion on

Ethics of Genome Editing

Opinion no. 32

Brussels, 19 March 2021

2021 Directorate-General for Research and Innovation

Table of contents

KEY INSIGHTS: A GLIMPSE INTO THE OPINION 4
1. INTRODUCTION 9
1.1. Terminological clarifications: what we mean by genome editing 12
2. CROSS-CUTTING AND UNDERPINNING ASPECTS 15
2.1. Metaphors, narratives and framings 15
2.2. Naturalness, custodianship and responsibility 16
2.3. Humanness and humanisation 16
2.4. Diversity, human diversity and biodiversity 18
2.5. Transcending the 'safe enough' framing 20
2.6. Governance and 'who should decide' 21
3. GENOME EDITING IN HUMANS 23
3.1. Conceptual considerations 24
3.2. The 'safe enough' criterion 31
4. GENOME EDITING IN ANIMALS 37
4.1. Introduction 37
4.2. Animal experimentation 38
4.2.1. Genome editing in research animals 39
4.2.1.1. Genome editing in xenotransplantation research 41
4.3. Genome editing in livestock breeding 43
4.4. Current European regulation 44
4.5. Key ethical questions and concerns related to genome editing in animals 47
5. GENOME EDITING IN PLANTS 58
5.1. Introduction 58
5.2. Why do we want genome editing in plants? 65
5.3. New technologies 67
5.4. Regulation 68
5.5. Are genome edited foods safe? 69
5.6. Identification 71
5.7. Biodiversity 73
5.8. Industrialisation of agriculture 75
5.9. Biosecurity 76
5.10. Justice 77
5.11. Societal considerations 78

6. GENE DRIVES 80
6.1. What characterises gene drives? 80
6.2. Concerns 82
7. RECOMMENDATIONS 84
7.1. On overarching matters and concerns 84
7.2. On genome editing in humans 86
7.3. On genome editing in animals 88
7.4. On genome editing in plants 91
7.5. On gene drives 93
REFERENCES 94
THE MEMBERS OF THE EGE 105
ON THE DEVELOPMENT OF THE OPINION 106
THE EGE TEAM 108

KEY INSIGHTS: A GLIMPSE INTO THE OPINION

The advent of new genome editing technologies such as CRISPR/CasX has opened new dimensions of what and how genetic interventions into our world are possible. This Opinion addresses the profound ethical questions raised and revived by them. It analyses various domains of application, from human health to animal experimentation, from livestock breeding to crop variety and to gene drives. With its wide view across areas, it identifies underlying and overarching issues that deserve our concerted attention, among them, the different meanings that ought to be attributed to humanness, naturalness or diversity. This enables conclusions that provide panoramic perspectives complementing narrower, area-specific analyses. In the same vein, the Opinion is concerned with the global dimension of genome editing and its regulation and formulates recommendations with a particular focus on the international level. Its main overarching considerations are the following:

- How the human ability to edit the genome should be regulated is closely linked to questions about the status of humanity in 'nature'. Are we its masters with a right to transform it, or are we one of many parts of it that all thrive in relation to each other? Does our growing knowledge about it postulate that we care for it and protect it where we can? Awareness of one-sided positions, such as anthropocentrism and speciesism, can help us to engage in the debate about genome editing on the basis of the values of diversity, respect and responsibility.
- The application of genome editing in human and non-human animals raises questions about what defines us as humans and what distinguishes species from each other. Our genome is often taken as foundational of our humanness, providing us with distinct capacities. Should we, or should we rather not, experiment with the delineations defining and distinguishing species? What risks and responsibilities would this entail? On the other hand, genetic exceptionalism and determinism (the idea that the genome plays the central role in shaping who we are and determines our behaviour) can prevent us from taking a more holistic perspective on the many factors defining us and our lives, as well as other species and theirs. Awareness of this can help us to put genome editing and discourses about it into perspective.
- Diversity, human diversity and overall biodiversity, can be impacted by genome editing in different ways. The technology may both offer possibilities to preserve and diversify biospheres, and come with risks of reducing genetic pools and, hence, diversity – both in biological terms and in terms of what kind of diversity is socially appreciated. This requires us to reflect about the responsibilities of humans towards other species and the planet, most importantly as regards anthropogenic climate change; as well as towards other humans, as regards

determining what kinds of persons a society might want to have and what specific variations are, or are not, a problem in need of a genetic, technological 'solution'. When thinking about diversity and genome editing, we therefore also need to think about freedom, autonomy and risks of oppression and marginalisation.

- The focus on the broader picture of this Opinion also raises awareness of the risk that genome editing could be hailed as a technological solution for issues of social nature. An approach that does not consider the ethics and governance of genome editing in a technology-specific way enables us to pinpoint the broader societal questions in the realm of which technologies, or socio-technical systems, can have an impact. What world do we want to live in and what role can technologies play in making it reality?
- Debates about genome editing often focus on the question about the conditions that would render it 'safe enough' for application. This Opinion draws attention to the importance of nuancing and resisting this framing, as it purports that it is enough for a given overall level of safety to be reached in order for a technology to be rolled out unhindered, and it limits reflections on ethics and governance to considerations about safety. Much to the contrary, ethics should serve to tackle broad governance questions about how technologies can serve our common goals and values, and not be limited to providing a 'last step' of 'ethics-clearing' of a technology. Safety, if to be a safe concept, must be framed in its broadest sense, including psychological, social and environmental dimensions, as well as questions about who gets to decide what is safe enough, and by which processes.
- With the increasing adoption of genome editing, claims were made that scientists were not only able to 'read' the 'Book of Life', but also to 'write' it and 'edit' it. Any words that are chosen to describe a new technology have an impact on the discourse about it. They shape how we perceive it and engage in debates about it, they frame what questions scholars ask about it and investigate, they influence how policy makers respond to it. Awareness of this can help us to find terms that appropriately capture and transmit the complexity of new genome editing applications and of the ethical questions they raise.

The Opinion begins with an overarching chapter assessing the preceding points and continues with detailed ethical analyses of pertaining questions in the main areas of application of genome editing. Some of the key reflections of those chapters are the following:

Genome editing in humans

If the genome of one human being can be submitted to deliberate, targeted editing by another human being, what implications does this have for the relationship between the two persons? Would this undermine the fundamental equality of all human beings, or is it necessary to assume the responsibility of such an intervention when it can help to prevent a serious disease? In this context, we often distinguish between therapy, prevention and enhancement, as different purposes that genome editing can serve, with the use of genome editing for purposes of therapy or prevention of disease being by many considered far more acceptable than the use for enhancement purposes.

While somatic genome editing therapies have been developed for decades, there appears to be general agreement that germline genome editing, hence introducing heritable changes, is not to be applied at this point. In many fora have its potentially severe risks – for the individuals concerned and for society overall – been discussed. Together with the difficulty to conduct long-term studies and the availability of alternative methods for avoiding heritable disorders, they require us to ask: Are research on embryos and the risk of harm caused by the technology ethically acceptable and proportionate for the few cases for which there is no alternative solution? Questions like these require broad and well-informed societal deliberation on the basis of an awareness about how heritable genome editing may result in major changes of a society overall, its composition and its values.

Genome editing in animals

Animals can be considered by humans as having an intrinsic value in their own right, or they can be considered in their instrumental value for humans. Against this background, genome editing revives old questions about inter-species relationships and relational values. In what is the intrinsic value of non-human animals different from that of human animals? How do we define respect for non-human animals and what rights do we attribute to them?

In human health research, genome editing might on the one hand offer opportunities to replace animal experimentation with alternative laboratory methods; on the other hand, the mere ease of creating genome edited animals with the precise genetic traits useful for a given research purpose could also lead to an increase in their use. Genome editing in research animals moreover raises questions about animal welfare, for example if

traits leading to disease are introduced; about de-animalisation, if traits that are natural for a species are knocked out; about humanisation, if non-human primates (or other animals) are genetically changed in a way so that they resemble humans more than they would naturally do; and about justice if the technology would serve exclusive scientific and commercial health services, for example in the context of xenotransplantation.

In farm animals, genome editing applications largely serve the same goals as selective breeding practices, namely, to increase yields, strengthen disease resistance and improve product quality. Ethical considerations in this context relate to animal welfare, biodiversity, sustainability and the necessity of an unbiased public dialogue. Genome editing has the potential to facilitate or exacerbate commercial practices in livestock breeding that are already highly contested.

Genome editing in plants

Current forms of agriculture contribute significantly to the anthropogenic climate crisis. There is a need to ensure food security, provide renewable resources for fuel, feed and fibre, safeguard the retention of biodiversity and protect the environment. Genome editing technologies could, with appropriate and proportionate control, enhance our ability to achieve these goals, just as they could result in the opposite without it.

Social and justice considerations play a role in this too. The economic impact of choosing to use or not use plants produced with new genome editing technologies may be significant and public authorities should ensure that society overall benefits. This includes that small farmers and holistic approaches to production are supported; that new varieties will not result in greater industrialisation leading to increased unemployment and precariousness in agriculture; that the ability of small companies and research organisations to produce new varieties is strengthened and monopolisation of the production of seed restrained and prevented.

In Europe, genetically modified food is contested in large parts of society. This can be attributed, in parts, to mistakes made in the past in not involving the public in choosing what was introduced onto the market, as well as a lack of safeguards preventing false information or hype provided by all sides in the debate.

Gene drives

Gene drives are a specific use of genome editing that has drawn particular attention as it offers the possibility to guide 'biased' inheritance of certain genes into entire animal or insect populations, for example pests or mosquitos, usually with the aim to make them harmless or more vulnerable. This raises a number of ethical concerns that have been discussed in various fora. Among them are also important concerns about global and epistemic justice, as well as anthropocentrism: If one day applied, how can we ensure that those populations that need it the most have access to the technology? How can we ensure that we solve those scientific questions that address the alleviation of the greatest suffering? Given the increasing recognition that animals and plants and our ecosystem as a whole should not only be protected for the sake of human health and wellbeing, but also in their own right, how can we ensure that the interests of all species are considered in regulation and governance decisions?

There is a clear need for collective, inclusive, democratically legitimate ways to decide what new genome editing techniques should be used for in each area, as well as how such responsible use should be safely regulated.

1 INTRODUCTION

The possibility of intervening in the genome in order to change the molecular structure or the function of a gene has reached new dimensions with the development of technologies[1] that can change genetic and epigenetic features in a targeted way. These rapidly evolving technologies can in principle be applied to every living organism – be it a microorganism, a plant, an animal or a human being. There are several aspects that distinguish them from previous technologies: in comparison with earlier methods to change a gene, what is now called genome editing is more precise and effective and can sometimes be carried out inexpensively and without complicated technical challenges. This opens up new dimensions with regard to the accessibility and the scope of application of genome editing.

As with any ground-breaking technology, high hopes are matched by far-reaching fears. Genome editing comes with promising potentials as well as major risks. In the human domain, treatment or prevention of serious diseases, which are as yet barely medically controllable, might become possible.[2] In the context of the COVID-19 pandemic, for example, genome

[1] Early means to genetically modify human cells used vector-triggered random integration of DNA into the genome of somatic cells, including in clinical settings. Targeted (non-random) genetic modification, gene addition, replacement or inactivation was achieved by homologous recombination (HR) of engineered DNA, an extremely rare event, which is mostly restricted to dividing cells. However, both technologies were used to generate genetically modified organisms, including germline modified animals to generate transgenic or gene knock-out or knock-in strains. The discovery that double strand breaks (DSBs) increase the efficacy of HR by orders of magnitude, and the availability of tools to induce such DSBs at defined genetic locations allowed the targeted editing of genes at unprecedented efficacy. Increasingly effective and robust tools to induce targeted DSBs included zinc finger nucleases (ZFNs) (2007), transcription activator-like effector nucleases (TALEN) (2009), and clustered regularly interspaced short palindromic repeat (CRISPR)-associated nuclease 9 (Cas9) (2013). This technological progress in efficacy and precision allows the application of genome editing in virtually all cells, dividing or non-dividing, and led to a growing number of clinical studies (listed in *Table 2* of Li et al, 2020, https://www.nature.com/articles/s41392-019-0089-y/tables/2). The ease, precision and velocity of inducing DSBs together with high genome scanning efficacy specifically characteristic of CRISPR/Cas9 based tools allows the combination of scalable targeting of multiple genomic sites with a multitude of possible genetic modifications.

[2] Genome editing presents an exciting prospect for treatment of numerous common and rare diseases that are caused by changes in the genetic code. A number of genome editing clinical trials are currently ongoing (e.g. NIH, https://commonfund.nih.gov/editing). The first trials were launched in the early 1990s in the USA and China, targeting ADA-SCID, a severe immune system deficiency, and hemophilia B (Wang et al, 2020, https://doi.org/10.1038/s41434-020-0163-7). Clinical trials have also been taking place in Europe, targeting, for example, leukemia, with promising results (Qasim et al, 2013, https://doi.org/10.1126/scitranslmed.aaj2013; for an overview see also

editing was used to develop and scale up rapid tests for SARS-CoV-2. But there are also deep concerns that human embryos could become designable according to the preferences of parents and scientists.

---

https://en.wikipedia.org/wiki/Gene_therapy). Yet, studies also indicate that gene therapies may entail risks, among them off-target effects that inadvertently alter untargeted sequences (e.g. Kosicki et al, 2018, https://doi.org/10.1038/nbt.4192).

In 2012, the European Medicines Agency and the European Commission approved a gene therapy treatment for the first time: Alipogene tiparvovec, sold under the brand name Glybera, was developed to fight lipoprotein lipase deficiency (LPLD) and pancreatitis. The treatment was estimated to cost $1 million, making it the most expensive drug in the world at the time. Due to its cost, together with LPLD being 'ultra-rare', it remained underused and was withdrawn from the EU market after two years (Warner, 2017, https://www.labiotech.eu/more-news/uniqure-glybera-marketing-withdrawn/). In the meantime, other gene therapies have been approved and research involving genome editing in somatic tools is proceeding in a seemingly rapid pace (see e.g. Ernst, 2020, https://doi.org/10.1016/j.omtm.2020.06.022, Daley, 2019, https://doi.org/10.1038/d41586-019-03716-9).

Research involving editing of the human germline, however, has been much more controversial, since such changes would be rendered heritable and would, thus, affect future generations. Relevant research and clinical applications are restricted in many countries by laws related to research in human embryos as well as legislation that bans changes in the human germline. Examples of such legislation in Europe are the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, often referred to as the Oviedo Convention (Council of Europe, 1997) and the EU Clinical Trials Regulation (Regulation No. 536/2014). (For more details on the relevant international regulatory landscape see e.g. Araki & Ishii, 2014, https://doi.org/10.1186/1477-7827-12-108 and Isasi et al., 2016, https://doi.org/10.1038/nature.2015.18394).

To date, studies in different animal models have indicated the feasibility of genome editing in animals at the zygote stage (e.g. Yoshimi et al, 2014, https://doi.org/10.1038/ncomms5240; Heo et al, 2015, https://doi.org/10.1089/scd.2014.0278; Kang et al, 2015, https://doi.org/10.1093/hmg/ddv425). The potential of the technology to prevent the onset of a genetic disorder in mice has been demonstrated, for example, by the studies of Wu et al. (2013, https://doi.org/10.1016/j.stem.2013.10.016) and Long et al. (2014, https://doi.org/10.1126/science.1254445), for cataract and Duchenne muscular dystrophy respectively. Furthermore, relevant studies in non-human primates led to the birth of targeted genome edited offspring (Niu et al, 2014, https://doi.org/10.1016/j.cell.2014.01.027; Liu H. et al, 2014, https://doi.org/10.1016/j.stem.2014.01.018; Liu Z. et al, 2014, https://doi.org/10.1007/s12264-014-1434-8).

With regard to relevant research in humans, two Chinese studies (Liang et al, 2015, https://doi.org/10.1007/s13238-015-0153-5; Kang et al, 2016, https://doi.org/10.1007/s10815-016-0710-8) involving abnormally fertilized zygotes resulted in genome edited embryos being mosaic, while a substantial number of 'off-target' mutations were observed. However, it should be noted that neither of these studies used the most up-to-date CRISPR/CasX methods. Yet, another breakthrough study (Ma et al, 2017, https://doi.org/10.1038/nature23305) described the correction of certain mutations in human embryos with CRISPR-Cas9, concluding that "[t]he efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations" (ibid).

Despite the strict regulations in many countries and the ongoing debate on the ethical implications of germline editing, in November 2018, a Chinese researcher, He Jiankui, stunned the global scientific community by claiming to have created the world's first babies from embryos that were genetically edited to prevent them contracting HIV. Scientists in China and worldwide denounced this work as a step too far, with many academies and professional organisations calling for an urgent international effort to prevent scientists from creating any more genome edited babies without proper approval and supervision (e.g. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b).

While the technology could be used to increase animal welfare, genome editing can also contribute to the instrumentalisation of animals for human interests in problematic ways. Interventions in ecosystems through genome editing could serve their flourishing and those of the people and animals living in them, just as they can have profound negative systemic consequences.

All of this urgently requires ethical reflection, debate and assessment in order to shape the application of the technology and to develop governance in a way that is in accordance with fundamental rights and freedoms as well as basic beliefs regarding how we should treat human and non-human living beings and the environment. Against this background, the European Commission requested the EGE to submit an Opinion and recommendations on genome editing, thereby following up on the EGE's *Statement on Gene Editing*, issued in January 2016.[3] To develop this Opinion, the EGE draws on an already wide range of opinions and statements of national ethics councils, scientific academies, professional societies and other organisations, as well as on scientific literature. In addition, the EGE has organised an Open Round Table and an International Dialogue in Brussels in order to incorporate the experience and expertise of various stakeholders. Furthermore, the EGE has liaised with the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.

With this Opinion, the EGE does not intend to provide an exhaustive overview of the scientific state of the art, or a comprehensive ethical analysis across all domains. Genome editing of microorganisms, for instance, could result in bioweapons in the hand of people with criminal intentions. Such dual use is an aspect of concern which the Opinion does not address. Instead, our approach is to focus on salient cross-cutting issues while considering a wide range of different application areas, and to examine how specifically the EU can and should shape governance and policies for genome editing. The Opinion highlights the questions that we have identified as key ethical concerns because they are deemed particularly ethically problematic, they are new and distinctive to this technology, or they have particular salience at the EU level.

The EGE has endeavoured to balance taking into account of specific application areas and due consideration of crosscutting themes. The focus on the broader picture also raises awareness of the problem that genome

[3] EGE, 2016, *Statement on Gene Editing*, https://ec.europa.eu/info/publications/ege-statements_en

editing could be hailed as a technological solution for serious issues of other kinds, such as issues resulting from entrenched social and economic inequalities. Some key leitmotifs emerged which run through the entire Opinion, in particular:

- Metaphors, narratives and framings
- Naturalness, custodianship and responsibility
- Humanness and humanisation
- Diversity, human diversity and biodiversity
- Safety and proportionality, risk and uncertainty, and in particular how to transcend the 'safe enough' framing
- Governance and 'who gets to decide'

They are presented succinctly in the short horizontal chapter that follows. In addition, they are taken up further in the relevant chapters of the Opinion.

1.1 Terminological clarifications: what we mean by genome editing

It is difficult to precisely define the process of *gene editing*, and few have attempted a definition. The term involves a (relatively) precise modification of DNA compared to that which was previously available for genetic modification (defined in Directive 2001/18/EC[4] and in the Cartagena Protocol[5]), particularly of eukaryotes.[6]

A more inclusive term that has become widely used is *genome editing*.[7] It involves the modification of the genome through targeted adding of, replacing of, or removing one or more DNA base pairs in the genome, regardless of whether the modifications occur in a particular gene or a non-

[4] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02001L0018-20190726

[5] Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2000), https://www.cbd.int/doc/legal/cartagena-protocol-en.pdf

[6] Eukaryotes are cells or organisms with a clearly defined nucleus that contains DNA and is surrounded by a nuclear envelope. Eukaryotes comprise simple one-celled animals and plants through to complex multicellular organisms like humans. They are different from prokaryotes with no nuclei, such as bacteria.

[7] E.g. National Academies of Sciences, Engineering, and Medicine, 2017, *Human Genome Editing: Science, Ethics, and Governance*, https://doi.org/10.17226/24623

coding region of the genome. Genome editing does not necessarily involve transgenesis – the transfer of genetic elements from an unrelated or non-sexually related organism. The techniques used in genome editing[8] are meant to be more precise than those which have in the past been used to genetically modify organisms, and include technologies such as CRISPR/CasX[9] (where X is usually a digit, e.g. 9), zinc finger nuclease (ZFN)[10], transcription activator-like-effector based nucleases (TALEN)[11] and meganucleases.[12]

The European Union chose the term *genetic modification* when referring to organisms "in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."[13] The preferred terminology in the United States has been genetic engineering; in 2017 the United States Department of Agriculture suggested a new definition for *genetic engineering* as a family of "techniques that use recombinant or synthetic nucleic acids with the intent to create or alter a genome."[14] In 2018, the Court of Justice of the European Union ruled[15] that organisms obtained by mutagenesis[16] are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive (Directive 2001/18/EC), with a caveat that, "However, organisms obtained by mutagenesis techniques which have conventionally been used in a number of applications and have a long safety record are exempt from those obligations, on the understanding that the Member States are free to subject them, in compliance with EU law, to the obligations laid down by the directive or to other obligations."[17]

---

[8] Nuffield Council on Bioethics, 2016, *Genome Editing – An Ethical Review*, https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf; and 2018, *Genome Editing and Human Reproduction: social and ethical issues*, https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction

[9] CRISPR stands for "clustered regularly interspaced short palindromic repeats".

[10] ZFNs are a chain of zinc finger proteins fused to a bacterial nuclease, capable of making site-specific double stranded DNA breaks.

[11] TALENs are restriction enzymes that can be engineered to cut specific sequences of DNA.

[12] Meganucleases are homing endonucleases that can be used to replace, eliminate, or modify target sequences of DNA.

[13] Directive 2001/18/EC

[14] USA Federal Register, Vol. 82, No. 12, 19 January 2017, Proposed Rules, p. 7015, https://thefederalregister.org/82-FR/Issue-12

[15] Court of Justice of the European Union, Case C-528/16, 25 July 2018, http://curia.europa.eu/juris/documents.jsf?num=C-528/16

[16] Mutagenesis encompasses both directed (targeted) mutagenesis including genome editing, and random (conventional) mutagenesis, often induced by chemicals or radiation. The Court's classification as GMO applies to directed mutagenesis.

[17] Court of Justice of the European Union, Press Release No. 111/18, 25 July 2018, Judgement in Case C-528/16 https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf

In 2020, France's highest administrative court ruled that any genetic modification technique developed since the adoption of the original GMO Directive in 2001 generates a product considered to be a GMO that falls under the respective regulations, including in vitro chemical and radiation mutagenesis on plant cells.[18]

The processes available for genome editing are continually evolving, in particular with regard to the precision of the insertion or deletion of bases. An example is that which has been termed 'prime editing', designed to address some of the problems with current technologies using a "catalytically impaired Cas9 endonuclease fused to an engineered reverse transcriptase, programmed with a prime editing guide RNA (pegRNA) that both specifies the target site and encodes the desired edit."[19] Editing of messenger RNA[20] has also become possible, just as has editing of the eukaryotic epigenome ("which has an instrumental role in determining and maintaining cell identity and function"[21]).

Genome editing, the overall term used throughout this Opinion with the caution underscored here, is not to be taken to mean just a change of the whole genome, but also a specific change (or set of changes) in the genome.

[18] Conseil d'État, 7 février 2020, Organismes obtenus par mutagenèse, https://www.conseil-etat.fr/ressources/decisions-contentieuses/dernieres-decisions-importantes/conseil-d-etat-7-fevrier-2020-organismes-obtenus-par-mutagenese
[19] Anzalone et al, 2019, https://doi.org/10.1038/s41586-019-1711-4
[20] Reardon, 2020, https://10.1038/d41586-020-00272-5
[21] Holtman & Gersbach, 2018, https://doi.org/10.1146/annurev-genom-083117-021632

2 CROSS-CUTTING AND UNDERPINNING ASPECTS

2.1 Metaphors, narratives and framings

It is well established that the language that we use to frame reality does not merely represent reality but also shape it.[22] With the increasing adoption of genome editing, claims were made that scientists were not only able to 'read' the 'Book of Life' (and 'see' who we, as humans, are, such as in the context of the Human Genome Project in the 1990s and 2000s), but were now also able to 'write' it and 'edit' it. These metaphors are more than mere semantics: The words used to describe a phenomenon have an impact on people's understandings and attitudes. Metaphors are important in guiding the general understanding of scientific advances and are believed to influence people's views on the use of CRISPR/CasX.[23] As also the media play an important role in this, the specific terminology – and the metaphors – used by media reports also have an impact on people's views and understandings, and not always in the ways intended by scientists. Regarding a technology such as CRISPR/CasX it is thus particularly important for ethical reflection to pay careful attention to the words we use to describe the problem at hand. The problem description makes certain ways to address it more plausible than others.

For science, bioethics, and the public, a key question is also: how can our language be honest about the uncertainties in how we will develop and use the technology, and what promise and risk its use holds, without employing terms that trigger gut reaction rather than thoughtful deliberation?[24] Words may have consequences and they need to be used 'responsibly' in order to help ensure that the public and public policy stakeholders are well informed regarding this new technology, since words influence how we act upon and shape the world in which we live.[25]

---

[22] Lakoff & Johnson, 2008; Fischer & Forester (eds), 1993
[23] O'Keefe et al, 2015, https://doi.org/10.1080/15265161.2015.1103804; Steen, Reijnierse & Burgers, 2014, https://doi.org/10.1371/journal.pone.0113536
[24] O'Keefe et al, 2015, https://doi.org/10.1080/15265161.2015.1103804
[25] McLeod & Nerlich, 2017, https://doi.org/10.1186/s40504-017-0061-y[25] Lakoff & Johnson, 2008; Fischer & Forester (eds), 1993
[25] O'Keefe et al, 2015, https://doi.org/10.1080/15265161.2015.1103804; Steen, Reijnierse & Burgers, 2014, https://doi.org/10.1371/journal.pone.0113536
[25] O'Keefe et al, 2015, https://doi.org/10.1080/15265161.2015.1103804
[25] McLeod & Nerlich, 2017, https://doi.org/10.1186/s40504-017-0061-y

2.2 Naturalness, custodianship and responsibility

Genome editing questions common understandings of naturalness. Naturalness, in turn, is an ambiguous notion (and sometimes best understood in relation to contrary ones: what is unnatural?). First and foremost, we have to start by recognising that what is *natural* is often taken to be what is 'normal', or even self-evident, or indeed seen as in accordance with the laws of nature – through to natural law and natural rights as a bedrock of human rights. Against that backdrop, secondly, the *natural* is in a close connection (or in a generative tension) with the supernatural, the spiritual, the divine, the demiurgic, 'the whole of creation' or 'Mother Nature'. Gene drives throw into sharp relief the fact that a 'targeted' intervention in a genome can have sweeping implications for entire species, for the precarious evolving balance between species, and indeed for entire ecosystems. The previous considerations also underscore that, thirdly, the *natural* stands in relation to its antithetic or complementary notions, the cultural, the technical, the artificial, the 'human-made'.

Those three dimensions jointly foreground this key area of reflection: the role of humans – and of humanity – in relation to 'Nature', from alienation and emancipation through to belonging and interdependence, from 'masters and possessors' through to humility and inspiration, to stewardship and custodianship. Here it is also anthropocentric and speciesist presumptions that are opened up, and with them new ethics perspectives.

This is a central set of issues with regard to the ethics of genome editing, not only because of possible perceptions of 'tampering with the book of life' or 'challenging divine creation' (notably humans created in the likeness of the divine in certain traditions), not only because of the weight of responsibility attached to transforming nature as well as to transforming human nature (under the looming spectre of eugenics), but also because of core issues of justice, solidarity and dignity thrown open by the political economy of the genome.

2.3 Humanness and humanisation

As humans, we have an existential concern for what it is that makes us human, for what distinguishes humans from other forms of life, of intelligence, sentience, consciousness; and also for what responsibilities are incumbent upon humans – and humanity – with regard to others.

This deep concern takes on newfound significance in the context of genome editing, as the human genome, taken as essential or foundational of humanness, becomes up for grabs. This raises the question which role genes have for the human species and the human individual, which is in part discussed under the notions of 'genetic exceptionalism' and 'genetic determinism'.[26]

The term 'humanisation' is ambiguous and may refer to several different dimensions: it may pertain to a scientific/technical definition (e.g. changing receptor cells on organs of non-human beings into human ones or changing a given sequence of a gene into its human equivalent; thus mice modified to carry one or more human genes are often referred to as 'humanised mice') or it may refer to scenarios where cognitive capacity is modified ('enhanced') to such an extent that species categories, or distinctions between human and animal, become blurred (or that new 'between-species' categories are created). In the context of this Opinion, a key question and concern is the following: when non-human beings could gain characteristics normally associated with humans, what is their status and what are the rights and obligations that arise? In addition, when considering *humanisation*, it is also crucial to extend the reflection to its correlates: *de-humanisation* and *de-animalisation* (or more broadly *de-speciesation*).

This set of questions is relevant across all species, applications and areas. It is even more saliently so in the context of genome editing involving ('non-human') animals – and more particularly non-human primates (NHPs).

Compounded by genome editing, boundary-work around humanness is also deserving of particular ethical attention in the context of xenobiotechnology and specifically of xenotransplantation.

As is the case for each of the cross-cutting issues drawn attention to in this preliminary section, these matters are discussed in the relevant chapters of the Opinion.

[26] 'Genetic exceptionalism' is the idea that the genome, together with genetic data, is of a radically different (more sensitive, more important, or more *essential*) nature compared to everything else. 'Genetic determinism' is the notion that human behaviour is directly controlled – indeed determined – by a person's genes, at the expense of the role of other factors. By extension, it is the notion that human nature, what makes a being a human being, is nothing more and nothing less than that being's genes.

2.4 Diversity, human diversity and biodiversity

Genome editing affects diversity in important ways. As this Opinion will show, the new avenues offered by genome editing open the possibility to expand or narrow genetic diversity across the different domains of these technologies' application, including in people, agricultural plants and livestock, and wider ecosystems. While the ethical implications, including the desirability or otherwise of such outcomes, will be explored within the relevant chapters, it is useful to foreground this discussion by examining the broad values attached to the notion of diversity and the obligations that may flow from it.

Diversity is commonly understood[27] as the richness and variety of distinct objects or types, whether that be at the level of genomes, organisms, species or ecosystems.[28] Measures of diversity take into account not only the variety but also the commonness or rarity of a species, trait or object.

In many contexts, diversity has risen to the status of an accepted 'good', and a social goal to be protected and promoted,[29] often against a background of its perceived precariousness due to human activity. What kinds of values are being attached to a multiplicity of life forms – from where do they derive?

One set of approaches focuses on the instrumental or anthropocentric value, in so far as diversity serves the interests of humankind. In the ecological sphere, evidence indicates that more diverse ecological communities are more stable and resilient than those that are less diverse.[30] A wider range of genes or species within an ecosystem improves

[27] This notwithstanding, conceptually the issue of defining and quantifying diversity is not straightforward. See the longstanding debates over the concept and measurement of biodiversity in the ecological arena. (Maclaurin & Sterelny, 2008)

[28] The Convention on Biological Diversity applies the definition as follows: "the variability among living organisms from all sources including, inter alia, terrestrial, marine, and other aquatic ecosystems and the ecological complexes of which they are a part; this includes diversity within species and of ecosystems." (Article 2, Convention on Biological Diversity)

[29] The Convention on Biological Diversity, for instance, emerged out of a universal consensus that biodiversity is of immense value to humankind and must be protected by international law. Similarly by the early 2000s, the protection of cultural and/or linguistic diversity had emerged as a socio-political movement with the endorsement of international bodies such as UNESCO.

[30] Although the 'diversity-stability' hypothesis is not conclusive (see May, 1973).

its functioning and adaptability.[31] Humans benefit insofar as they are dependent on, and profit from, a flourishing natural world.

For others, diversity derives its value from the presumption of an inherent or intrinsic value within all beings, that nature is worthy of moral consideration, and that this confers relevant obligations and duties.[32] The assumption of a 'balance of nature', which has developed in many societies, can be seen as an attempt to bridge these positions – the instrumental and the intrinsic – by presuming that the planetary community is and persists in a natural equilibrium due to the interactions between its constituent entities.[33]

Current debates surrounding potential uses of genome editing technology tap into the above-described approaches, both instrumental and intrinsic. Genome editing has been proposed as a means to understand and preserve corals and their ecosystems,[34] to diversify agriculture to shore up food security,[35] to combat invasive species plaguing ecosystems around the world,[36] and even to resurrect extinct species.[37]

Debates surrounding such propositions invoke notions of human responsibility towards non-human species, human custodianship over nature, as well as critiques of human hubris in our relationship with non-human life (commodification of nature, 'who are we to decide?' questions). Here the role of human causality is often used as a guide for action, an environmentalist ethos that invokes human responsibility where anthropocentric effects are found to have driven diversity loss or species extinction (which, by extension and in passing, would rule out any obligation to reverse-engineer the woolly mammoth).

An examination of humans' responsibility towards other species must also consider human responsibility towards other humans. This is particularly relevant in light of the potential of genome editing to impact on the scope and nature of human genetic variation. By opening the prospect to curb serious diseases and disabilities, it prompts a serious discussion both about

[31] For a summary of the debate and the evidence, see https://www.encyclopedia.com/science/science-magazines/does-greater-species-diversity-lead-greater-stability-ecosystems
[32] E.g. Albert Schweitzer's ethics of Reverence for Life (1987), Peter Singer's ethics of Animal Liberation (1975) and Paul W. Taylor's ethics of Biocentric Egalitarianism (1981, 1986)
[33] Sarkar, 2010, https://doi.org/10.3390/d2010127
[34] Cleves et al, 2018, https://doi.org/10.1073/pnas.1722151115
[35] Zaidi et al, 2019, https://doi.org/10.1126/science.aav6316
[36] Esvelt & Gemmell, 2017, https://doi.org/10.1371/journal.pbio.2003850
[37] Shapiro, 2015, https://doi.org/10.1186/s13059-015-0800-4

the biological impacts of tinkering with the reservoir of human genetic variation, as well as the social implications.

Diversity does not stand alone as a value, rather it is context-dependent. Our relationship to diversity, the norms and obligations surrounding it, and in particular any attempt to draw conclusions about those features to be deemed worthy of protection or liable to be jettisoned, must recognise the cultural, historical, biological and ecological factors guiding those choices. These must take into account past, present and future generations in all their diversity.

2.5 Transcending the 'safe enough' framing

Whereas debates about genome editing often focus on the question '*how safe is safe enough?*', the EGE draws attention to the importance of nuancing and resisting this framing. The 'safe enough' narrative purports that it is enough for a given level of safety to be reached in order for a technology to be rolled out unhindered, and limits reflections on ethics and governance to considerations about safety.

Three perspectives are particularly important in this regard. Firstly, the 'safe enough' narrative correlates with the risk analysis framework and more particularly with the fraught notions of 'zero risk' and of 'acceptable risk'. The latter is problematic in several ways. We always take risks. Which risks we accept depends on the situation and the possible benefits. In this context, the 'safe enough' narrative can lead us to falsely believe that if a technology is 'safe enough' there are no risks. Further, what is considered 'safe enough' is highly context-dependent. What is needed instead is a consideration of the complete decision problem; to take sound, well-reasoned decisions; to look at both the pros and the cons; indeed to consider not just the risks and costs but also the possible benefits, in the widest sense, and the distribution thereof.

Secondly, the restrictive focus on 'safe enough' for genome editing is akin to the process of 'securitisation' discussed in EGE Opinion 28 in the context of security technologies.[38] In the crispest form, that is, 'safe enough'

[38] EGE, 2014, Opinion n°28, *Ethics of Security and Surveillance Technologies*, https://op.europa.eu/en/publication-detail/-/publication/6f1b3ce0-2810-4926-b185-54fc3225c969/language-en/format-PDF/source-77404258

becomes the alpha and omega, both the cop-out and the carte blanche as well as the tree that hides the forest.

Thirdly, the 'safe enough' framing is reminiscent of the 'technological imperative', the notion that 'if it is technologically feasible then it ought to be done'. This eschews more ethically pressing questions such as whether genome editing is in fact necessary, acceptable, and under what conditions. To be clear, it is not that the technological imperative necessarily entails a 'safe enough' narrative, but capturing the attention and imagination with 'safe enough?' can lead to obfuscating other questions and indeed to making this one question the 'one door – one key' of technological roll-out. All of this under the guise of promoting sound decision making and shared values, with safety as (least or sole) common denominator.

Questioning the 'safe enough' narrative is cognate to questioning the tendency of scientific and technological developments to mould governance and indeed ethics. This also extends to questions of coordination, diversity, inequalities and power relations (i.e. *Who gets to decide* how safe is safe enough? And by which processes?). In fact, 'safety' or 'trustworthiness' do not pertain solely to technologies but also to institutions and forms of governance in societies – including matters of oversight as well as of democracy and rule of law.

2.6 Governance and 'who should decide'

Governance is a cross-cutting issue and it is important to unpack its different facets. A first component is the state of the existing and emerging legislative and regulatory approaches across the different purposes and domains (humans, non-human animals, plants, microorganisms, gene drives). These are indicated in the subsequent chapters of the present Opinion. A related component is the historical dimension and legacy of legislative approaches (with questions of path dependency, institutional mimesis, transnational epistemic communities, forms of socialisation and learning), which is also addressed there.

The most salient feature of the current situation is the lack of robust structures of global governance, as strikingly brought to light by the genome editing revelations at the end of 2018.[39] We recognise that genome editing technologies, particularly their application in humans, amongst other

[39] E.g. Greely, 2019, https://doi.org/10.1093/jlb/lsz010

technologies, require a global governance approach. As a corollary, it is difficult to take regulatory measures of worldwide scope that are efficient and respected by all States, so that these commit to ensuring compliance in their respective territories.

Proposing criteria for the governance of genome editing, notably concerning human germline, is not an easy task. This requires reflection on the forms of uncertainties, on the rights and values involved (notably human dignity, solidarity, right to identity), on the expectations generated by this technique, and on the limits and principles that should govern its application (safety, effectiveness, efficiency, transparency, common good, accountability, proportionality, etc.).

Key questions with regard to the different aspects of governance are: How are decisions to be made? Who decides and who ought to decide? These questions pertain to the geopolitical level (e.g. the strong influence of the USA and China in the global governance arena to date), to the disciplinary level (e.g. divisions and dominance of certain branches of science; primacy of some natural scientific disciplines over other fields also in the humanities and social sciences), to the stakeholder level (the need for participatory approaches, questions of public trust), extending to the wider public (going beyond 'present generations' and 'political participation') and anticipatory governance. With respect to the collective experiments in developing forms of governance of genome editing, across the globe, we should address how we can establish systems which can both monitor developments and enable to draw lessons (including mutual learning across different areas in the ethics and governance of sciences and technologies, such as 'artificial intelligence', GMOs, genome editing).

3 GENOME EDITING IN HUMANS

Recent advances in the techniques available for the editing of the human genome have given rise to significant debate. There is a spate of committees, reports and recommendations on its feasibility, desirability, as well as ethical and governance implications.[40] Against this background, in this Opinion the EGE focuses on what it considers to be two key aspects of particular importance regarding somatic and germline genome editing in humans.

First, there are fundamental conceptual considerations that are crucial for an ethical assessment of genome editing applications, also with regard to their global impact. They concern views on the nature of human beings, the relevance and status of the genome in this, the identification of humans as a species and the implications of belonging to it,[41] as well as the relationships of people to themselves, to each other and to the environment. Our conceptualisations of this shape how we perceive the plethora of phenomena in the world, how we behave and how we intervene in our environment.

Second, the safety of a technology is generally seen as a criterion of crucial ethical importance. A technological intervention is meant to benefit people and society without undue (disproportionate) negative consequences for individuals or groups. There are different views on what constitutes a benefit, a risk or a harm, depending, among other factors, on scientific evidence, but also on personal preferences and values, as well as wider contexts of culture, societal attitudes, existing governance frameworks and the framing of the scientific landscape. Determining what is 'safe enough' is not only about knowledge, but also about values, and scientific theories and practices are themselves value-laden.

There is a longstanding practice of weighing potential benefits and risks in clinical research and in healthcare for somatic genome editing, but with regard to germline editing the question of safety is more complex. Its

[40] E.g. Nuffield Council on Bioethics, 2016 & 2018; National Academies of Sciences, Engineering and Medicine, 2017; German Ethics Council, 2019; Danish Council on Ethics, 2016; Italian Committee for Bioethics, 2017; Spanish Bioethics Committee, 2019; The WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Gene Editing (ongoing); etc.

[41] Declaration on the Responsibilities of the Present Generations Towards Future Generations, 1997, Art. 6.

difficulty mainly relates to the fact that the genetic conditions – the biological starting point for the entire organism throughout the whole life of the person – are changed, and that future generations will be affected by this. The question as to which criteria must be fulfilled so that germline genome editing can be considered 'safe enough' and how to come to this conclusion requires discussion. This will be part of the second section.

3.1 Conceptual considerations

Given the powerful technologies available today to edit the human genome, there is a requirement to assess their impact on shared ethical principles and fundamental rights and freedoms, including the dignity of every human being, the right to life, health and bodily as well as mental integrity, respect for autonomy, freedom of research, justice, non-discrimination and solidarity. These aspects are already discussed in detail elsewhere.[42] In addition, there are other important conceptual frameworks underlying and orienting the ethical discussion. They refer to general concepts of humanness, naturalness and diversity, as well as to distinctions between therapy, prevention and enhancement.

These concepts and related values are invoked when thinking about a technology and setting up guidance for its use. A division into science on the one hand and ethics on the other, or ethics as kind of an afterthought,[43] overlooks the fact that the entire process of scientific activity, from the formulation of the research question to the conduct of research and the evaluation and interpretation of data is permeated with preferences and values. Also science governance systems necessarily involve overarching conceptual ideas and ethical perspectives. Accordingly, the expert advisory committee established by the WHO in 2018 "to develop global standards for governance and oversight of human genome editing" is committed to take into consideration "the scientific, ethical, social and legal challenges" associated with somatic and germline genome editing, with the aim to issue recommendations on appropriate institutional, national, regional and global governance mechanisms.[44]

[42] Cf. the references above.
[43] This kind of view is implicit in the approach of the International Commission on the Clinical Use of Human Germline Genome Editing in its report from September 2020.
[44] https://www.who.int/ethics/topics/human-genome-editing/en/

3.1.1 Humanness and naturalness

The question of humanness and thus of what constitutes a human being can be discussed from various perspectives, including biomedical, philosophical, sociological, ethical or religious ones, and by referring to biological, ontological, or social features. It is an anthropological question that people have dealt with for centuries. What is typical for the human species, what is unique to the human species? It also asks about the positioning of humans in nature and in the cosmos – eventually in the context of all that exists.

Until the late 1970s, no deliberate targeted technological intervention could bring a human into being. With the technical possibility of bringing together egg and sperm outside of the female body, the emergence of a human being came into the hands of third parties who are otherwise not involved in the process of natural conception. It thus became available for intervention. With the CRISPR/CasX techniques, the opportunity for intervention has become so specific that even the genetic make-up of the human embryo is at the designer's disposal. Is this an intervention in humanness? Biologically speaking, no – not as long as only such genetic changes are made that lead to genes that are otherwise present in humans. Even if DNA from another organism is introduced in a human genome this does not change the humanness of that entity. There is no percentage or sharp threshold beyond which the host is no longer considered to be human.

However, the question arises whether a change in the initial genetic condition of a human being fundamentally alters the nature of humanness or rather the relationship between humans by making them unequal with regard to their genetic starting conditions: those from one human being can be submitted to deliberate and targeted editing by another human being. In this manner, an engineering/design approach in human genomics may undermine fundamental equality of all human beings, which implies that there are "no discontinuities in the range of humanity that would accord some humans a lower status than others."[45] Such equality implies that all human beings have equal worth and are accorded human dignity, without exception. This basic equal regard cannot be earned and is never a matter of merit, desert or design.

How can it then be classified, ethically, that a human being does not owe his or her genetic make-up to chance – so to say to 'nature', in terms of

[45] Waldron, 2017, p. 86.

independency from deliberate and targeted human intervention – but to the deliberate shaping of it by other human beings? Is this intervention so fundamental that no human being should ever assume responsibility for it, and that germline genome editing should hence be categorically forbidden? Or does the possibility of the intervention make it necessary to assume this responsibility, for example when it enables to prevent a serious disease?

That the intervention in the genome of a human embryo is considered particularly serious is partly due to the consequence of this intervention – the change is also passed on to next generations. It is also due to the perception that the genome is something very special for living beings, as discussed under the notion of 'genetic exceptionalism'.[46] A view on the human genome as being the 'code' of the individual is countered by the fact that genes do not (solely) determine the individual, their personality and life; they only provide a framework within which human beings can determine themselves and lead their lives in many different ways. The role of the genome for the individual and the human community is also assessed differently in different cultures and can change over time.

A related question arises as to whether a human embryo whose genome has been edited is still the same human being after the occurred alteration. Is the genome of a human being considered so essential for the dignity and identity of a person that a genetic modification at zygote state makes her a different person? Or is it rather her entire living as a being with body, mind and emotions, her narrative? This question refers to the concept of genetic exceptionalism as well, in the sense that the genetic component of a person's individuality is considered more important, or in another way different, from other, non-genetic factors that make a person.[47] Genetic exceptionalism and determinism would imply that editing a disease-causing gene in a zygote means creating another human being, or an intervention 'by' creating another human being, rather than treatment or prevention.

Against the background of these far-reaching questions about concepts of humanness and naturalness and their ethical dimensions, it is clear that there is no one scientific, unambiguous and thus binding answer as to what the relation between the genome of a human embryo and humanness and naturalness is, and what ethical orientation this can provide. Rather, the need arises for a broad, inclusive and nuanced social debate on the

[46] See footnote 24

[47] E.g. also Fagot-Largeault, 1991, http://www.jstor.org/stable/24274649; Green & Botkin, 2003, https://doi.org/10.7326/0003-4819-138-7-200304010-00013; Prainsack & Spector, 2006, https://doi.org/10.1016/j.socscimed.2006.06.024

foundations of our view (or indeed many possible views) of humanity, which takes all perspectives into account and brings them into discussion.

3.1.2 Diversity

Genome editing, with its ability to modify genome types, bears on diversity in important ways. New genome editing techniques open the possibility to expand or narrow genetic diversity across the different domains of their application. Regarding humans, diversity is commonly understood as the richness and variety of cultures, age, gender, beliefs and world views, amongst others. It also entails biological features such as genes. Measures of diversity take into account not only the variety but also the commonness or rarity of a trait or feature. In many contexts, diversity has risen to the status of an accepted 'good', and a social goal to be protected and promoted.[48] In regard to genome editing in humans, a variety of implications has to be discussed.

In order to significantly influence the diversity of the human gene pool, a very broad use of genome editing on embryos over many generations would be necessary. Currently, such a development is not foreseeable, but no definite statements can be made about future application scenarios. That genome editing presents the prospect of curbing serious diseases and disabilities prompts important discussions about both the biological impacts of 'tinkering' with the reservoir of human genetic variation, as well as the social implications. *'Children of a Lesser God'* made such stakes palpable to a wide public in 1986. It has been argued that diversity "may encourage people to appreciate difference and care for and respect others, whereas having less diversity might make the lives of those with less common genetic traits still more marginal."[49] This is thus about the particularly fraught issue of determining the kind of people a society might want to have, and who gets to decide that a specific variation is – or is not – a problem in need of a genetic, technological 'solution'.

[48] The Convention on Biological Diversity, for instance, emerged out of a universal consensus that biodiversity is of immense value to humankind and must be protected by international law. Similarly by the early 2000s, the protection of cultural and/or linguistic diversity had emerged as a socio-political movement with the endorsement of international bodies such as UNESCO.

[49] Nuffield Council on Bioethics, 2018, https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction

It is important to recall at this point that the notion of 'diversity' on the human level is extended beyond the realm of (epi)genetics to encompass different human languages, cultures, identities and beliefs. The values placed on this kind of diversity can echo, or depart from, those in the biological domain (contending that cultural and linguistic diversity increases the adaptational strength of human societies, with a wider range of human knowledge and – by making us aware of a variety of distinct human ways of life – of counter-factual possibilities, 'other ways of living'). In fact, cultural and linguistic diversity is protected by the international human rights framework, reflecting the link between human diversity and values of freedom, autonomy, justice and solidarity. These links are historically embedded: we cannot reflect upon human diversity without taking into account relationships of power and histories of oppression, colonialism, exploitation and marginalisation that have come alongside.

Diversity therefore does not stand alone as a value, rather it is context-dependent. Our relationship to diversity, the norms and obligations surrounding it, and in particular any attempt to draw conclusions about those features to be deemed worthy of protection or liable to be jettisoned, must recognise the cultural, historical, biological and ecological factors guiding those choices. These must take into account past, present and future generations in all their diversity.

3.1.3 The distinction between therapy, prevention and enhancement

The editing of the genome in human germ cells and embryos can reduce or remove the risk that children (and subsequent generations) will develop genetic diseases. It also allows us to modify genetic traits of a person and shape them according to medical, societal and personal preferences, such as the eye colour or the sensitivity to pain.[50] The scientific, medical, regulatory and societal conditions under which germline genome editing may be determined to be necessary and acceptable remain contentious. In this debate, the distinction between therapy, prevention and enhancement as purposes of genome editing is often referred to.

Although therapy, prevention and enhancement cannot always be clearly separated from each other, there are some definitional characteristics that provide orientation. Prevention and therapy relate to a disease or

[50] Knoepfler, 2015, *Gmo Sapiens: The Life-Changing Science of Designer Babies*, p. 187.

impairment, whereas enhancement refers to the improvement of a statistically and medically 'normal' feature or function. Prevention means the avoidance of a disease or impairment, respectively avoiding their aggravation or recurrence, whereas therapy aims at restoring health or alleviating symptoms of a disease. The use of genome editing for purposes of therapy (also depending on the seriousness of a disease) seems to be far more acceptable for most people than its use for purposes of enhancement.

Therapy can only apply if there is disease and thus only refer to individuals who are suffering from a disease. A human embryo in an early developmental stage can be a carrier of a gene that will lead to a disease in the course of further development, but cannot suffer from a disease in the way a born human being can, with physical symptoms and the personal and social experience of illness. Therapeutic genome editing can therefore only apply to somatic genome editing.

Enhancement can be applied with regard to different kinds of features and impact, for example, biological, cognitive or social functions. It aims at changing them in a way that is considered as making them 'better than normal' for the individual concerned or better than what is 'normal' for humans in general. However, what is 'normal' is often not clearly defined and its definition changes over time and among societies.[51] Normal can, for instance, refer to a statistical distribution, to a defined threshold or to a biological function of an organ. To name an example, a new medical definition for the thresholds delimiting high or low blood pressure can render thousands of people ill who were previously considered healthy, without anything having changed in their body.[52]

The WHO-defines health broadly, as "a state of complete physical, psychological and social wellbeing"[53] and hence also highlights the complexity of distinguishing therapy and enhancement, with the delineation not only depending on objective parameters but also on subjective perception.

Dis-enhancement is discussed less often. When it is, it usually refers to a removal or worsening of biological functions. Some persons who are born deaf, for instance, do not perceive their deafness as a disease or impairment but rather as a condition that is normal for them and that

[51] For example, thresholds for high blood pressure or framings of mental health conditions differing among countries or regions (see also next footnote).
[52] E.g. Burnier, 2018, https://doi.org/10.1093/eurheartj/ehy063
[53] Preamble to the Constitution of WHO, 1948

contributes to their specific culture with, for example, their own language. They may therefore also wish their children to be deaf and, after preimplantation diagnosis, transfer only the respective embryos. With germline genome editing, it would be technically feasible to alter a gene so that deafness occurs. While the community concerned may not describe such intervention as dis-enhancement, the wider public may perceive it as a diminishment of capacities usually present in humans.

Prevention has been defined as "activities that are designed to reduce the likelihood that something harmful will occur, or to minimise that harm if it does occur."[54] There is a blurring line between prevention and enhancement; some genome editing modifications could serve both objectives.

The EGE holds that distinctions between therapy, prevention and enhancement can be of some use for assessing the ethical acceptability or even desirability of somatic and germline genome editing. They can be helpful for weighing potential benefits and harms (see also *3.2. The 'safe enough' criterion*), mostly with regard to the alleviation or avoidance of harm justifying greater risks than the enhancement of otherwise 'normal' functions. Furthermore, social consequences have to be taken into account, at least if an intervention is applied on a larger scale and with transmissible modifications.

Another aspect to be considered is feasibility. Complex traits such as cognition or common disease phenotypes are the result of the interaction of a large number of factors, including genetic ones, over the course of development. Research in genetics and developmental biology shows that editing a single gene, or even small groups of genes will only have a minor impact on complex traits. Current research into germline genome editing in humans involves targeting single genes that are heavily implicated in the etiology of a set of genetic diseases (monogenic, autosomal, inherited genetic disorders). In this sense, applications for the purpose of enhancement are currently not possible.[55] Yet, they might become a technologically feasible option in the future.

[54] National Public Health Partnership, 2006, *The Language of Prevention*, p. 2.
[55] Cwik, 2019, https://doi.org/10.1017/S0963180119000641; Macpherson, 2019, https://doi.org/10.3389/fgene.2019.00767

3.2 The 'safe enough' criterion

Safety often is at the centre of the debate on genome editing. All too often, the (more or less explicit) underlying assumption is that it is enough for a given level of safety to be reached in order for a technology to be rolled out; and all too often, ethics and governance reflections get restricted to safety aspects. The EGE however argues that a technological intervention has to be 'safe enough' in the terms of a broad and nuanced understanding of the notion. Against the background of a bio-psychosocial understanding of health, much has to be considered. Are there medical risks for the application of germline genome editing against serious diseases or impairments? Are there psychological risks for individuals after germline genome editing regarding their self-perception and their social relationships? Are there social risks with regard to discrimination towards people with disabilities or inherited disorders, as is already discussed regarding prenatal or preimplantation diagnostics? Are there long-term risks of heritable genome editing for the concerned individual or for future generations that can hardly be foreseen?

Safety cannot merely refer to the absence of any risk, as no technological intervention is without risk. The question rather refers to what can be considered as as 'safe enough'. The very first prerequisite for an intervention to be considered safe enough is knowledge about its effectiveness in terms of potential benefits, and about potential harms. There must be scientific evidence that the technological intervention contributes to the solution of the problem for which it is designed; and the robustness of this evidence needs to be assessed. The second prerequisite refers to the ratio between risks and potential benefits: risks must not exceed benefits.

3.2.1 'Safe enough' in the context of somatic genome editing

There is no novelty in the definition of 'safe enough' in genome editing of somatic cells. It follows the same ethical conditions recognised by the scientific community regarding research and the clinical application of interventions for therapeutic purposes, mainly the evaluation of risk/benefit proportionality by the researcher, the ethics committee, and the physician together with the patient, respectively. Furthermore, the informed consent of the study participant or the patient is necessary.

Today, laboratories around the world are working hard to develop somatic gene therapies, taking forward work that has been ongoing – the first somatic gene therapy trials were conducted decades ago. These therapies target genes in specific types of cells in an individual. Modifications of the genetic material affect only the patient and are assumed not to be passed on to future generations. Somatic genome editing is regulated by EU laws and guidelines on gene therapy, such as those governing Advanced Therapy Medicinal Products (ATMP),[56] and by national rules and regulations.

The EGE welcomes the development of new somatic therapies, but it does on the understanding that well-designed clinical trials assessing the safety and benefits of the therapies are carried out before they are introduced on a larger scale, that the risks are acceptable in relation to anticipated benefits, and that there is an absence of alternatives (with lower risks). Long-term studies are important and are already foreseen under the ATMP Regulation. Also registries are imposed when gene therapy products are authorised for the market.

The EGE wants to stress the importance of specific genome editing expertise within ethics committees charged with approving and supervising such activities as clinical trials or the use of therapies involving genome editing. These committees have the difficult task of determining, on a case-by-case basis, when genome editing is warranted. It goes without saying that, in general, ethics committees have highly competent members, but not all of them are familiar with the technical aspects of genome editing. Therefore, it could be considered whether specialist bodies should make risk/benefit determinations on a project/case-specific basis, rather than leaving those determinations to research ethics committees, which are generalist and may not have the expertise to make these assessments. For medicines, the Clinical Trial Regulation lays down, that "Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience."57 However, there is room for different organisational approaches to fulfil this requirement.

[56] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, http://data.europa.eu/eli/reg/2007/1394/2019-07-26

[57] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, http://data.europa.eu/eli/reg/2014/536/2014-05-27

'Safe enough' in the context of DIY genome editing

A benefit/risk-analysis is more difficult the more institutional frameworks of clinical research and healthcare are left behind so that existing governance frameworks do not apply. This is true for so called 'do-it-yourself kits' (DIY kits) for genome editing that have been commercially offered by promoters of the so-called 'bio-hacking' movement. The movement presents itself as advocating for a 'democratisation' and acceleration of science by enabling 'anyone' to experiment with latest biological techniques.[58] After first 'at home' use cases of DIY CRISPR engineering were reported, regulatory institutions have reacted to the risks of private experimentation with genome editing tools.[59] Existing EU legislation has been referred to,[60] and in several EU Member States genome editing is only allowed in licensed laboratories, implying that DIY applications are prohibited.[61]

In 2017, the European Centre for Disease Prevention and Control (ECDC) recommended that national authorities review their authorisation of commercial DIY kits.[62] In a 2017 Communication outlining an *Action Plan to enhance preparedness against chemical, biological, radiological and nuclear security risks*, the European Commission warned that "[c]ommercially available 'do-it-yourself' bio-kits make it possible for a user to produce genetically modified microorganisms. Progress in this area may lead to intentional attack or accidental contamination with modified viruses or bacteria."[63] Beyond security concerns of this kind, DIY genome editing kits

[58] E.g. https://diybio.org/ and https://www.hackteria.org/about/, websites centralising information about and for the movement, including its European networks and groups; https://www.nybooks.com/articles/2007/07/19/our-biotech-future/, a widely cited article on the alleged promises of the 'domestication of biotechnology' in the early years of the movement.

[59] E.g. Smalley, 2018, https://doi.org/10.1038/nbt0218-119; https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/information-about-self-administration-gene-therapy; https://www.technologyreview.com/2019/08/09/65433/dont-change-your-dna-at-home-says-americas-first-crispr-law/

[60] E.g., in its 2017 rapid risk assessment of a contaminated DIY CRISPR kit, the European Centre for Disease Prevention and Control referred to *Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms* and *Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms*.

[61] The German federal genome editing law, for example, provides that „genome editing can only be conducted in laboratories for genome editing" (free translation of the authors), ("Gentechnische Arbeiten dürfen nur in gentechnischen Anlagen durchgeführt werden", Gesetz zur Regelung der Gentechnik).

[62] ECDC, 2017, https://www.ecdc.europa.eu/sites/default/files/documents/2-May-2017-RRA_CRISPR-kit-w-pathogenic-bacteria_2.pdf

[63] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: Action Plan to enhance preparedness against chemical, biological, radiological and nuclear security risks

raise ethical questions around, for instance, naturalness, biodiversity, humanness, safety and responsibility.

Yet, bio-hacking comes in many forms and researchers have found European DIY bioengineering activities to involve serious initiatives of citizen science, activism and art, with their initiators often operating in collaboration with universities and on the basis of ethics codes.[64] A better understanding of the current situation, through studies of more recent developments around DIY genome editing activities and existing and possible governance tools, would be an important step towards establishing how a clear and coherent European regulatory approach to it should be developed. It is without doubt that regulation is necessary as an unregulated use of DIY genome editing tools can clearly be hazardous.

3.2.2 'Safe enough' in the context of heritable genome editing

A much bigger problem is the definition of 'safe enough' in genome editing on human embryos for reproductive purposes, so-called 'heritable' human genome editing. There is (almost) unanimous consensus that, at the moment, genome editing for reproductive purposes is far from being safe enough for application (e.g. mosaicism, off- and on-target effects). However, several interdisciplinary ethics councils and other bodies have already discussed its potential future application. The WHO expert panel[65] is currently preparing guidance on this, and the International Commission on the Clinical Use of Human Germline Genome Editing released its consensus study report in September 2020.[66]

The proportionality of benefit in terms of preventing a serious genetically transmitted disorder has to be balanced with the risk not only of not correcting the genetic defect but also of introducing unintentional modifications that could have serious implications for the child and future generations – perhaps even more serious than the one that should be prevented. The proportionality of potential benefits and risks differs with regard to the aim of the intervention.

(COM/2017/0610), https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2017:0610:FIN

[64] E.g. Keulartz & van den Belt, 2016, https://doi.org/10.1186/s40504-016-0039-1; Seyfried, Pey & Schmidt, 2014, https://doi.org/10.1002/bies.201300149; Kirksey, 2016, http://somatosphere.net/2016/03/who-is-afraid-of-crispr-art.html

[65] https://www.who.int/ethics/topics/human-genome-editing/en/

[66] https://www.nationalacademies.org/our-work/international-commission-on-the-clinical-use-of-human-germline-genome-editing#sectionPublications

Before the technology can be proven 'safe enough', also only in biomedical terms a lot of research is required. Specific to this kind of research is that hundreds and thousands of human embryos may have to be used and discarded. This alone is ethically condemned and illegal in some Member States, whereas others allow research on embryos up to 14 days of their development. Some scholars also hold that this research is ethically required in order to prevent harm for future children through disorders that could possibly be avoided. However, in view of the EU subsidiarity principle governing legislation on human embryo research, the EGE holds back with a recommendation on this issue.

There are a number of values and concepts and value-laden criteria that determine what kinds of risks and what level of probability and severity of a harm may challenge the 'safe enough' criterion. Libertarian theories are in favour of 'procreative beneficence', justifying even a risky intervention if it is intended to provide the best possible conditions for the child and acknowledging its parents' reproductive self-determination.[67] Other theories, in contrast, defend the right of the child to be born without any intentional genome editing.[68]

Another central proportionality question is posed by the availability of technological alternatives to genome editing for avoiding heritable disorders, such as preimplantation genetic diagnosis and donation of gametes (yet, those raise other ethical questions). Only few reproductive constellations exclude all strategies but genome editing to ensure that a child is born without a disorder. This is the case, for example, if both parents are carriers of two alleles of a recessive disorder, so that every embryo can only inherit disease-causing alleles. Are research on embryos and the risk of harm caused by the technology ethically acceptable and proportionate for the few cases for which there is no alternative?

Another ethical challenge consists in the scenario of some children being born with technologically induced disorders because the technology is, at some point, meant to be safe enough and put forward to clinical studies. Some see this as an instrumentalisation of these embryos and children, thus violating their dignity. In any such case, life-long and multi-generational monitoring would be necessary in order to gain insight into long-term effects on the biological, psychological and social level. Which

[67] E.g. Savulescu & Kahane, 2017, https://10.1093/oxfordhb/9780199981878.013.26; Harris, J., 2010, https://press.princeton.edu/books/paperback/9780691148168/enhancing-evolution
[68] E.g. Sandel, 2007, *The Case Against Perfection: Ethics in the Age of Genetic Engineering*

implications and risks would these life-long studies mean for the person concerned and their relatives and social environment?

In light of the variety of ethical challenges posed by heritable human genome editing, inclusive societal debate is necessary. A broad societal consensus is precondition for the reproductive use of human genome editing to be considered. Societal engagement with it must be well-informed and be based on an awareness that the accumulation of individual choices, as also elicited by competitive societies and hidden (or not hidden) market forces, could result in heritable human genome modification that may change the society itself. Public engagement should involve a range of publics, scientists, scholars in the social sciences and humanities, ethicists, legal and policy specialists, and other experts, organised civil society, with special attention to representatives of women's rights, rights of the child, gender equality, social equality, reproductive rights and justice, disability rights, and human rights in general.[69] The EGE supports the initiative to found a Global Genome Editing Observatory for the purpose of hosting such a debate[70] and recommends that an affiliated European platform be instituted.

In fact, 'safety' does not pertain solely to technologies but also to institutions and forms of governance in societies – including matters of oversight as well as of democracy and rule of law.

[69] In accordance with Article 28 "Public debate" of the Oviedo Convention of the Council of Europe and with its Committee on Bioethics' 2019 Guide to Public Debate on Human Rights and Biomedicine.

[70] Hurlbut et al, 2018, https://doi.org/10.1016/j.tibtech.2018.04.009; Saha et al, 2018, https://doi.org/10.1016/j.tibtech.2018.04.008

4 GENOME EDITING IN ANIMALS

4.1 Introduction

Animals[71] can be considered in two different ways: in an instrumental one, and in terms of their intrinsic value. Sacrificing animals for human interests is common practice today, although it is far from ethically neutral. Different perspectives exist on the acceptability of farming and eating animals, as well as of animal experimentation. Critics argue that animal experimentation is morally unjustified, regardless of the kind of experimentation, its purpose or potentials; many others accept animal experiments under strict conditions. A set of principles, 'the three Rs' (3Rs), standing for *replacement*, *reduction* and *refinement*, has become a broadly accepted tool to strike a balance between enabling animal experiments and respecting animals.[72]

Against this background, we have identified two main domains of application of genome editing that are relevant with regard to EU competencies and regulation. The first relates to genome editing in experimentation implying the use of animals, including their 'humanisation'. Among the many fields of application of genome editing in animal experimentation, this chapter provides ethical reflection on experimentation with non-human primates, the use of animals for research on xenotransplantation and the potential consequences of genome editing on the 3Rs. The second domain of application that this chapter will consider relates to genome editing in animal farming.

In addition to ethical concerns in relation to biosafety and biosecurity, the rapid increase and deployment of genome editing techniques for various applications poses the challenge of determining a consensus on the conditions and boundaries of acceptability of genetically modifying animals for both livestock breeding and research, in light of animal welfare concerns and animal dignity, especially when non-human primates are involved.

The EGE acknowledges that other areas of genome editing in animals require ethical reflection as well, such as genome editing in pets, the potential of a respective industry emerging and related questions on the intrinsic value of animals and their instrumental value for humans.

[71] Hereby non-human animals are meant.
[72] Bredenoord, Clevers & Knoblich, 2017, https://doi.org/10.1126/science.aaf9414

A use of genome editing in animals that has recently drawn attention is the case of gene drives, i.e. the possibility to drive the biased inheritance of certain genes into entire animal or insect populations (e.g. pests) to make them harmless or more vulnerable. Gene drives appear to offer a broad scope of application, such as eliminating insect-borne human diseases, developing and supporting more sustainable agricultural models, and controlling environmentally damaging invasive species.[73] Ethical questions around gene drives are explored in a dedicated chapter (*6. Gene drives*).

Theoretically, genome editing could also be used to reintroduce extinct animal species or restore populations of endangered animal species. Using genome editing for these purposes is a niche application that is still in an exploratory research phase and requires careful analysis of potential consequences before being considered in practice.[74]

Generally speaking, many issues and, indeed, values that have been discussed in the context of the use of animals by humans, irrespective of genome editing technologies, arise with genome editing, reviving and exacerbating 'old' questions such as: What is the intrinsic value of animals? In what is it, or not, different from that of humans? Is there a hierarchy in the value of different animals? How do we define animal welfare? What do we mean by respect and rights for animals?

4.2 Animal experimentation

The use of animals and specifically vertebrates, among them mammals, has been debated for a long time and has led to the development of strong regulation, with requirements for due justification, considering purpose and necessity, animal welfare, conditions to be ensured, among them those to avoid animal suffering, minimise it and end it when present according to set criteria and methods. There are many guidelines on the use of animals in research and since 1986 a dedicated EU Directive addresses the protection of animals used for scientific purposes (revised in 2010).[75] In line with this

[73] Esvelt et al, 2014, https://doi.org/10.7554/eLife.03401
[74] The Netherlands Commission on Genetic Modification (COGEM), 2018, *CRISPR & Animals: Implications of Genome Editing for Policy and Society*, https://cogem.net/en/publication/crispr-animals-implications-of-genome-editing-for-policy-and-society/
[75] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, http://data.europa.eu/eli/dir/2010/63/2019-06-26

Directive, the European Commission publishes reports on statistics about the use of animals for scientific purposes in the EU.

The first and most recent report indicated an overall number of animals used for research and testing of between 9.4 and 9.8 million per year between 2015 and 2017.[76] The number of animals used for the first time ('naïve animals') for the creation and maintenance of genetically altered animal lines to meet the research needs in the EU amounts to around 1.2 million. Species of particular public concern (dogs, cats and non-human primates) represented less than 0.3% of the total number of animals used in 2017. Between 2015 and 2017, the numbers of non-human primates saw an increase of 15%. There are also animals that are purpose-bred for use in science, and dispatched without having been used, in order to ensure what is indicated as required numbers and quality of animals to support EU research.[77] Information on animals bred, not used and dispatched identifies those as a result of the creation of new genetically altered animal lines (525 085 in 2017) and of the maintenance of existing lines (5 588 196 in 2017).

4.2.1 Genome editing in research animals

The animal genome has been manipulated by humans, directly or by breeding, for decades, but CRISPR/CasX in particular, has given new impetus to using animal models for different purposes.[78] A UK report indicated that "animal use in science started declining in the mid-1970s, at least in the United Kingdom, resulting in a drop in the number of animals used approaching 50% between the mid-1970s and mid-1980s."[79] Yet, this development was reversed with the advent of genetically modified animals.[80] Fifteen years ago, it took a geneticist close to a year to introduce a gene into an animal. Since then, the use of genome edited animals in research on human health has strongly developed. Today genome editing

[76] Report from the Commission to the European Parliament and the Council, 2019, Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017, https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1581689520921&uri=CELEX:52020DC0016

[77] P. 37-42 of the related Staff Working Document accompanying the report, https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1581689520921&uri=CELEX:52020SC0015

[78] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y

[79] UK Home Office, 2016, *Statistics of Scientific Procedures on Living Animals: Great Britain 2015*, http://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2015

[80] Bailey, 2019, https://doi.org/10.1163/9789004391192_020

can, for example, be applied directly to DNA in reproductive cells, say, of a mouse, producing a new mouse in just three weeks.[81]

Given the potential of genome editing and the width of possible applications, one risk is that it leads to an increase in the overall use of animals for experimentation, even if in line with 'the 3Rs rule' (replacement, reduction, refinement) the number of animals is kept to a minimum for each single experiment. But ease of use should not lead to less rigour, on the contrary. The study of specific gene modifications with greater precision and the creation of refined animal models of human diseases, for example, neurodegenerative diseases such as Huntington disease or Parkinson disease, are two areas where genome editing is offering new insights.[82] Overall, this new generation of genome editing technologies allows scientists to modify the genomes of animals more efficiently, more meaningful experiments are possible (basic and translational), and experiments become possible that were impossible before[83] – although off-target effects still exist and need to be recognised and understood. CRISPR has generated significant excitement, having "swept through labs around the world" at a "breakneck pace [that] leaves little time for addressing the ethical and safety concerns such experiments can raise."[84] What does this mean for the 3Rs? Are research ethics committees for animal experimentation fully aware of the known and unknown risks and benefits of this new technique? Is the widespread use of genome editing in animal research likely to reverse efforts to reduce the number of animals used for research purposes? Will its use require to review our commitments to research animals?

We are ethically obliged to seek ways of implementing the 3Rs[85] and improve research animal welfare more broadly, by virtue of the fact that many animals only exist because of our scientific aspirations. There is no contradiction in thinking that the use of animals is justified and believing that researchers, through the production of research animals, thereby inherit commitments to those animals. Somebody opposed to the use of animals in research could still endorse the 3Rs: "if you are going to do it (and you shouldn't) you should adhere to the principles of the 3Rs."[86]

---

[81] Singh, Schimenti, Bolcun-Filas, 2015, https://doi.org/10.1534/genetics.114.169771
[82] Yang et al, 2016, https://doi.org/10.3389/fnmol.2016.00030
[83] de Graeff et al, 2019, https://doi.org/10.1098/rstb.2018.0106
[84] Ledford, 2015, https://doi.org/10.1038/522020a
[85] https://ec.europa.eu/environment/chemicals/lab_animals/3r/alternative_en.htm
[86] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y

Work on animal models is often a pre-requisite to human applications or is done with the objective of comparing between animals and humans (e.g. the OncoMouse in cancer research), and genome editing has improved the processes for this. Yet, "while it is commonly and frequently claimed that genome editing has become significantly (perhaps radically) quicker, cheaper, more efficient, easier to use, and therefore more accessible, care is needed when interpreting these claims."[87] Similarly, it has been suggested that "progress has often been technically challenging […]. ES (Embryonic Stem) cells have not been obtained for most species and, even in mice, where the technology is relatively refined, it is time-consuming, expensive, variable, often highly inefficient, and requires a special skill set."[88]

Likewise, genome editing is being developed also for animal health and veterinary science. Protocols should be rigorously and critically assessed in all areas of application.

4.2.1.1 Genome editing in xenotransplantation research

Because of organ donor shortage, transplantation of organs from animals to humans has been considered for a long time. Yet, xenotransplantation faces numerous difficulties. One of these relates to finding appropriate sources of organs. Pigs have been found to be the most suitable since the 1980s, in terms of their organs' size and the ease of raising them, while non-human primate organs are too small for adult humans. Another difficulty relates to overcoming problematic human immune system reactions, which could partly be resolved by manipulating certain pig genes that code molecules triggering these reactions (indeed, in the 1990s pigs with alpha 1,3-galactosyl transferase gene-knockout were created).[89] A third challenge relates to the endogenous pig retrovirus, the Porcine Endogenous Retrovirus (PERV), which could infect human cells and unleash a deadly human epidemic.[90] This risk stopped nearly all industrial developments in the field of xenotransplantation at the beginning of the 21st century.[91]

Nevertheless, xenotransplantation kept being researched, with more porcine sugars and key antigens having been identified and pigs without

[87] Nuffield Council on Bioethics, 2016, *Genome Editing – An Ethical Review*, https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf
[88] Skarnes, 2015, https://doi.org/10.1186/s13059-015-0673-6
[89] Lai et al, 2002, https://doi.org/10.1126/science.1068228
[90] Patience, Takeuchi & Weiss, 1997, https://doi.org/10.1038/nm0397-282
[91] Bach & Fineberg, 1998, https://doi.org/10.1038/34766

them created.[92] The possibilities offered by genome editing now open new perspectives for this area. In 2017, researchers used the CRISPR/CasX system to inactivate 62 PERV genes in pig cells and created embryos from these foetal cells. None from the resulting 37 piglets showed any trace of the PERV virus.[93]

Genome editing thus revives the genetic modification of large animals that can serve as sources for xenotransplants to treat organ losses or dysfunctions in humans.[94] One approach to testing transplantation outcomes and mechanisms is xenotransplantation of animal organs into non-human primates, meaning that research on xenotransplantation can also increase the use of non-human primates for research.

Another route pursued in biomedical research on organ (re)generation is the creation of human organs from pluripotent stem cells (PSCs) in animal foetuses. For this purpose, animal foetuses deficient in one or more specific organs are created to use the 'empty space(s)' for the growth of induced PSCs and, ultimately, organs.[95] The resulting pig-derived donor organ is identical with the organ of the host. This means that humanised pig embryos can be created and frozen to 'save' personalised 'libraries' or banks for the case of organ failure. Among other ethical concerns, the 'personalised pig' raises obvious questions as to 'who can afford this' – a recurring problem in the ethics of biotechnological innovation, as well as questions around the humanisation of animals, i.e. enhancing traits in animals that are considered to be exclusively or typically human.

A related strategy currently explored in biomedical research is the generation of stem-cell generated organoids in animals and in vitro. Organoids are organ-like structures useful for investigating organ development and disease and for toxicology and drug testing. This new possibility also affects the ongoing ethical debate. Organoids might help to reduce the number of animals needed and the harm caused to them, but "should not be seen as a morally neutral alternative."[96]

[92] E.g. Dor et al, 2004, https://doi.org/10.1097/01.TP.0000130487.68051.EB; Sachs & Galli, 2009, https://doi.org/10.1097/MOT.0b013e3283292549
[93] Niu et al, 2017, https://doi.org/10.1126/science.aan4187
[94] Reardon, 2015, https://doi.org/10.1038/527152a
[95] Nagashima & Matsunari, 2016, https://doi.org/10.1016/j.theriogenology.2016.04.056
[96] Bredenoord, Clevers & Knoblich, 2017, https://doi.org/10.1126/science.aaf9414

4.3 Genome editing in livestock breeding

Genome editing applications in farm animals largely serve the same goals as selective breeding practices, namely, to increase yields, strengthen disease resistance and improve product quality.[97] To date, genome editing tools have been successfully applied to a wide variety of farm animals, including swine, cattle, sheep and goats.[98] Examples of such applications of genome editing in farm animals are the CD163 genome edited pig, resistant to porcine reproductive and respiratory syndrome, and the SP110 gene knock-in cow, less susceptible to tuberculosis. The claims of benefits include advantages for both animals and farmers:[99] Genome editing to modify the susceptibility of animals to diseases (e.g. African swine fever or Porcine reproductive and respiratory syndrome) could prevent diseases in farm animal populations and thus avoid animal suffering, medical treatment of animals (e.g. with antibiotics), culling of diseased animals and the resulting vast economic losses for the farmers. The introduction of the hornless gene of Black Angus cattle into that of Holstein-Friesian dairy cows was presented as an example for the possible prevention of injuries and suffering of farm animals. Genome editing has also been applied to poultry and to salmons.[100]

The EGE underlines that considerations from its Opinion n°23 from 2008 on *Ethical aspects of animal cloning for food supply* can also be applied to the application of genome editing in livestock.[101] These include reflections and recommendations on animal welfare, biodiversity, sustainability and the necessity of an unbiased public dialogue.

[97] The Netherlands Commission on Genetic Modification (COGEM), 2018, *CRISPR & Animals: Implications of Genome Editing for Policy and Society*, https://cogem.net/en/publication/crispr-animals-implications-of-genome-editing-for-policy-and-society/

[98] Ruan et al, 2017, https://doi.org/10.1007/s11248-017-0049-7

[99] Friedrichs et al, 2019, https://doi.org/10.1007/s11248-019-00154-1

[100] High Level Group of Scientific Advisors, 2017, *New Techniques in Agricultural Biotechnology*, https://doi.org/doi:10.2777/17902

[101] EGE, 2008, Opinion n°23, *Ethical aspects of animal cloning for food supply*, https://op.europa.eu/en/publication-detail/-/publication/37ab868f-f414-42e7-b448-761879949403/language-en/format-PDF/source-77404396

4.4 Current European regulation

4.4.1 Regulation of genome editing in research animals

Animal welfare is a value of the Union that is enshrined in Article 13 of the Treaty on the Functioning of the European Union, as recited in *Directive 2010/63 on the protection of animals used for scientific purposes*.[102] Recital 12 of the Directive also states, "Animals have an intrinsic value which must be respected. There are also the ethical concerns of the general public as regards the use of animals in procedures. Therefore, animals should always be treated as sentient creatures and their use in procedures should be restricted to areas which may ultimately benefit human or animal health, or the environment. The use of animals for scientific or educational purposes should therefore only be considered where a non-animal alternative is unavailable. Use of animals for scientific procedures in other areas under the competence of the Union should be prohibited."[103]

Article 3 of Directive 2010/63/EU defines 'procedure' as "any use, invasive or non-invasive, of an animal for experimental or other scientific purposes, with known or unknown outcome (…) which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice. This includes any course of action intended, or liable, to result in the birth or hatching of an animal or the *creation and maintenance of a genetically modified animal* line in any such condition (…)."[104]

According to Article 5 such procedures may be carried out for the following purposes only: "(a) basic research; (b) translational or applied research with any of the following aims: (i) the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants; (ii) the assessment, detection, regulation or modification of physiological conditions in human beings, animals or plants; or (iii) the welfare of animals and the improvement of the production conditions for animals reared for agricultural purposes; (c) (…) development, manufacture or testing of the quality, effectiveness and

[102] Recital 2, Directive 2010/63 of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, http://data.europa.eu/eli/dir/2010/63/oj
[103] Ibid., Recital 12
[104] Ibid., Art. 3

safety of drugs, foodstuffs and feed-stuffs (…); (…) (e) research aimed at preservation of the species (…)."[105]

The Directive also contains specific measures regarding non-human primates. Article 8(1) states that "specimens of non-human primates shall not be used in procedures, with the exception of those procedures meeting the following conditions: (a) the procedure has one of the following purposes: (i) translational or applied research undertaken with a view to the avoidance, prevention, diagnosis or treatment of debilitating or potentially life- threatening clinical conditions in human beings, or (ii) basic research or research aimed at preservation of the species and (b) there is scientific justification to the effect that the purpose of the procedure cannot be achieved by the use of species other than non-human primates. A debilitating clinical condition for the purposes of this directive means a reduction in a person's normal physical or psychological ability to function."[106]

According to Article 8(3) "great apes shall not be used in procedures, subject to the use of the safeguard clause in Article 55(2)."[107] This article provides that "[w]here a Member State has justifiable grounds for believing that action is essential for the preservation of the species or in relation to an unexpected outbreak of a life-threatening or debilitating clinical condition in human beings, it may adopt a provisional measure allowing the use of great apes in procedures having one of the purposes referred to in points (b)(i), (c) or (e) of Article 5, provided that the purpose of the procedure cannot be achieved by the use of species other than great apes or by the use of alternative methods."[108] It is worth noting that, since the Directive took effect in January 2013, no such safeguard clause has been initiated in the EU.

4.4.2 Regulation of genome editing in farm animals and livestock

In 1976, the Council of Europe adopted the *European Convention for the Protection of Animals kept for Farming Purposes*, which requires compliance with certain rules to protect livestock from unnecessary suffering or damage

[105] Ibid., Art. 5
[106] Ibid., Art. 8
[107] Ibid.
[108] Ibid., Art. 55

as a result of accommodation, food or transport conditions.[109] Twelve years later, in 1998, at the level of the European Union the *Council Directive 98/58/EC concerning the protection of animals kept for farming purposes*[110] established common minimum standards for the protection of animals on farms, as well as specific regulations for certain species and farming methods. Although these legal efforts to protect the welfare of farm animals have been criticised by animal defenders to not meet required standards, they confirm that the wellbeing of farm animals is a socially shared concern and goal, recognised as such by European institutions.

In addition, and as mentioned above, research on genome editing in livestock animals, also if for the purposes of 'improving' animals for food production, does fall under the scope of *Directive 2010/63/EU on the protection of animals used for scientific purposes*.

A relevant interpretation of the legislation that is expected to have an impact on research on genome editing in animals (as well as in plants) and on the commercialisation of relevant applications in Europe is the judgment of the Court of Justice of the European Union of 25 July 2018 in Case C-528/16.[111] According to this judgment, organisms obtained by mutagenesis techniques are genetically modified organisms (GMOs) within the meaning of *Directive 2001/18/EC on the deliberate release of genetically modified organisms into the environment* (the 'GMO Directive'),[112] and only organisms obtained by mutagenesis techniques which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of the Directive. Based on the Court's interpretation, new genome editing techniques, including CRISPR/CasX, are thus subject to the obligations laid down by the GMO Directive.

[109] Council of Europe, 1976, European Convention for the Protection of Animals kept for Farming Purposes, https://rm.coe.int/1680076da1
[110] Council Directive 98/58/EC of 20 July 1998 concerning the protection of animals kept for farming purposes, http://data.europa.eu/eli/dir/1998/58/oj
[111] Court of Justice of the European Union, Case C-528/16, 25 July 2018, http://curia.europa.eu/juris/documents.jsf?num=C-528/16
[112] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02001L0018-20190726

4.5 Key ethical questions and concerns related to genome editing in animals

The ethics of genome editing of animals can be considered from two perspectives, or on two levels: the one of an instrumental use of genome-edited animals for purposes of human benefit, from human health to food; and the welfare of animals with respect to their intrinsic value. The EGE is, however, also aware of the problematic nature of this distinction, with any discussion about animal welfare positioning humans as guardians, with power over them. In other words, even taking this perspective can be problematic as we cannot escape our human viewpoint.

Many questions raised by genome editing revive older, general questions about the instrumentalisation of animals, for example concerning their mass production or the use of non-human primates in experimentation. In this context, one could either consider the novel elements that genome editing brings to the discussion of these questions and engage in targeted ethical reflection on those; or revive these older questions considering that a new technique might shed new light on them in their general nature, beyond the concrete technical innovation that it introduces. The EGE considers that the genome editing debate offers an opportunity to reconsider present practices globally, and this should not be neglected or avoided fearing a risk of 'not moving forward'.

Thus, although some of these questions go beyond what can be fully analysed in this Opinion, the EGE calls attention to:

- our relationship with non-human animals and, as part of this, our practices to 'design animals' to fit the environment as we are 'engineering' it, opposed to an understanding of the environment shaping (us) animals over time, involving sustainable practices of mutual adaptation and care;
- animal rights, animal ethics, and a wider related literature, attempt – or warn against –fitting animals into our general ethical frameworks, a situation that might be further enriched in view of our evolving scientific understanding of animal cognition and emotions, and in view of the human publics' evolving sensitivities;
- the various levels of concern at play: those that pertain to human welfare, to species, or to ecosystems in their entirety.

On this basis, the EGE identified a series of key questions with regard to genome editing in animals. Does genome editing affect the implementation of the 3Rs and the balance among the three principles? Does it, for

example, contribute to refinement, at the expense of reduction? What are the implications of and which should be the limits to 'humanisation' of animals? Are there specific requirements for the use of genome editing in non-human primates, beyond those already established? In what way is animal welfare in farming fostered or hampered by genome editing and what criteria should control its application? Can genome editing increase both animal welfare and efficiency in farming? What are the broader implications of genome editing for biodiversity?

4.5.1 Genome editing and the 3Rs

One lens of analysis is offered by the question as to whether the framework established by the 3Rs to protect animals in experimentation requires review in face of new genome editing techniques.

4.5.1.1 REPLACEMENT

On the one hand, genome editing helps to overcome technical and financial obstacles to animal research.[113] On the other hand, it is possible that genome editing will offer opportunities to replace animal experimentation with laboratory methods that do not require the use of living animals.[114] Genome editing techniques can, for example, be used to replace standard laboratory-grown animal model organisms by generating cell lines with specific characteristics that provide disease models. These can then be used to investigate pathologies and evaluate potential medicines before they are considered for trials and use in animals and humans.[115]

Another possibility to replace animals in research is the creation of organoid models using new genome editing techniques. Their development is becoming increasingly sophisticated,[116] making them a promising technique for a wide variety of scientific and clinical purposes, including in developmental biology, disease modelling, drug development, and precision and regenerative medicine.[117] Although unable to substitute the use of animals, "organoids provide an additional screening step between cell-lines

[113] Nuffield Council on Bioethics, 2016, Genome Editing – An Ethical Review, https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf
[114] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[115] Nuffield Council on Bioethics, 2016, Genome Editing – An Ethical Review, https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf
[116] Clevers, 2016, https://doi.org/10.1016/j.cell.2016.05.082
[117] Boers & Bredenoord 2018, https://doi.org/10.1038/s41556-018-0112-5

and animal models meaning fewer potential therapies and interventions will move on to testing in animal models and a higher rate of success in those animals."[118] Scientists even expressed concerns about further developments in organoid and synthetic tissue technology potentially placing a greater onus on scientists to carefully justify their requirement for animal experimentation.[119] "Of course, the development and functioning of organs within a greater whole, a physiological system, cannot be replicated without using whole animals. But in this context, genome editing has made almost any organism amenable to genetic manipulation and may result in mammals being more readily replaced by simpler organisms, if scientifically appropriate."[120]

4.5.1.2 REDUCTION

It has been stated that the impact of genome editing might be "most apparent in our attempts to reduce the use of animals in experimentation."[121] Reduction can be defined as obtaining the same amount of data with less animals, or obtaining more data with the same amount of animals. It implies the use of methods that minimise the number of animals used per experiment, which includes appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base.[122]

However, there appears to be potential for both reduction and increase through genome editing. CRISPR/CasX means that, for example, fewer mice are likely to be required to establish a given line.[123] However, the relative efficacy and ease of use of CRISPR/CasX mean that more researchers are likely to use it to research questions in whole animals in ways that were previously, technically, beyond their reach. This might increase the overall number of animal experiments performed, which might in turn mean decreased animal use relative to the rate of knowledge production, but also an increased rate of experimentation and increased risk of poorly planned or coordinated research.[124] For example, genome editing techniques might allow specific diseases that animals would naturally not contract or develop

[118] https://www.sanger.ac.uk/about/who-we-are/research-policies/animals-in-research/
[119] Bredenoord, Clevers & Knoblich, 2017, https://doi.org/10.1126/science.aaf9414
[120] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[121] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[122] National Centre for the Replacement, Refinement & Reduction of Animals in Research, https://nc3rs.org.uk/the-3rs
[123] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y, de Graeff et al, 2019, https://doi.org/10.1098/rstb.2018.0106
[124] Nuffield Council on Bioethics, 2016, Genome Editing – An Ethical Review, https://www.nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf

to be investigated in animals. This would increase animal suffering in the form of new disease models.

It has also been pointed to the fact that these distinct ethical issues, "minimising per-experiment use versus minimising overall use," might not always be "kept separate" and that it is unclear "what attitudes exist towards them amongst the wider public."[125]

4.5.1.3 REFINEMENT

Refinement relates to minimising animal suffering through the advancement of studies on research animal welfare "by exploiting the latest in vivo([126]) technologies and by improving understanding of the impact of welfare on scientific outcomes."[127]

A contribution to refinement by genome editing is not obvious. Animal geneticists "still need to generate embryos for microinjection of guide RNA/CasX/template cocktails, and these zygotes still need to be delivered to pseudopregnant females. There is a drive to refine such procedures, for example, by developing robust non-surgical embryo transfer techniques. But these refinements (…) are not specifically affected by genome editing methodologies."[128] There also is a need to be able to characterise the genetically altered animals in order to confirm the modification. This is still mostly being done through invasive tissue sampling (punch, tail or toe clipping) and non-invasive techniques need to be developed. In order to decrease the suffering of animals, the development of animals with an impaired ability to feel pain has also been advanced. However, no proof-of-concept experiment has been done on animals so far, and "conducting these experiments may itself cause suffering."[129]

"CRISPR/CasX is making it much more feasible to quickly introduce transgenes of known copy number into a safe harbour (such as Rosa26) such that phenotypic consequences of transgene expression should be more predictable, also requiring fewer lines. More sophisticated approaches, such as the editing of specific non-coding elements that control gene expression in a stage- and cell dependent fashion, promise even more control and

[125] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[126] "In vivo" refers to experimentation done in a whole organism, rather than in live isolated cells.
[127] National Centre for the Replacement, Refinement & Reduction of Animals in Research, https://nc3rs.org.uk/the-3rs
[128] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[129] de Graeff et al, 2019, https://doi.org/10.1098/rstb.2018.0106

predictability over phenotype."[130] The use of induced or Cre-Lox genetically altered animals, for which the onset of the mutation, especially when harmful, can be better controlled, is another example of science-based refinement. Thus, scientific refinement may lead to increased refinement in animal experimentation.[131]

There are risks to the welfare of experimental animals also due to technical difficulties in the use of genome editing. Off-target mutations may lead to loss of function of a gene, adverse events, or even fatal abnormalities.[132] They may consequently cause the "animals further pain and suffering, due to the off-target effects, and death as they succumb to adverse off-target effects or are killed."[133]

On the other hand, genome editing could be used to decrease the suffering of research animals, for example, by decreasing the occurrence of unwanted genetic effects. Moreover, it was argued that routine genome editing of non-human primates could come within reach, substantially compromising their welfare and quality of life.[134] It has to be added here that all involved appear to agree that, in general, far too little data exist to reach any robust conclusions about off-target effects associated with CRISPR.

"Authors noted that genome editing could decrease animal welfare if somatic cell nuclear transfer (SCNT) cloning was used to deliver the nuclease-mediated modifications; SCNT is associated with embryonic losses, postnatal death and birth defects. Authors also mentioned that genome editing could result in off-target mutations or unintended effects, which could negatively affect animal health."[135]

"Indeed, increased scientific refinement here—the provision of much better models of disease-associated human genetic variation—can be viewed as an ethical good in itself, since it will arguably result in more rapid and significant advances in scientific understanding i.e., progress towards better treatments. It is in this sense that research itself can be viewed as an ethical good."[136] However, genome editing could "lead humans to ignore the predicament of the animal and to accept negative effects on animal welfare

[130] Greenfield, A., 2017, https://doi.org/10.1007/s00335-017-9702-y
[131] Ibid.
[132] Herrmann & Jayne, 2019, https://doi.org/10.1163/9789004391192
[133] Bailey, 2019, https://doi.org/10.1163/9789004391192_020
[134] Neuhaus, 2017, https://doi.org/10.1136/medethics-2016-104088
[135] de Graeff et al, 2019, https://doi.org/10.1098/rstb.2018.0106
[136] Greenfield, 2017, https://doi.org/10.1007/s00335-017-9702-y

for the sake of other goals, although this risk could be prevented by using less drastic gene drive designs and using them to promote animal welfare."[137]

Thus, we find that with genome editing a possible new balance between the 3Rs, as compared to what is usually the case, might appear. Genome editing can contribute significantly to refinement, but apparently not to reduction overall. Although the 3Rs are considered equally important, how we balance them does sometimes change with different technologies. One can also recall that the addition of a fourth R for 'Responsibility' was proposed by Max Planck, in line with the concept of Responsible Research and Innovation. In the context of genome editing, one might consider a further R for 'Recourse to innovative alternative strategies', which would go beyond refinement and which would, at least in the context of NHP research, require investment in alternative solutions.

4.5.2 Humanisation

The idea of the 'humanisation' of non-human animals is ambiguous and has several dimensions: it may imply a scientific/technical rapprochement of animals to humans, for example, changing animals' receptor cells on organs to human ones in order to impact immune response, or knocking out specific genes, or changing a specific gene sequence according to the human equivalent. Mice carrying a human gene are, for example, often referred to as 'humanised mice'. Humanisation might also refer to scenarios of enhancing animals' cognitive capacity to such an extent that the species categories or the distinction between human and animal become blurred (or new 'inter-species' categories are created). In the context of this Opinion, we are particularly concerned with the crossing of lines distinguishing species, not necessarily in a biological sense, but in so far as animals may gain functions or characteristics normally attributed to humans. What considerations on rights and obligations are brought about by such scenarios?

The potential to change the nature of animals, sometimes referred to as 'de-animalisation', i.e. to add or remove certain capacities from animals (such as cognitive capacities or the ability to feel pain), is of ethical concern (see also *section 4.5.3.* on humanisation and non-human primates). In that regard, humanisation can also be understood as a form of de-animalisation.

[137] de Graeff et al, 2019, https://doi.org/10.1098/rstb.2018.0106

Whether one considers humanisation or de-animalisation, the purpose of the related intervention is of key importance.

A main concern identified with respect to non-human primates (aside from broader ethical questions around the use of primates – and other animals) is the potential of genome editing research to humanise them.

With regard to xenotransplantation research and its clinical application, the outlook of large-scale farms of pigs carrying human organs raises major concerns. Among them are concerns around animal welfare and around humanisation, but also the potential for health research, funding and resources to be directed by an increasing demand for xenotransplantation, instead of investigating and addressing the root causes of the increasing need for organ transplants. It could be an expensive and potentially exclusive technical solution to a mostly societal problem.

4.5.3 The ethics of genome editing in non-human primates

A specific area of concern is the application of genome editing techniques in non-human primates (NHPs). Singling out NHPs is justified by the recognition of their special social and cognitive capacities. The public debate has established the need of particular protection for the wellbeing of NHPs, reflected also by *Directive 2010/63/EU on the protection of animals used for scientific purposes*, which provides specific requirements and additional limitations for the use of NHPs in research. However, the EGE is aware of the problematic implications of such a singling-out of NHPs.[138]

Many of the moral considerations concerning genome editing in plants and animals in terms of costs and benefits, risks, safety, security, efficiency, proportionality and responsibility, discussed in this opinion, apply in some form to the genetic engineering of NHPs. An important set of moral concerns is that NHPs are too much seen as just other animals and that their specific morally relevant properties are not recognised. In this section we focus on moral considerations that are specific to NHPs as we endorse their specific status, already underlined in the current regulation.

[138] Speciesism is "the practice of treating members of one species as morally more important than members of other species." (Duignan, Encyclopædia Britannica, https://www.britannica.com/topic/speciesism)

There has been a steady increase in appreciation of the moral standing of animals in general and NHPs in particular in recent decades. This can be seen as part of what Peter Singer refers to 'the expanding circle' in the course of human history, i.e. the expansion of the set of entities that are given moral standing, either as moral agents or as moral patients.[139] Peter Singer's work on animal rights has had great impact in society regarding our thinking about the moral standing of animals. His radical utilitarian views dislodged a dominant rationality-based view and replaced it by a view that focuses on our common capacity to feel pain and suffer. A range of standards seem morally required of human beings in their interaction with animals.

Against this background, we need to look at the question of what we owe to NHPs over and above what we owe to other animals. Is there even a reason to assume that some of the types of moral principles that apply between human beings, apply to them as well? If this would be the case is it because we have morally relevant properties in common with them? How do we identify this set of overlapping moral properties between humans and NHPs on which our moral judgments supervene?

There were a number of developments in the last decades that have led to the consensual identification of sets of properties for determining moral standing.

First, scientific research on primate cognition, primate behaviour and evolutionary biology and genomics of primates and humans, has brought even more striking similarities between us and them to light as is the case with other animals: their communication, theory of mind, self-awareness, pro-social behaviour, hunting in groups and foraging collaboration; they have elaborate social ties, in addition to forming pairs and family-type structures, have friends with whom they form alliances and engage in grooming, they assess and reciprocate social actions, they show emotions, transmit knowledge, and use tools. This means that their lives may go better or worse in these and other dimensions and they may have negative and positive experiences accordingly, which are observable. Furthermore, genomic research indicates that we share up to 99% of the protein-coding genome.[140] They are humans' living nearest relative.

This points to a more acute issue in NHPs than in other species, that is the 'humanisation', as genome editing may lead to (unforeseen or intended)

[139] Singer, 1975, *Animal Liberation: A New Ethics for our Treatment of Animals, HarperCollins*
[140] Suntsova & Buzdin, 2020, https://doi.org/10.1186/s12864-020-06962-8

'advanced humanisations' of NHPs as compared to evolutionary more distant species. Finally, many philosophers have been following Singer, Regan and others, by arguing for the moral standing of animals; some of these views build on the work of primatologists, such as Frans de Waal. Some calls for a 're-anthropomorphisation' of our understanding of NHPs on scientific and methodological grounds and propose that we may ascribe sorrow, grief, jealousy, shame, joy and anger to them. Some adopt a moral version of this line of reasoning (or run them together) and suggest that we disregard our humanity when we do not take our own emotional responses serious to their grief and joy and suffering. Lori Gruen, in *Entangled Empathy*, advocates an ethics of care along these lines.[141] Christine Korsgaard, in her *Fellow Creatures*, advocates expanding a Kantian approach to our thinking about animals. Her monograph is a defence of the claim that "we human beings are obligated to treat all sentient animals, that is, all animals who have subjective experiences that are pleasant or painful, as what Kant called 'ends-in-themselves', in at least one sense of that notion."[142] That sense is the one in which being an 'end-in-itself' allows an individual to have moral claims on us; individuals who are 'ends-in-themselves' have goals and means of accomplishing such goals that obligate us to constrain how we humans can justifiably act toward them. Martha Nussbaum wants to extend her capability theory to justify animal rights,[143] and "develop a life-quality standard for animals based on generic categories such as bodily integrity and health, which emphasise personal autonomy. This framework could be used to shape policies that protect animal rights, which would be species-specific. 'If the human list (of capabilities) is a template for constitution making, so too might be the list for each animal species,' she said."[144]

What these philosophical projects show is that very prominent proponents of utilitarianism, care ethics, Kantian ethics and the capability approach have tried to accommodate considered judgments about how we should deal with animals into ethical theory. Our sensitivities have changed accordingly. This seems to suggest that we have an elaborate set of strong moral obligations towards NHPs that moves beyond the standard 3Rs methodology and standard ethics of animal experimentation.

---

[141] Gruen, 2014, *Entangled Empathy: An Alternative Ethic for Our Relationships with Animals*
[142] Korsgaard, 2018, *Fellow Creatures: Our Obligations to the Other Animals*
[143] Nussbaum, 2006a, *Frontiers of justice: Disability, nationality, species membership*; Nussbaum, M., 2006b, *The moral status of animals*
[144] Gutman Argemí, 2019, *Renowned philosopher Martha Nussbaum addresses animal ethics*, https://www.browndailyherald.com/2019/04/10/renowned-philosopher-martha-nussbaum-addresses-animal-ethics/

Analysis of the literature at this stage seems to suggest that experiments with NHPs are morally acceptable only if (1) serious human suffering can be prevented by carrying out scientific research on primates, that can in no other way be alleviated, and (2) our way of dealing with the NHPs in these processes accommodates the wealth of scientific findings on their physical, mental and emotional lives and the modalities of their wellbeing and suffering. A third condition may be found in (3) a corollary obligation to find alternatives to experiments and genome editing with harmful phenotype expressions. A principle that could be entertained is that a budget should be reserved and spent on finding alternative methods when experiments are carried out on NHPs.

This leaves the question of genome editing that enhances NHPs, and especially great apes, and seeks to genetically augment their cognitive or physical capacities, without causing any harm and suffering beyond living in generous and suitable free range conditions of captivity. Arguments of proponents of human enhancement (e.g. Savulescu) may also defend the position that the ability to make NHPs more human without causing pain and suffering would translate into a moral obligation to do so. Not endorsing such positions, any stance of respecting the 'animalness' also leads to reject the fact that 'making them more human' would be a desirable goal in itself.

The EGE wishes to underline that much of the argumentation regarding NHPs relates to animals in general, and it is fair to recognise the high level of intelligence and self-awareness of other species (e.g. corvids).

4.5.4 Genome editing and animal welfare in farming

As regards farming for food production, we acknowledge that as a society we instrumentalise animals and that there are serious moral problems with industrial farming and the mass production of animals. Commercial practices of pushing farmed animals to their 'biological limit' are highly problematic and genome editing has the potential to facilitate or exacerbate them. In this context, the EGE refers to the wider discussion on technological solutions as a presumed 'quick fix' to broad societal problems.

As analysed, genome editing technologies may offer possibilities to improve both animal welfare in farming and productivity, but a number of questions remain open as we lack knowledge (for example, on off-target modification consequences) and large societal debates on the matter. What should be

the limits to practices of genetically modifying animals? Is it acceptable to modify an animal to suit its breeding environment, or to improve its wellbeing by altering an attribute that is characteristic of its species? Is it ethically appropriate to introduce into a local population of wild animals or insects a gene that will lead to its elimination (see *6. Gene drives*)? What are purposes for which the use of the CRISPR/CasX system is acceptable? What level of uncertainty or certainty is required to refuse or to implement an application?

4.5.5 Genome editing in animals and biodiversity

As for all processes of genetic alteration, utmost prudence is necessary as to potential consequences of genome editing applications on biodiversity, ecosystems and the environment. Genome editing technologies applied to animals may serve purposes of protection or recreation of diversity, or may endanger it if not appropriately controlled. We presently lack data, and we need to consider long-term time scales.

Theoretically, genome editing could be used to reintroduce extinct animal species or restore populations of endangered animal species. Using genome editing for these purposes is a niche application that is still in an exploratory research phase and should be considered with caution and with careful analyses of potential consequences before being considered in practice.[145]

Given the relative ease to produce, with new genome editing techniques, new characteristics in animals, even outside the usual professional and regulated contexts of research or food production, governance tools that are fit for purpose must regulate it. Gathering information on progress of knowledge in this domain and transparency vis à vis publics on all related matters are key.

[145] The Netherlands Commission on Genetic Modification (COGEM), 2018, *CRISPR & Animals: Implications of Genome Editing for Policy and Society*, https://cogem.net/en/publication/crispr-animals-implications-of-genome-editing-for-policy-and-society/

5 GENOME EDITING IN PLANTS

5.1 Introduction

Plants are used for many purposes, including for providing food, feed, fibre and fuel, and they may be the source of many chemicals used by human societies. Technology could be used for developing new uses of plants not previously available, for example, the production of vaccines in tobacco.

Most reports addressing the use of new techniques for editing the genome have stressed their use in humans. The use of these technologies in plants is more likely to happen quickly, and in Europe particularly, may be controversial. Science provides almost unlimited power to modify our environment. The problem is no longer as to what can be done, but rather what should be done (Philippe Goujon). **The economic impact of choosing to use or not use plants produced using any new technologies is likely to be significant and should be addressed by public authorities and society at large.**

"Throughout history humanity has transformed and adapted to the world's various climates. (…) The first farmers would choose the seeds of plants that produced the most favourable traits, such as that with the most fruit, to plant in the following season. Over many years, this selection process produced domesticated plants that are very different from their wild precursors."[146] Maize (*Zea mays),* wheat (*Triticum aestivum*) and barley (*Hordeum vulgare)* bear little resemblance to the original plants. All of the vegetables in the figure below have been developed using natural selection over many generations from the same precursor.

[146] Schroder, 2018, https://scholarship.law.uc.edu/uclr/vol87/iss4/9

These vegetables have all been developed from the same precursor using natural selection over many generations.

Deliberately induced mutations using chemicals or radiation or genetic modification by changes at random points within the genome of plants have been used for a long time to attempt to produce new ('improved') varieties of plants. In addition, techniques like embryo rescue or the production of hybrids with related plants that could not normally occur (due, for example, to flowering at different times of the year) are a major step in the production of new varieties suited to particular environmental conditions. Most commercially produced plants currently cultivated are the results of deliberate modification and subsequent selection. This process can (and does) take considerable time.

Most of the plant cells modified by these techniques will be non-viable or lacking the desired characteristics. However, the ability to regenerate (many) whole plants from a single cell becomes of extreme importance in this process, which has always required selection and sexual reproduction to select the plants which have 'suffered least' from the modification process and which can then be grown as uniform and stable varieties. The plants that demonstrate both the desired modification and least disruption

of other properties would be selected. This is an important step in the process of commercialising new varieties, regardless of the mechanism of production of the variety – whether selection or modification using a range of technologies.

New varieties[147] are continuously being created that are better suited than current varieties to the local conditions or have desired agronomic or other desired characteristics – to meet challenges including responding to anticipated consumer choice, longer shelf life of the products or to defeat weeds and pests. The effective lifetime of a new variety depends on the 'crop' but is relatively short, sometimes no more than five years. Many of the plants obtained using new genetic technologies may not be suitable for particular agricultural conditions and will be crossed with appropriate varieties to further improve that which is actually used in production.

'Traditional techniques' (including mutagenesis) for producing new plant varieties have received little press and almost universal acceptance within Europe. They are not fully defined, but Annex I B to *Directive 2001/18 on the deliberate release into the environment of genetically modified organisms*[148] lists those organisms which are not subject to the requirements of the Directive, namely those obtained through mutagenesis and cell fusion, subject to certain conditions. The EU Court of Justice has recently clarified the interpretation of the legal status of mutagenesis techniques under that Directive, by ruling that organisms obtained by mutagenesis techniques/methods are GMOs within the meaning of the Directive, and that only organisms obtained by mutagenesis techniques/methods which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of the Directive.[149] Many of the varieties produced using the exempted techniques are even acceptable for being labelled organic. Most EU Member States have resisted using varieties produced using 'modern biotechnology'.[150]

---

[147] To meet "plant variety rights" rules for registration as a new variety, the modified plants must be (i) new, (ii) distinct (where they are clearly distinguishable from other known varieties), (iii) uniform and (iv) stable (characteristics are unchanged after repeated propagation).

[148] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02001L0018-20190726

[149] Court of Justice of the European Union, Case C-528/16, 25 July 2018, http://curia.europa.eu/juris/documents.jsf?num=C-528/16

[150] Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2000), https://www.cbd.int/doc/legal/cartagena-protocol-en.pdf, Article 3(i): "'Modern biotechnology' means the application of: a. In vitro nucleic acid techniques, including

The United Nations Convention on Biological Diversity[151] requires its contracting parties to "Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health" (Article 8(g)), and to address the needs, firstly, assisting less developed countries in providing access to the results and benefits arising from biotechnology, and secondly, considering whether a protocol to the Convention addressing the impact of living modified organisms was required (Article 19).

The Cartagena Protocol on Biosafety[152] was adopted on 29 January 2000, and the European Union ratified it on 27 August 2002. The Protocol outlines the risk assessments required for the trans-boundary movement of modified organisms, and specifically places the precautionary approach as a fundamental concept when permitting the use of these organisms. The precautionary approach in environmental law was first enunciated in Principle 15 of the Rio Declaration on Environment and Development[153] (1992):

In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

The use of the precautionary approach (or principle) has had a significant impact on the choice not to use genetically modified plants in Europe, even though there is little evidence of serious or irreversible damage to the widespread use of these crops in the rest of the world. Whilst there are strong proponents of the use of precaution in order to protect the environment, others argue that the concept has been used as a vehicle to stop progress. There is no evidence of harm to the environment due

recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection."

[151] The Convention on Biological Diversity, 1992 (1760 U.N.T.S. 69), https://www.cbd.int/convention/text/

[152] Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2000), https://www.cbd.int/doc/legal/cartagena-protocol-en.pdf

[153] The Rio Declaration on Environment and Development, 1992, https://www.cbd.int/doc/ref/rio-declaration.shtml

specifically to the introduction of new varieties, although changes in farming practice made possible by the characteristics of new varieties have impacted on the conservation of biodiversity – fields being larger and the absence of hedges are examples.

Precaution dictates that case-by-case consideration of the products of genome editing and of their use in particular environments is required. **Should this analysis identify both risk and benefit to humans and the environment?**

The European GMO legislation (particularly Directive 2001/18[154]) requires, in accordance with the Cartagena Protocol (to which the EU is bound), that a risk assessment be undertaken to assure that harm to the environment is avoided. In many cases, the interpretation of the legislation within most European countries is that, based on the precautionary principle, the risk may be too great. The European Food Safety Authority (EFSA), fulfilling its statutory role, has considered the risks for most of such organisms approved in other jurisdictions and has recommended in the vast majority of cases that these plants are safe for the environment. The European Commission's *Communication on the precautionary principle*[155] identifies a set of criteria in implementing the principle, inter alia:

- proportional to the chosen level of protection,
- non-discriminatory in their application,
- consistent with similar measures already taken,
- based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis),
- subject to review, in the light of new scientific data,
- capable of assigning responsibility for producing the scientific evidence,
- necessary for a more comprehensive risk assessment.

Where a change in the genome involves many new protein and enzyme genes (synthetic biology), or where the position of changes is random, it may mean that the risk assessment is very detailed and deliberate, in order to avoid or minimise the risk of serious and irreversible harm to either the environment or to human health. Where the change is in a position in the

[154] For an overall overview see https://www.biosafety.be/content/eu-regulatory-framework-deliberat-e-release-gmos

[155] Communication from the Commission on the precautionary principle, COM (2000) 1, https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A52000DC0001

genome which has been well characterised, and the change is one which renders that portion of the genome similar or even identical to that found in similar organisms, the proportionality requirement would indicate a light-handed approach.

Directive 2001/18 has been amended several times since its publication in 2001, in particular in 2018, to update the annexes as regards the environmental risk assessment with a view to incorporating and building upon the Guidance published by EFSA, and in order to adapt to technical progress and taking into account the experience gained in the environmental risk assessment of genetically modified plants.[156]

In Opinion no. 24 on the ethics of modern developments in agricultural technologies, the EGE recognised that "[p]ositions on GMOs are sharply divided across the EU. Industrial stakeholders point to the advantages of this technology in terms of ecological sustainability, economic sustainability and social sustainability and underline both the increasing public acceptance of this technology and its potential to produce enough healthy food for the population, while preserving precious resources, such as soil and water, and mitigating climate change. Consumers' organisations, environmental protection organisations and several NGOs underline the risks associated with coexistence of GM crops alongside natural species, the lack of public acceptance and the risks stemming from the monopoly which this sector of industry could induce." The group suggested that "[m]any are now arguing for mechanisms for performing an environmental impact assessment of new technologies, taking into account the risks and benefits of new technologies and the risks of not implementing them – persisting with inefficient, unsustainable agriculture, for example."[157]

Chemicals produced in industrial complexes (in containment) using transgenic organisms are not subject to the same strictures as plants grown in the environment. They are used as additives in food (for example, vitamin C) and there has been little or no unfavourable consumer reaction

[156] Recitals 4 and 5 of Commission Directive (EU) 2018/350 of 8 March 2018 amending Directive 2001/18/EC of the European Parliament and of the Council as regards the environmental risk assessment of genetically modified organisms, http://data.europa.eu/eli/dir/2018/350/oj

[157] EGE, 2008, Opinion n°24, Ethics of modern developments in agricultural technologies, https://publications.europa.eu/en/publication-detail/-/publication/9369a035-5a5e-45da-8e37-09717ed806d5/language-en/format-PDF/source-77404379

to their use. The use of such genome edited micro-organisms is controlled through Directive 2009/41/EC.[158]

Contained use is defined as "any activity in which micro-organisms are genetically modified or in which such genetically modified micro-organisms (GMMs) are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment."[159]

Plant products that contain the derivatives of GMOs are remarkably absent from European supermarkets. Labelling requirements are strict, as are traceability requirements.[160] Very few GMOs are grown in Europe, but a vast amount of plant products containing derivatives of GMOs are imported primarily for animal feed.

It is envisaged that the European Union's upcoming research funding programme Horizon Europe might "allocate €5 million for projects aimed at understanding the benefits and risks of genome editing technologies in agriculture over the next two years." The 'Farm to Fork' plan has established the aim of reducing the use of fertilisers by 30% and turn 25% of conventionally farmed land into organic farming. In pursuit of these aims, the EU would prepare to "enable major advances in the life sciences and biotechnology, in new genomic techniques, such as gene/genome editing."[161]

Whilst most agricultural producers around the world argue that there is a need to use all available technologies to ensure the availability of adequate agricultural products for food, feed, fibre and fuel, there are many that argue that a holistic approach to production that respects traditional production methods is a priority. There is a view within Europe that the production of new varieties is unnecessary. We have more than enough food and feed. Why use techniques that may have an impact on human health and the environment when change is unnecessary? It is argued that alternative agricultural solutions that do not require the use of plants produced using modification of the genome could achieve more stability and

[158] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, http://data.europa.eu/eli/dir/2009/41/oj

[159] Ibid., Article 2(c), see also https://www.biosafety.be/content/eu-regulatory-framework-contained-use-genetically-modified-micro-organisms

[160] https://ec.europa.eu/food/plant/gmo/traceability_labelling_en

[161] Zubașcu, 2021, https://sciencebusiness.net/framework-programmes/news/horizon-europe-fund-research-genome-editing-agriculture

sustainability of agricultural production, as well as help to maintain biodiversity and environmental flourishing. These arguments include maintaining a variety of crops, returning to small fields, surrounded by hedges and non-farmed land flanked by resource saving land and water management, avoidance /minimisation of chemical usage (herbicides, pesticides and fertilisers) by increasing biodiversity and reducing sensitivity to monoculture driven pests and weeds.

Adherence to these and related locally adapted principles could lead to long-term resource savings of soil and water while the increased need for labour could be set off by increased automation and the use of AI technologies for monitoring and intervening on a very fine-grained level. It is argued that the risks for the user of the agricultural product are better controlled by not using GMO varieties, and that environmental risks are mitigated using these alternative methods.

The inverse argument is also made using the same criteria, that the use of modified plants could improve our use of land resulting in the (re)creation of *more* natural environments. Choosing the modification carefully could result in better pest management, less reliance on chemical fertiliser, and a better shelf life for plants. Whichever argument is considered, the need for a holistic view of the use of land, water and the environment is recognised.

5.2 Why do we want genome editing in plants?

New varieties of plants are introduced into the market for many reasons, including improvements in characteristics – yield, resistance to pests, adaption to particular or changing environments and even catering to the whims of consumers. Many changes can be accomplished by traditional farming methods that require crossing with related sexually compatible varieties, but this is a slow process, requiring many generations.

Understanding the impact of climate change, including desertification, drought or even excess water in particular climatic areas, provides an impetus for producing new varieties of plants that can be adapted to the changes.

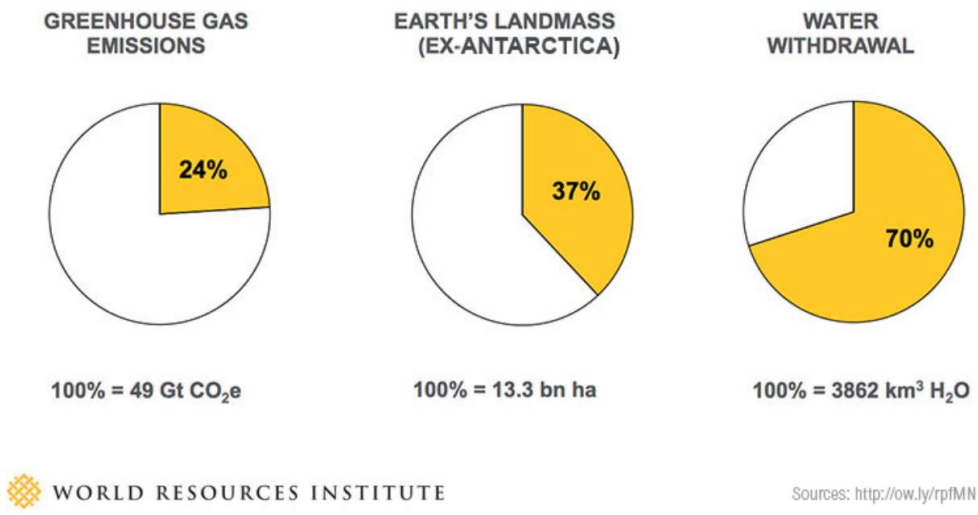
Changes have been introduced by using chemical or radiation mutagenesis. These techniques harm most of the subjected plants, but enough can be salvaged and selected to allow traditional farming methods to choose those plants which display the wanted 'improved' characteristics. Genetic

modification (as used during the last 30 years) took a lot of the guesswork out, but most of the plants are damaged during the modification process, and selection and back crossing are still required to obtain improved useful varieties as the position of insertion is not defined, and disruption of the genome still has a major impact. Genome editing provides greater precision as to the site of changes and makes it possible to (largely) accurately identify the position of modification in the genome, resulting in greater precision in producing new varieties, and hence more rapid introduction of new, 'improved' varieties to the marketplace.

Both genetic modification and genome editing make it possible to insert genes from other, non-sexually compatible organisms providing the possibility of using plants for purposes other than that for which they were originally domesticated. The techniques of genome editing also make synthetic biology more likely – where multiple changes can be made that could fundamentally change the characteristics of the plant.

There is a need to examine the agricultural techniques currently used to facilitate the growing and distribution of plant products. The impact of agriculture on the global environment is illustrated below. "Agriculture contributes nearly one-quarter of global greenhouse gas emissions, uses 37 percent of landmass (excluding Antarctica), and accounts for 70 percent of all freshwater withdrawn from rivers, lakes, and aquifers."[162] An impact analysis should be holistic, taking the impact of using all technologies into account, including the manner in which choices are made as to which plant, on what land and what resources are needed to cultivate and bring the products to market.

[162] https://www.wri.org/blog/2013/12/global-food-challenge-explained-18-graphics



Agriculture's share of global environmental impact (2010)[163]

New genetic technologies provide systems for identifying the targets for disease-causing pests in plants and in many instances the defence mechanisms developed by plants to attempt to mitigate disease. Genome editing could then be used to make the plants hardier and less susceptible to the many challenges which nature provides. An example is technology being used to resist fungus infection on wheat. The most devastating fungus (UG99) derives from rust strains fusing through somatic hybridisation. Scientists have been able to stack five resistance genes into one wheat plant to fight this rust.[164]

5.3 New technologies

Genome editing using CRISPR/CasX (Cas9, Cas12 or similar) has revolutionised the tedious process by allowing acceleration of the initial selection process – already the process used in plants is a cheaper and much faster method for achieving the same ends. The system permits gene knock-out, deletion, insertions and even gene silencing.

[163] https://www.wri.org/blog/2013/12/global-food-challenge-explained-18-graphics
[164] Li et al, 2019, https://doi.org/10.1038/s41467-019-12927-7

The use of CRISPR with associated enzymes has proved to provide powerful tools to modify nucleic acids. The technique involves cutting the double stranded DNA at a specific position and, where appropriate, the insertion of new DNA using the cell's own repair mechanisms through either homologous recombination or non-homologous end-joining. "These processes are inefficient and vary greatly depending on cell type. (…) However, base editing is restricted to nucleotide substitutions, and thus efficient and targeted integration of DNA into the genome remains a major challenge."[165]

New techniques of genome editing are being developed all the time to increase both the efficiency and specificity of the editing system. For example, the work of Strecker et al. (2019)[166] has indicated a new method for inserting large stretches of DNA at a precise point in the DNA sequence.

5.4 Regulation

In July 2018 the Court of Justice of the European Union (CJEU) ruled in Case C-528/16, *Confédération paysanne and Others,* that organisms obtained by methods of mutagenesis are GMOs ("those techniques/methods alter the genetic material of an organism in a way that does not occur naturally", "It follows that organisms obtained by means of techniques/methods of mutagenesis must be considered to be GMOs within the meaning of Article 2(2) of Directive 2001/18", paragraphs 29 and 30).[167] The Court further ruled that "organisms obtained by mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of the directive" (paragraph 54), and that "organisms obtained by means of new techniques/methods of mutagenesis which have appeared or have been mostly developed since Directive 2001/18 was adopted" fall within the scope (paragraph 51). The Court understood that mutagenesis permits the modification of the genome without the insertion of foreign DNA, unlike transgenesis.

The Court considered amongst others that "the risks linked to the use of these new mutagenesis techniques might prove to be similar to those that

[165] Strecker et al, 2019, https://doi.org/10.1126/science.aax9181
[166] Ibid.
[167] Court of Justice of the European Union, Case C-528/16, 25 July 2018, http://curia.europa.eu/juris/documents.jsf?num=C-528/16

result from the production and release of a GMO through transgenesis," that "the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into that organism" and that "the development of those new techniques make it possible to produce genetically modified varieties at a rate and in quantities quite unlike those resulting from the application of conventional methods of random mutagenesis" (paragraph 48). In view of these potential risks, the Court concluded that excluding organisms obtained by mutagenesis techniques from the scope of the GMO Directive would compromise the objective pursued by that Directive, which is to avoid adverse effects on human health and the environment, and would fail to respect the precautionary principle which the Directive seeks to implement. It follows that **the GMO Directive is applicable to organisms obtained by mutagenesis techniques that have emerged since the adoption of the Directive**.[168]

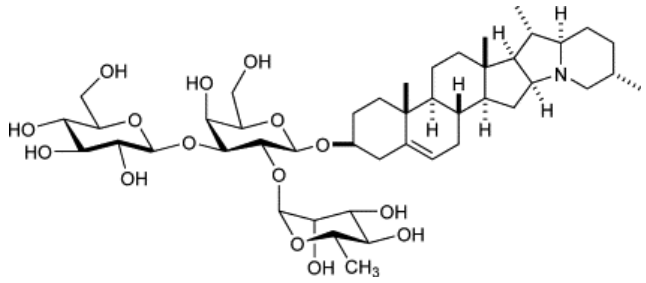
The CJEU judgment implies that a risk assessment has to be performed in accordance with the Directive on plants genetically modified using these new techniques. This may prove expensive for those attempting to produce new improved varieties and hence exclude small research or commercial establishments from the development process, for all sorts of assessment in relation to these new products are different from the introduction of new varieties which have been used for a relatively short time (such as chemical or radiation mutagenesis).

5.5 Are genome edited foods safe?

All agricultural products contain mechanisms developed by the plants as protection against predators. Some use spines or thorns, and many use various types of poison. Ricin is found in castor beans. A further example are the cyanogenic glycosides which occur in at least 2000 plant species, of which a number of species are used as food in some areas of the world. Cassava, sorghum, stone fruits, bamboo roots and almonds are especially important foods containing cyanogenic glycosides. The potential toxicity of a cyanogenic plant depends primarily on the potential that its consumption will produce a concentration of cyanide that is toxic to exposed humans. Many types of beans contain lectins, and kidney beans have the highest concentrations – especially red kidney beans. As few as 4 or 5 raw beans

[168] Van der Meer et al, 2021, https://doi.org/10.1017/err.2020.105

can cause severe stomach ache, vomiting and diarrhoea. Lectins are destroyed when the dried beans are soaked for at least 12 hours and then boiled vigorously for at least 10 minutes in water.[169] Solanine is an extremely poisonous glycoalkaloid found in the genus Solanum (for example, potato (Solanum tuberosum), tomato (Solanum lycopersicum), eggplant (Solanum melongena) and deadly nightshade (Atropa belladonna)). It can occur naturally in any part of the plant, including the leaves, fruit, and tubers. No maximum levels for glycoalkaloids in potatoes have been established at EU level. Some Member States have a national maximum level of 200 µg/kg.[170] Plant breeding could increase the concentration of such toxins or allergens in plants, yet there have been a negligible number of food poisoning issues due to the introduction of new varieties into the food chain.[171]



Solanine

It is unlikely that a modification will have deliberately or incidentally introduced new toxins into a plant, but the introduction of new genetic material will almost certainly result in a change in the production of some chemicals by a plant – hence some form of risk assessment would normally be expected. Tests to ensure that toxicity remains within safe bounds would always be necessary for any new variety, regardless of the technology used in its production.

The impact on the environment of new varieties may also impact on the perception that their use may be unsafe.

[169] WHO, 2018, Natural toxins in food, https://www.who.int/news-room/fact-sheets/detail/natural-toxins-in-food
[170] Standing Committee on plants, animals, food and feed, 2015, Summary report, https://ec.europa.eu/food/sites/food/files/safety/docs/reg-com_toxic_20150623_sum.pdf
[171] Louwaars, 2019, https://doi.org/10.3920/978-90-8686-885-8_5

What therefore constitutes safe? Is a new variety to be tested on the basis of 'as safe as that currently on the market'? Does the new variety have to be safer than that currently used? Should the whole system, including chemicals used, land used and protection (or otherwise) of the agricultural diversity be taken into account in deciding on safety? Should the requirement "based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis)" be part of this analysis?

5.6 Identification

Genetically modified plants could be identified (in all instances so far) as introduced genes included DNA like the cauliflower mosaic virus promoter for which probes existed. This has enabled relatively simple traceability, testing and labelling.

Genetically modified feed products are more readily imported and used within the EU. Their traceability is assured, but there is no requirement for labelling of animals that have been fed on genetically modified feed.

Genome edited products may not include easily identifiable elements that could be used to mark products as having been made using genome editing. There would be a possibility of requiring the introduction of some form of marker through genome editing when producing the plant within the EU. Genome editing might involve the insertion of new genes from both related and unrelated species, deletion of large or small sections of the DNA, and even the insertion of single bases to change a particular protein to that found in other organisms. Where major changes have been introduced the requirement to 'mark' the product may be imposed, but if there is a small change to make the plant produce gene-products which are found in related plants the impact of requiring such a marker may be deleterious to the plant. In some instances a change might be introduced using genome editing where the modified gene is the same as that found in sexually compatible species where genome editing is simply quicker. It is argued that off-target (unintended) modifications, where they occur, may help in identifying the plant as having been modified. Introduced changes of

flanking coding bases, which do not lead to amino acid changes, are possible and could be used to distinguish edited from non-edited plants.[172]

However, much food and feed and seed used in the EU is imported from countries which have no such requirement – such as most of South and North America and China. It may be difficult if not impossible to distinguish between imported genome edited plants and other new varieties, or any derived products, when imported. There would have to be significant scientifically justifiable grounds for excluding such products from the market due to WTO rules.

Traceability requirements apply in the EU, where the producers of the plant or seed have to provide documentary evidence to show that a product contains, consists or is produced from a GMO.[173] The cost could be considerable and non-European producers have to, but may not be willing to comply. As the new varieties are then used as the starting point for further varieties using traditional methods the complexity of the system would mitigate against any such approach.

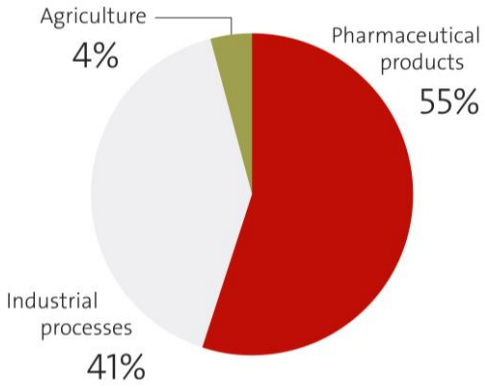
It is likely that modifications introduced through conventional breeding techniques (even those preceding 2001), occurring naturally or through genome editing may not be able to be distinguished from one another.

It may be possible to use patent or plant variety rights registers as a means to identify plants which have been modified using the new techniques. However, if controls on cross-breeding are not instituted uniformly across the world and if licences for using patents are not generally maintained, even this would not provide a robust traceability technology. The Enlarged Board of Appeal of the European Patent Office[174] ruled on the 14 May 2020 that plant or animal products that are exclusively obtained by means of an essentially biological process are not eligible for patent protection and may be protected through plant variety registration. Genetically modified or edited plants remain patentable. The use of a genetically modified plant as the starting material for new varieties may be costly for breeders in Europe.

[172] See also the European Network of GMO Laboratories' (ENGL) report on the "Detection of food and feed plant products obtained by new mutagenesis techniques" (2019).

[173] The existing GMO legislation already requires the operators to hold and transmit information to the next operator regarding the presence of a GMO in a product (Article 4 of Regulation 1830/2003).

[174] European Patent Office, Datasheet for the Opinion of 14 May 2020, https://www.epo.org/law-practice/case-law-appeals/pdf/g190003ex1.pdf



Patents in biotechnology[175]

How can the perceived concerns of the European consumer be addressed? How do traceability criteria work given that the products are grown throughout the world, and if not regulated in one jurisdiction, may be used as the starting material for a host of new varieties?

5.7 Biodiversity

The loss of a vast range of plants due to urbanisation and climate change is unavoidable even if action is taken. However, the production of new varieties of edible plants that have desired characteristics using the whole gamut of scientific tools may cause a decrease in agricultural biodiversity. Differences in climate and soil characteristics mean that different varieties are grown in different habitats – farmers choosing the best variety for their purposes. The CGIAR institutes[176] collect and maintain genetic resources for particular plants to ensure their survival. "The purpose of the CGIAR System is to advance agri-food science and innovation to enable poor people, especially women, to better nourish their families, and improve productivity and resilience so they can share in economic growth and

[175] European Patent Office, https://www.epo.org/news-events/in-focus/biotechnology-patents/pie-chart-large.jpg
[176] Consultative Group on International Agricultural Research

manage natural resources in the face of climate change and other challenges."[177]

Many argue that the rapid pace of development of new varieties given modern tools will have a deleterious effect on plant genetic resources. Older methods of enhancement took time, and their impact was thus probably lower on the agricultural environment.

New varieties with traits attractive to farmers, whether due (for example) to an increase in yield, resistance to depredation by insects or resistance to abiotic stress – drought, excess water – could 'crowd out' current varieties, leading to a loss of a whole range of current varieties and if care is not taken, to the development of the equivalent of monocultures where too much of the particular variety is chosen. This would clearly pose serious challenges if it later became obvious that the new variety was more susceptible to disease or other stress related issues.

The impact of genome edited plants on the natural environment could be both positive and negative. If a gene inserted into a plant is transferred to natural relatives the result could be the creation of weeds and the loss of control (e.g. herbicide tolerance). The opposite may be true if the new genetic element has food or feed advantages or is toxic to some insects – allowing the plants within the environment to better adapt to their environment. The effects may seriously impact the ecosystem – resulting in a deleterious change in the whole environment. Increase in yield per hectare, on the other hand, may allow the retention of uncultivated land which could impact the natural environment in a positive manner – this is discussed in detail in EGE Opinion n°24.[178] An example is deforestation in order to grow crops which is a major issue in tropical regions where the needs of the European consumer may impact on the lives and environment in unexpected ways.

Should companies introducing new varieties, regardless of method of the provenance, be required to identify the impact of their use on biodiversity and the environment?

[177] Charter of the CGIAR System Organization, 2016, https://cgspace.cgiar.org/bitstream/handle/10947/4370/Charter%20CGIAR%20Organization.pdf?sequence=8

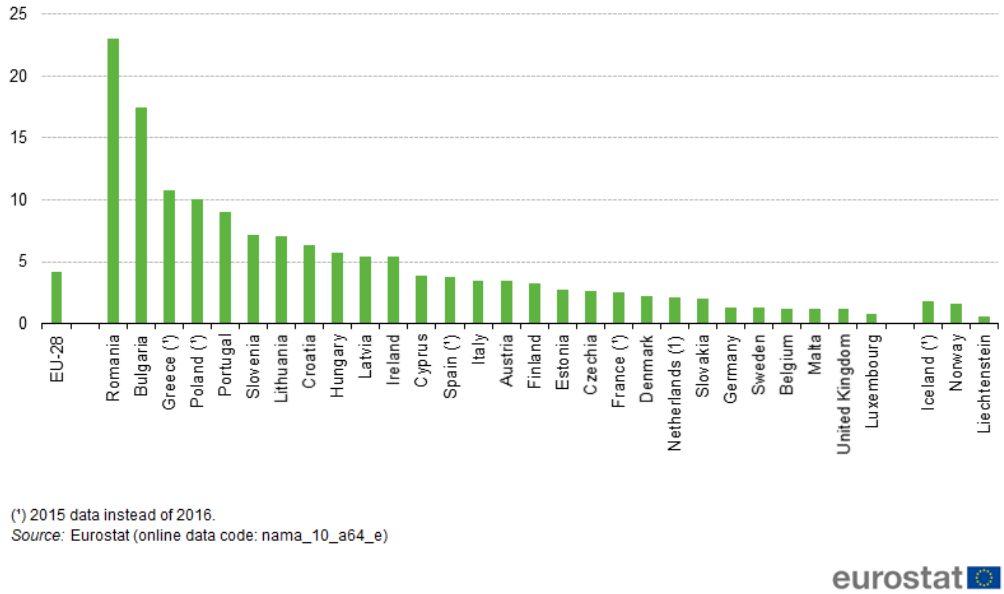
[178] EGE, 2008, Opinion n°24, Ethics of modern developments in agricultural technologies, https://publications.europa.eu/en/publication-detail/-/publication/9369a035-5a5e-45da-8e37-09717ed806d5/language-en/format-PDF/source-77404379

5.8 Industrialisation of agriculture

The impact of the industrialisation of agriculture should not be taken lightly. New varieties have often resulted in greater industrialisation as the selected traits impact on the way the crops are grown. This could be exacerbated by the ready availability of new traits specifically chosen to (apparently) benefit the farmer.

- Larger farms have an impact on the general biodiversity (rather than agricultural biodiversity) through the disappearance of hedges and non-farmed areas of a field. ("When you reap the harvest of your land, do not reap to the very edges of your field or gather the gleanings of your harvest." – Leviticus 19:9).
- Smallholders struggle to compete with larger farms, even where the quality of their produce may be higher, or more desirable to consumers. The *terroir* argument remains an important facet of agriculture, where the nature of the plant-soil interaction is important. The importance of *terroir* impacts on the price of both the product and items made from that product, and there the Slow Food movement appreciated the history of the plant (or animal) variety, the story of the farmer and the quality of the product.[179]
- The number of individuals employed in agriculture falls as industrialisation occurs. Agriculture is a large employer in the EU, with about 9.7 million people, about 4.2% of the employed. The less industrialised the country, the greater the proportion of individuals employed in the agriculture sector.[180] As the proportion employed in agriculture increases, urbanisation and problems relating to distribution of food are exacerbated.

[179] https://www.slowfood.com/
[180] Eurostat, Farmers and the agricultural labour force, 2020, https://ec.europa.eu/eurostat/statistics-explained/index.php/Farmers_and_the_agricultural_labour_force_-_statistics



Employment in agriculture, 2016 (% of total employment)

5.9 Biosecurity

Biosecurity has been defines as "a strategic and integrated approach that encompasses the policy and regulatory frameworks (including instruments and activities) that analyse and manage risks in the sectors of food safety, animal life and health, and plant life and health, including associated environmental risk. Biosecurity covers the introduction of plant pests, animal pests and diseases, and zoonoses, the introduction and release of genetically modified organisms (GMOs) and their products, and the introduction and management of invasive alien species and genotypes. Biosecurity is a holistic concept of direct relevance to the sustainability of agriculture, food safety, and the protection of the environment, including biodiversity."[181]

There is a concern that modern techniques of genome editing may impact adversely on biosecurity when defined in this manner. In particular, the security of supply of particular major crop species could be impacted, especially where possible monocultures are used.

[181] http://www.fao.org/biosecurity/

Food security has become an important issue, particularly with a growing urban population, the impact of climate change, limited land available for agricultural expansion and the need to have an efficient distribution system where losses during transportation are minimised. The new techniques may have a role to play.[182]

What incentives could be introduced to ensure that new varieties address biosecurity and security of supply for food, feed, fibre and fuel?

5.10 Justice

The issue of justice is addressed in EGE Opinion n°24**Error! Bookmark not defined.**.[183] Commercial agriculture competes with small farms, which again may well compete with subsistence agriculture. The expansion of commercial agriculture will often be at the expense of smaller farmers who do not have the resources to compete. New varieties better able to compete within the agricultural sphere may exacerbate the conflict. The technologies could, however, be used to improve the lives of subsistence farmers through developing plants providing quality products both in terms of yield per hectare and nutritional quality.

Modern techniques for the production of new varieties, whether or not by genome editing, have been the prerogative of large seed companies, due to the cost of producing them. This has led to the monopolisation of the production of seed within a small group of companies, and considerable public reaction to some of these companies. Very considerable testing of new varieties produced using genetic modification ensuring their safety resulted in high costs, which made the production of such varieties by small companies or research organisations prohibitive. This in turn led to the monopolisation about which there are many concerns. The techniques could have an impact on distribution systems, resulting in quality food becoming available where it is needed, in the urban environment.

Should the requirements linked to the introduction of plants developed with the techniques of mutagenesis involving genome editing be the same as that for other GMOs (as essentially required by the CJEU judgment), the ability of small companies, research organisations or universities to produce

[182] Ma, Mau & Sharbel, 2017, https://doi.org/10.1016/j.tibtech.2017.08.004
[183] EGE, 2008, Opinion n°24, Ethics of modern developments in agricultural technologies, https://publications.europa.eu/en/publication-detail/-/publication/9369a035-5a5e-45da-8e37-09717ed806d5/language-en/format-PDF/source-77404379

new varieties (initially for local use) would be seriously curtailed, and this could result in monopolisation due to the costs entailed in assuring safety.

Any additional risk assessment requirements could prove costly and impose a high regulatory burden, further preventing smaller companies and research centres from commercialising products. **Should consideration be given to structures that support smaller actors to undertake risk assessments and enter the market?**

5.11 Societal considerations

Food quality is an extremely important issue within the EU. It is often regional and of cultural importance. Many reject the importation of cheaper foods and choose to buy regional varieties. There are many who argue that there is no need for new varieties or products within the food sector. The debate about scientific risk could once again become an overtly political debate about food quality, *paysan* survival, and trade policy. Culture and history are important.[184]

A mistake made during the introduction of genetically modified products was to not involve the public in choosing that which was introduced onto the market. There is a clear need for honest dialogue and the inclusion of all the public in framing the decision-making process for introducing new products to the market. There is much false information or hype provided by all sides in the debate about new technologies that produce this most basic commodity. Mechanisms for ensuring the veracity of the information provided to the public should be carefully considered.

The effects of increased prices and availability where strong regulation is required should also be considered. This would impact on the poorest segment of society.

The use of patents in the introduction of new traits regardless of whether genome editing technologies are used creates problems which must be addressed.[185] The costs of developing new traits are significant, as in general, the identification of the trait and its insertion into a variety is costly and the new varieties have normally to undergo extensive field trials.

[184] Heller, 2013, https://doi.org/10.1007/s10460-015-9635-6

[185] The Enlarged Board of Appeal of the European Patent Office has ruled that plants and animals obtained through essentially biological processes are not patentable. (https://www.epo.org/law-practice/case-law-appeals/communications/2020/20200514.html)

Patents are a mechanism for cost recovery. Patents also increase the costs of those using the patented varieties and may inhibit the use of new varieties by the farmer.

The patent system makes it difficult for stacked traits to exist in varieties where the patents are held by different patentees, especially where strict protocols are imposed on farmers using the varieties in which the patented trait is expressed.[186] Plant variety rights, however, provide plant breeders with rights to use existing varieties as a starting point for creating a new variety which is distinct, uniform and stable.

It is likely that the use of patents in plants impacts on the ability of small and medium sized plant-breeders to introduce new varieties to the market especially where it is desirable to introduce multiple traits.

There is a need to ensure food security, provide renewable resources for fuel, feed and fibre, safeguard the retention of biodiversity and protect our environment. Genome editing technologies could, with appropriate and proportionate control, enhance our ability to achieve these goals.

[186] Louwaars, 2019, https://doi.org/10.3920/978-90-8686-885-8_5

6 GENE DRIVES

Gene drives are a specific use of genome editing that has drawn particular attention as it offers the promise of the possibility to guide a 'biased' inheritance of certain genes in entire animal or insect populations to make them harmless or more vulnerable. Gene drives would thus offer a broad scope of application, including to eliminate insect-borne human diseases, support more sustainable agricultural models and control environmentally damaging invasive species.[187] Studies have, for example, assessed the possibility of releasing transgenic mosquitoes to combat the spread of malaria and other mosquito-borne diseases.[188] Yet, gene drives also pose serious risks and a range of ethical considerations are imperative.

6.1 What characterises gene drives?

Gene drives change the way in which certain genes (and therefore the traits that they encode) are inherited: they 'drive' a trait into a population. They comprise different molecular and non-molecular mechanisms and can only occur in species that reproduce sexually. For example, a trait that would 'normally' be passed on from parent to offspring with a 50% chance of being inherited (depending on whether the offspring inherits the maternal or paternal variant) would, with a gene drive, be inherited by virtually all offspring. This is meant by 'biased' inheritance.

Such 'bias' – that is, such increased likelihood for a trait to be passed on – could stem from human intervention, or it could result from the chance of external framework conditions (such as radiation), or the change of factors within the genome that increase the likelihood of some traits being inherited. Genome editing by human intervention is only one among several possible ways through which biased inheritance could occur.

Gene drives are not a new phenomenon, and certainly not one that has only been made possible through genome editing: naturally occurring gene drives do exist. For the purpose of this Opinion, however, we consider only those gene drives that came into existence through direct, targeted human

[187] Esvelt et al, 2014, https://doi.org/10.7554/eLife.03401
[188] Benedict et al., 2008, https://doi.org/10.1089/vbz.2007.0273

intervention via the editing of genomes.[189] Table 1 contains an overview of two types of gene drives, according to the different kind and level of human intervention. The grey row signifies the gene drives that we consider in this Opinion.

Compared to genome editing approaches described in other sub-sections of this Opinion, gene drives represent a unique ethical challenge not only because of the rapid pace by which they can change large populations of species, but also because in the context of gene drives, the very tool that modifies the genome is being released. In other forms of genome editing, the finished 'product', namely the genome-edited organism, is released. In addition, the effects of gene drives may be difficult or impossible to detect and undo.

This means that in the context of gene drives uncertainty is particularly high. It also extends to the capacity of the technology to deliver on certain scientific promises, for example, that the effects of knocking out a specific gene/trait on mosquitos would persist over generations and that the ability to carry viruses would not return; uncertainty also over the technical ability (claimed by some gene drive scientists) to reverse the process, and uncertainty about the factors that can have bearing on the effects of gene drives.

Level	**What is being modified?**	**Direct, targeted human intervention?**	**Example**
1	'Natural' gene drive. Gene drive has existed in nature for a long time, or external framework conditions are changing, affecting processes of selection	no	P element in the Drosophila genome
2	Genes are modified directly	yes	Increasing the inheritance of white fur in mice[190]

Overview of different types of gene drives, according to the level of human intervention. This Opinion considers only gene drives at level 2.

[189] An example would be the changing of the genome of female mosquitoes in such a way that sterility is 'driven' into the population at a rate of over 90% instead of ~50% (Alphey, 2016, https://doi.org/10.1038/nbt.3473). This is done in attempt to prevent the transfer of infectious diseases from mosquitoes to humans.

[190] Grunwald et al, 2019, https://doi.org/10.1038/s41586-019-0875-2

6.2 Concerns

These unique features of gene drives have raised a number of ethical concerns that have been discussed in various fora.[191] Dimensions that have, in our view, not yet received sufficient systematic attention are global and epistemic justice, as well as anthropocentrism:

6.2.1 Social justice considerations

If specific gene drives will ever be found to be a safe and effective tool in limiting human diseases, how can we ensure that those populations that need it the most have access to gene drives? How can we ensure that people in low resource contexts can participate in decisions on research and development in this context, including the setting of research priorities? How can we ensure adequate funding for projects that will benefit those who need it most? How can we ensure that we try not only to solve the questions that are scientifically most interesting, but also those that seek to alleviate the greatest suffering?

6.2.2 Epistemic justice

Epistemic justice means an honest attempt at describing problems, and formulating solutions, in such a way that they reflect the views and needs of different groups of people within and across societies. What elites in some parts of the world consider the most pressing issues, and what solutions they may consider just, does not necessarily reflect the preferences and needs of all people in the world. We need democratically legitimate and epistemically just ways to decide what gene drives should be used for, on what species and for what purposes, seeking to ensure that those who need it most benefit from gene drives.

6.2.3 Overcoming anthropocentrism

Besides the rights and interests of humans, we also need to consider the wellbeing of non-human entities. There is an increasing recognition that animals and plants, and our ecosystem as a whole, should not only be

[191] E.g. EFSA Panel on Genetically Modified Organisms, 2020, https://doi.org/10.2903/j.efsa.2020.6297; WHO, 2009, https://www.who.int/tdr/publications/training-guideline-publications/gmm-report/en/; Oye et al, 2014, https://doi.org/10.1126/science.1254287

protected for the sake of human health and wellbeing, but also in their own right. What this means in practice, and how it is, and can be enshrined in the law, is not always clear. While there is large body of work on the rights of primates and other mammals,[192] the status of insects, fish and plants, is less clear. Does an individual mosquito have rights? What about Anopheles gambiae? Does nature have rights? Some countries have started to give personhood status to rivers; are there other parts of nature that should have rights in ways analogous to humans? How would these rights be enforced? How can we ensure that the interests of all species are considered in regulation and governance decisions?

There is a clear need for collective, democratically legitimate ways to decide what gene drives should be used for, on what species and for what purposes. At the same time, the fact that gene drives are relatively easy to make also presents a dilemma in the context of democratising science: If people decide to make use of gene drives for purposes they deem important, should (scientific or political) elites tell them not to do this? According to what criteria? Should we treat gene drives in analogy to weapons and limit access? How can such access be policed? Should mandatory approval or certification processes for newly created gene drives be in place, and should these be located at institutional, national, supranational, or international levels?

[192] E.g. Bryant, 2007; Tague, 2020; DeGrazia, 1997

7 RECOMMENDATIONS

On the basis of the manifold aspects and potential implications of genome editing in humans, animals and plants, including a particular attention to gene drives, outlined and ethically analysed in the preceding chapters,

and noting that the recommendations presented here should not be seen as an endorsement of specific technologies, applications, or application areas,

the EGE recommends to:

7.1 On overarching matters and concerns

Foster broad and inclusive societal deliberation on genome editing in all fields of application and with a global scope

In its 2016 statement[193] the EGE called for an inclusive societal debate on new genome editing technologies which it deems a pre-condition to permitting the use of these technologies. It recommends that genome editing should not be applied without a general agreement resulting from informed global dialogue, constantly striving for global consensus. Public debate should address how genome editing is perceived and assessed by citizens, which opinions, hopes and fears they hold, across fields of application, and whether germline genome editing is seen as necessary and/or acceptable, or would be so under what conditions. Fora for debate should be organised on local and European levels that are integrated in international dialogue, acquiring global scope.

In this context, the EGE proposes an increase of resources to develop and employ innovative formats for public engagement (including, but not limited to, education) and deliberation (e.g. citizens' assemblies) on ethical questions related to genome editing. Such deliberation should be based on democratic principles, be open to everyone, involve a wide variety of stakeholders and forms of expertise and be inclusive, interdisciplinary and pluralistic.

[193] EGE, 2016, *Statement on Gene Editing*, https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_statement.pdf

Avoid narrow conceptualisations to frame debates about the ethics and governance of genome editing

Whereas debates about genome editing often focus on the question of 'how safe is safe enough', the EGE draws attention to the importance of providing nuance to this framing. Resisting this narrow framing, it is necessary to extend the scope of analysis and debate to underlying concepts and approaches, with regard to, notably, humanness, human diversity and biodiversity, naturalness and the value of living beings.

The 'safe enough' narrative limits reflections on ethics and governance to considerations about safety; it purports that it is sufficient for a given level of safety to be reached in order for a technology to be rolled out unhindered, thereby eschewing ethically important questions such as whether genome editing is in fact necessary, acceptable, and under what conditions. Notably, those who are using the technology must ensure that they are monitoring for unpredicted and unintended events, and act upon them accordingly and without delay. This also extends to questions of coordination, inequalities and power relations. In fact, 'safety' or 'trustworthiness' do not pertain solely to technologies but also to institutions and forms of governance in societies – including matters of oversight as well as of democracy and rule of law.

The EGE points to the need to use common conceptual categories with caution and regularly analyse them with regard to their aptness. Traditional dichotomies and divisions, such as those between somatic and germline genome editing, between therapy, prevention and enhancement, or between basic, translational and clinical research, can offer useful operational distinctions in certain cases, but caution is needed where they constitute artificial, meaningless or misleading boundaries and especially where such categories are imbued with ethical or legal value.

Develop international guidelines and strengthen national, regional and global governance tools

The EGE recommends that the European Commission, together with appropriate international bodies who are also already working in this area (notably WHO, FAO, ISO), develop standards and guidelines for the ethical and safe use of genome editing across all areas of application.

The EGE also recommends to establish regulatory oversight for 'do-it-yourself' (DIY) genome editing tools. The relative ease and simplicity of applying new genome editing tools in humans, animals and plants

prompted the development and commercial distribution of DIY genome editing kits, accessible for purchase to anyone. The EGE is of the opinion that their application requires regulatory oversight, which in case of humans may be based on the gene therapy regulatory framework. For the application of genome editing tools in other organisms, the EGE proposes to establish regulatory structures that assesses risk of application for the organism and the environment and certifies their safety. The European Commission is advised to develop mechanisms to avoid or mitigate harm through unregulated availability of DIY kits on the internet, for example, by implementing strong liability rules.

Further recommendations on governance follow in the sections below, applying to genome editing in humans, animals and plants and to gene drives respectively.

7.2 On genome editing in humans

Engage in global governance initiatives and create a platform for information sharing and inclusive debate on germline genome editing

The EGE asks the European Commission to engage in a global mechanism to guarantee that heritable human genome editing is not prematurely clinically applied and is not applied for purposes other than against serious diseases that cannot be prevented or treated otherwise. On this basis, the EGE calls for the creation of a European Platform to facilitate exchange of information and a broad and open public debate on the ethical and social implications of germline genome editing in human beings on the basis of sound and evidence-based information. The functioning of the platform should, importantly, also integrate international dialogue and cooperation beyond Europe, for example, with the Global Observatory for Genome Editing, in order to acquire global scope and contribute to processes towards global consensus.

In this debate, awareness should be raised about the implications of widely used terminologies and distinctions, such as those between somatic and germline editing or between prevention, therapy and enhancement, about the need to examine them and to use them with caution regarding their ethical and legal normativity. This responds to the need for values to shape technology and helps to ensure that, in case heritable genome editing will be advanced and applied in countries under certain circumstances, this is

preceded by careful consideration of the conceptualisation, acceptability and desirability of the technology.

The proposed platform can also aim at the participatory development of a governance framework that determines, for example, who decides on cases, on what premises decisions are based, and what oversight structures are adequate. Its efforts and actions should be aligned with the work of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The EGE recommends that the European Commission collaborates with the WHO and, where appropriate, with the WMA to facilitate the universal adoption of standards on the ethical use of genome editing in human beings.

Establish a public registry for research on germline genome editing

Transparency and evidence-based information is of utmost importance to foster an inclusive societal debate. To support an informed debate, the EGE recommends to establish a European and/or global registry for germline genome editing (that could also be part of the proposed European Platform). It should cooperate with the global registry for human genome editing established by the WHO. The registry should be publicly accessible to ensure transparency for monitoring scientific progress and ethical soundness. Ethical approval and legal compliance must be a precondition for any registry entry.

Project registration is already compulsory for all research on germline genome editing funded by the EU and should become mandatory for all research.

Protect social justice, diversity and equality

Given the potential of genome editing techniques to be used for interventions that are not related to preventing or treating diseases but primarily serve enhancement purposes, their potential for fostering social inequality and undermining diversity should be considered. The EGE recommends to proactively safeguard against enhancement or de-enhancement of traits and to ensure that investments in research on germline genome editing have the purpose of protecting health. This also serves protecting human dignity, identity, diversity, equality, social justice and solidarity. In this context, guidelines should be developed that allow research ethics committees to distinguish between technologies and applications of genome editing that are to be considered as preventive,

diagnostic or therapeutic, and those that are to be considered as 'human enhancement', if such distinctions are to be used.

Furthermore, somatic genome editing has the potential to alleviate suffering from diseases that could not be treated effectively before. The EGE recommends that access to clinical studies and, once approved, to clinical application in healthcare is granted according to the principle of social justice and without discrimination.

Ensure adequate competencies in expert bodies

Genome editing technologies are evolving quickly and expertise to assess research and application has to keep pace with new developments. It is important to widen the basis of expertise and broaden what counts as relevant knowledge at the level of expert committees, fora and other bodies established to examine and set guidelines and standards for research and application of genome editing technologies. In light of the global variety of views on the essence of human nature, it is important to organise ethics oversight of international research collaboration and prevent ethics dumping.

Such adequacy of expertise is crucial also for ethics committees charged with approving and supervising clinical trials involving genome editing. The EGE suggests that guidelines for safety assessments and risk/benefit determinations of clinical trials are developed and training modules are provided for research ethics committees and other involved bodies to ensure high-standing and consistent application of ethical standards.

If national legislation of Member States allows research involving human embryos this suggestion also applies to this kind of research. Different Member States have different laws on embryo research. The principle of subsidiarity should continue to be respected.

7.3 On genome editing in animals

Strengthen oversight of genome editing in animals for scientific experiments according to, and beyond, the 3Rs

The EGE calls for a careful monitoring of the impact of genome editing techniques on the implementation of the 3Rs, including the balance between Replacement, Reduction and Refinement. To this end, (1) the EGE recommends reinforcing reporting requirements with respect to scientific

experiments using genome edited animals, including documenting their purposes; (2) the EGE urges research ethics committees and bodies in charge of project evaluation to carefully evaluate the costs/benefits of genome editing experimentation taking the 3Rs framework into account; (3) the EGE recommends that researchers be required to ensure transparency, sharing of data and tissues, and the publication of negative results in order to minimise uncoordinated duplication of experiments.

The EGE also suggests to consider a further R in relation with research funding, Recourse to alternative strategies, as indicated below for non-human primates.

Apply strict standards to experimentation with non-human primates and invest in the development of alternatives

Where the advances of genetic engineering techniques provide new opportunities for the development of primate genetic models, the EGE recalls the specific status accorded to non-human primates (NHPs) in the EU legal framework on animal experimentation and supports the view that humans bear strong moral obligations towards NHPs that move beyond the standard 3Rs framework and standard ethics of animal experimentation. It considers that experimentation involving NHPs is morally acceptable only if (1) serious human suffering can be prevented by carrying out scientific research on primates, that can in no other way be alleviated, and (2) the way of dealing with NHPs in these processes accommodates the wealth of scientific findings on their physical, mental and emotional lives and the modalities of their wellbeing and suffering.

In the context of genome editing experiments on NHPs, the EGE recommends the introduction of an additional 'R' to the 3Rs framework for Recourse to alternative strategies. This principle would go beyond refinement and would require a channelling of research resources into the search for alternatives to experiments and genetic engineering with harmful phenotype expressions. This could for instance take the form of funding bodies requiring researchers conducting experiments on NHPs to allocate part of the research budget to finding alternative methods, for example, through a requirement in EU-funded projects of an integrated work package or clearly defined activities to develop alternative methods.

Because of the evolutionary closeness to humans, intentions to study humanisation in NHPs by genome editing are likely. The EGE proposes a humanisation assessment when genome editing is used to modify genes to model human phenotypes in order to anticipate possible outcomes and

refinement needs. Such projects ought to be registered in a public database under the responsibility of a public authority. In addition, criteria for constraints ought to be developed (see next recommendation).

Broadly discuss the humanisation of animals and implement appropriate limitations

The EGE calls for further reflection on the implications of, and moral obligations with regard to, genome editing experimentation on animals that results in humanisation, whereby animals may gain functions or characteristics usually attributed only to humans. Given the potential advances brought by genome editing technologies to this domain, in particular in the area of cognition and neuro-functioning, consideration should be given to constraints that should be imposed on such procedures. A scientific and public debate on such constraints and respective criteria would be desirable.

Regulate the banking and farming on animals carrying human organs for transplantation

In the case of developments towards banking and farming on animals carrying human organs for transplantation, the EGE recommends establishing a strict regulatory framework that fully takes into account safety, security and animal welfare.

Prevent unregulated use of genome editing tools

Given the relative ease of use of new genome editing technologies, and in order to prevent an unregulated use outside the regulated professional context, the EGE considers that potential impact on (bio-)diversity by generating new strains should be firmly regulated.

Strengthen ethical oversight of practices involving reductions of animals' natural abilities

Given the possibility to significantly affect natural abilities of animals through genome editing (sometimes designated as 'de-animalisation') and considering that animals with their natural characteristics have an intrinsic value (and not merely an instrumental one), the EGE recommends that, even outside the research context, the purpose of such reduction be explicit, transparent and balanced and subject to ethics oversight in line with the above recommendations.

Ensure the wellbeing of genome edited livestock animals

In a number of instances, genome editing of animals is used to modify or insert traits for commercial purposes. The EGE expects the EU and its Member States to ensure that the health and wellbeing of the concerned animals is assured during all stages of the procedures and of the animals' life.

Reconsider ethically contested industrial farming practices

The debate on genome editing also raises general questions around ethically contested industrial farming practices. The EGE considers wider reflection around sustainable and ethical food production models necessary.

7.4 On genome editing in plants

Carefully assess the potentials and risks of genome edited plants for agriculture

The EGE recognises that the introduction of new genome edited plants into the agricultural environment may be beneficial in providing products for an increasing population and in facing the impact of climate change. Their introduction could have both positive or negative effects on product availability (notably food), human and animal health, socio-economic conditions, the agricultural environment and the natural environment and care must be taken to minimise harm and maximise benefit.

Develop an (eco)systems approach for evaluating the costs and benefits of genome edited crops

The EGE recommends a systems approach to the evaluation of costs and benefits (including the impact of continuing to use current agricultural practice) in any potential future use of genome edited crops. Such a broadened evaluation could take into account wider impacts on ecosystems and agricultural and natural biodiversity, land use, economic impact and food security. The EGE recommends that regulation should be proportional to the risk – light touch regulation should be used where the modification achieved by genome editing is through techniques such as gene silencing or where the change in the plant could have been achieved naturally or where the editing involves the introduction of genetic material from sexually compatible plants. Where the modification involves genes from non-sexually compatible organisms or where multiple changes in the genetic material

have occurred, there should be a detailed evaluation of the changes including a requirement to test the new variety in the field under different conditions.

Develop mechanisms to ensure corporate responsibility

Companies introducing new varieties, regardless of method or provenance should be required to identify the impact of their use on both agricultural and natural biodiversity and the environment.

Investigate mechanisms for traceability and labelling of genome edited crops

It will be difficult to impose a requirement for ensuring traceability and labelling requirements where exporting countries impose no requirements on new varieties or the use of edited varieties as the starting point for newer varieties. The EGE recommends that traceability and labelling should only be required where the modification could not have occurred naturally through mutation or natural recombination with sexually compatible plants. Where multiple genes or those from non-related organisms are inserted, tests could identify such plants, hence traceability and therefore labelling is possible. The Commission should investigate the use of patent registers as a method of identifying genome edited plants. It is recognised that the use of current varieties of plants as the starting material for newer varieties may make such an approach impossible.

Develop measures to support small actors

The EGE acknowledges that any additional risk assessment requirements would prove costly and impose a high regulatory burden which may disproportionately impact small companies and research centres, preventing them from commercialising products or utilising patented traits from other organisations. Consideration could therefore be given to measures to support smaller actors in steering clear of or in engaging with these novel technologies, such as mechanisms to support them in undertaking risk assessments to enter the market.

Pay more attention to public debates about genome edited agricultural products

The EGE acknowledges the prevalence of public concern in relation to genetically modified organisms including the lack of public dialogue and informed debate, which accompanied the introduction of GMO products, and

calls for more attention to public dialogue on the question of genome edited plants. The EGE cannot endorse a model which assumes that it is the lack of information alone which shapes the public debate.

7.5 On gene drives

Acknowledge epistemic and other uncertainties

There are many aspects about the systemic effects of gene drives that are not yet known. Ecosystems, as complex systems, have emergent properties that cannot be comprehensively simulated. These unknowns should be acknowledged at the outset of processes of deliberation and regulation, and be openly discussed. Because of these uncertainties, gene drives should not be promoted as a panacea for public health and other problems. Before gene drives are considered as a solution, other measures should have been exhausted. Moreover, gene drives should only be used when the goals and underpinning values have been deliberated and democratically decided upon.

Use gene drives in ways that are based on shared values

The EGE urges all actors to make explicit, and discuss openly, the values underpinning plans to use gene drives, and the purposes for which they are used, proactively trying to include a diverse and broad range of perspectives. Equity and social justice considerations are of particular importance in this context.

Regulate, monitor after release and have mitigation plans in place

The EGE recommends, throughout the process of using organisms modified by gene drives, to monitor their release into the environment on the basis of a mitigation plan for risks and harms. Eco-technologies – such as, but not limited to, gene drives – should also be subject to a consolidated registry and to a coherent regulatory framework of governance as described above.

Retain stock of original organisms

The EGE recommends, because of the uncertainties regarding the traceability and reversibility of gene drives, to retain stock of original, unmodified organisms.

REFERENCES

Alphey, L., 2016, *Can CRISPR-Cas9 gene drives curb malaria?* Nature Biotechnology, 34, 149-150, https://doi.org/10.1038/nbt.3473

Anzalone, A.V., Randolph, P.B., Davis, J.R. et al, 2019, *Search-and-replace genome editing without double-strand breaks or donor DNA*, Nature 576, 149-157, https://doi.org/10.1038/s41586-019-1711-4

Araki M. & Ishii, T., 2014, *International regulatory landscape and integration of corrective genome editing into in vitro fertilization*, Reproductive Biology and Endocrinology 12(1), 108, https://doi.org/10.1186/1477-7827-12-108

Bach, F. & Fineberg, H., 1998, *Call for moratorium on xenotransplants*, Nature, 391, 326, https://doi.org/10.1038/34766

Bailey, J., 2019, *Genetic Modification of Animals: Scientific and Ethical Issues, in: Animal Experimentation: Working Towards a Paradigm Change*, Brill, https://doi.org/10.1163/9789004391192_020

Benedict, M., D'Abbs, P., Dobson, S., Gottlieb, M., Harrington, L., Higgs, S., James, A., James, S., Knols, B., Lavery, J., O'Neill, S., Scott, T., Takken, W. & Toureet, Y., 2008, *Guidance for Contained Field Trials of Vector Mosquitoes Engineered to Contain a Gene Drive System: Recommendations of a Scientific Working Group*, Vector-borne and Zoonotic Diseases, 8, 2, https://doi.org/10.1089/vbz.2007.0273

Boers, S.N. & Bredenoord, A.L., 2018, *Consent for governance in the ethical use of organoids*, Nature Cell Biology, vol. 20, no. 6, https://doi.org/10.1038/s41556-018-0112-5

Bryant, T.L., 2007, *Sacrificing the Sacrifice of Animals: Legal Personhood for Animals, the Status of Animals as Property, and the Presumed Primacy of Humans*, Rutgers Law Journal, 39, 247.

Bredenoord, A.L., Clevers, H., Knoblich, J.A., 2017, *Human tissues in a dish: The research and ethical implications of organoid technology*, Science, Vol. 355, Issue 6322, https://doi.org/10.1126/science.aaf9414

Burnier, M., 2018, *Hypertension Guidelines*, European Heart Journal, Volume 39, Issue 11, pp. 908–910, https://doi.org/10.1093/eurheartj/ehy063

Charter of the CGIAR System Organization, 2016, https://cgspace.cgiar.org/bitstream/handle/10947/4370/Charter%20CGIAR%20Organization.pdf?sequence=8

Children of a Lesser God, 1986, Haines, R. (dir), Paramount Pictures; based on a play of the same name by Medoff, M., 1979.

Clevers, H., 2016, *Modeling development and disease with organoids*, Cell, 165, 1586–1597, https://doi.org/10.1016/j.cell.2016.05.082

Cleves, P.A., Strader, M.E., Bay, L.K., Pringle, J.R., Matz, M.V., 2018, *CRISPR/CasX-mediated genome editing in a reef-building coral*, PNAS, 115(20), 5235-5240, https://doi.org/10.1073/pnas.1722151115.

Commission Directive (EU) 2018/350 of 8 March 2018 amending Directive 2001/18/EC of the European Parliament and of the Council as regards the environmental risk assessment of genetically modified organisms, http://data.europa.eu/eli/dir/2018/350/oj

Communication from the Commission on the precautionary principle, COM (2000) 1, https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A52000DC0001

Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: Action Plan to enhance preparedness against chemical, biological, radiological and nuclear security risks (COM/2017/0610), https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2017:0610:FIN

Conseil d'État, *Organismes obtenus par mutagenèse*, 7 février 2020, https://www.conseil-etat.fr/ressources/decisions-contentieuses/dernieres-decisions-importantes/conseil-d-etat-7-fevrier-2020-organismes-obtenus-par-mutagenese

Council Directive 98/58/EC of 20 July 1998 concerning the protection of animals kept for farming purposes, http://data.europa.eu/eli/dir/1998/58/oj

Council of Europe, Committee on Bioethics (DH-BIO), 2019, *Guide to Public Debate on Human Rights and Biomedicine*, https://www.coe.int/en/web/bioethics/guide-on-public-debate

Council of Europe, 1997/1999, *The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine ("Oviedo Convention")*, https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98

Council of Europe, 1976, *European Convention for the Protection of Animals kept for Farming Purposes*, https://rm.coe.int/1680076da1

Court of Justice of the European Union, Case C-528/16, 25 July 2018, http://curia.europa.eu/juris/documents.jsf?num=C-528/16

Court of Justice of the European Union, Press Release No. 111/18, Judgement in Case C-528/16, 25 July 2018, https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf

Cwik, B., 2019, *Moving beyond 'therapy' and 'enhancement' in the ethics of genome editing*, Cambridge Quarterly of Healthcare Ethics, 28, 4, pp. 695-707, https://doi.org/10.1017/S0963180119000641

Daley, J., 2019, *Gene Therapy Arrives*, Nature 576, S12-S13, https://doi.org/10.1038/d41586-019-03716-9

Danish Council on Ethics, 2016, *Statement on genetic modification of future humans: In response to advances in the CRISPR technology*, https://www.etiskraad.dk/~/media/Etisk-Raad/en/Publications/Statement-on-genetic-modification-of-future-humans-2016.pdf

de Graeff, N., Jongsma, K.R., Johnston, J., Hartley, S., Bredenoord, A.L., 2019, *The ethics of genome editing in non-human animals: a systematic review of reasons reported in the academic literature*, Philosophical Transactions of the Royal Society Biological Sciences, 374, 1772, 20180106, https://doi.org/10.1098/rstb.2018.0106

DeGrazia, D., 1997, *Great apes, dolphins, and the concept of personhood*, The Southern Journal of Philosophy, 35(3), 301-320.

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes,

http://data.europa.eu/eli/dir/2010/63/oj, http://data.europa.eu/eli/dir/2010/63/2019-06-26

Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, http://data.europa.eu/eli/dir/2009/41/oj

Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, http://data.europa.eu/eli/dir/2001/18/2019-07-26

Dor, F.J., Tseng, Y.K., Cheng, J., Moran, K., Sanderson, T.M, Lancos, C.J., Shimizu, A., Yamada, K., Awwad, M., Sachs, D.H., Hawley, R.J, Schuurman, H.J., Cooper, D., 2004, *Alpha1,3-Galactosyltransferase gene-knockout miniature swine produce natural cytotoxic anti-Gal antibodies*, Transplantation, 78(1), 15-20, https://doi.org/10.1097/01.TP.0000130487.68051.EB

Dyson, F., 2007, *Our Biotech Future*, The New York Review, https://www.nybooks.com/articles/2007/07/19/our-biotech-future/

Does greater species diversity lead to greater stability in ecosystems? 2021, Science in Dispute, https://www.encyclopedia.com/science/science-magazines/does-greater-species-diversity-lead-greater-stability-ecosystems

Duignan, B., *Speciesism*, Encyclopædia Britannica, https://www.britannica.com/topic/speciesism

ECDC, 2017, *Rapid Risk Assessment: Risk related to the use of 'do-it-yourself' CRISPR-associated gene engineering kit contaminated with pathogenic bacteria*, https://www.ecdc.europa.eu/sites/default/files/documents/2-May-2017-RRA_CRISPR-kit-w-pathogenic-bacteria_2.pdf

EFSA, 2020, *Scientific opinion on site directed nuclease type 1 and 2 and oligonucleotide directed mutagenesis*, https://www.efsa.europa.eu/en/efsajournal/pub/6299

EFSA, 2020, *Adequacy and sufficiency evaluation of existing EFSAguidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives*, https://www.efsa.europa.eu/en/efsajournal/pub/6297

EFSA, 2012, *Scientific opinion on the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function*, https://www.efsa.europa.eu/it/efsajournal/pub/2943

EGE, 2016, *Statement on Gene Editing*, https://ec.europa.eu/info/publications/ege-statements_en

EGE, 2014, Opinion n°28, *Ethics of Security and Surveillance Technologies*, https://op.europa.eu/s/oJ3l

EGE, 2008, Opinion n°24, Ethics of modern developments in agricultural technologies, https://publications.europa.eu/en/publication-detail/-/publication/9369a035-5a5e-45da-8e37-09717ed806d5/language-en/format-PDF/source-77404379

EGE, 2008, Opinion n°23, *Ethical aspects of animal cloning for food supply*, https://op.europa.eu/en/publication-detail/-/publication/37ab868f-f414-42e7-b448-761879949403/language-en/format-PDF/source-77404396

EPO, *Datasheet for the Opinion of 14 May 2020*, https://www.epo.org/law-practice/case-law-appeals/pdf/g190003ex1.pdf

EPO, *Press Communiqué of 14 May 2020 concerning opinion G 3/19 of the Enlarged Board of Appeal*, https://www.epo.org/law-practice/case-law-appeals/communications/2020/20200514.html

Ernst, M.P.T., Broeders, M., Herrero-Hernandez, P., Oussoren, E., van der Ploeg, A.T., Pijnappel, P.W.W.M., 2020, *Ready for Repair? Gene Editing Enters the Clinic for the Treatment of Human Disease*, Molecular Therapy - Methods & Clinical Development, 18, 532-557, https://doi.org/10.1016/j.omtm.2020.06.022

European Network of GMO Laboratories, 2019, *Detection of food and feed plant products obtained by new mutagenesis techniques*, https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf

Eurostat, *Farmers and the agricultural labour force*, 2020, https://ec.europa.eu/eurostat/statistics-explained/index.php/Farmers_and_the_agricultural_labour_force_-_statistics

Esvelt, K.M., Gemmell, N.J., 2017, *Conservation demands safe gene drive*, PLoS Biol 15(11), https://doi.org/10.1371/journal.pbio.2003850

Esvelt, K.M., Smidler, A.L., Catteruccia, F., Church, G.M., 2014, *Emerging Technology: Concerning RNA-guided gene drives for the alteration of wild populations*, eLife, 3, https://doi.org/10.7554/eLife.03401

Fagot-Largeault, A., 1991, *Respect du patrimoine génétique et respect de la personne*, Esprit, 171, 5, 40-53, http://www.jstor.org/stable/24274649

FDA, *Information About Self-Administration of Gene Therapy*, 2017, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/information-about-self-administration-gene-therapy

Fischer, F. & Forester, J. (eds), 1993, *The argumentative turn in policy analysis and planning*, Duke University Press.

Friedrichs, S., Takasu, Y., Kearns, P., Dagallier, B., Oshima, R., Schofield, J. & Moreddu, C., 2019, *Meeting report of the OECD conference on "Genome Editing: Applications in Agriculture—Implications for Health, Environment and Regulation"*, Transgenic Research, 28, 419–463, https://doi.org/10.1007/s11248-019-00154-1

Gentechnikgesetz in der Fassung der Bekanntmachung vom 16. Dezember 1993 (BGBl. I S. 2066), das zuletzt durch Artikel 95 der Verordnung vom 19. Juni 2020 (BGBl. I S. 1328) geändert worden ist (German federal genome editing law), https://www.gesetze-im-internet.de/gentg/BJNR110800990.html

German Ethics Council, 2019, *Intervening in the Human Germline*, https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/englisch/opinion-intervening-in-the-human-germline-summary.pdf

Greely, H.T., 2019, *CRISPR'd babies: human germline genome editing in the 'He Jiankui affair',* Journal of Law and the Biosciences, 6(1), 111–183, https://doi.org/10.1093/jlb/lsz010

Green, M.J. & Botkin, J.R., 2003, *Genetic Exceptionalism in Medicine: Clarifying the Differences between Genetic and Nongenetic Tests*, Annals of Internal Medicine, 138, 571-575, https://doi.org/10.7326/0003-4819-138-7-200304010-00013

Greenfield, A., 2017, *Editing mammalian genomes: ethical considerations*, Mammalian Genome, 28(7-8), 388-393, https://doi.org/10.1007/s00335-017-9702-y

Gruen, L., 2014, *Entangled Empathy: An Alternative Ethic for Our Relationships with Animals*, Lantern Publishing & Media.

Grunwald, H.A., Gantz, V.M., Poplawski, G., Xu, X.R.S., Bier, E., Cooper, K.L., 2019, *Super-Mendelian inheritance mediated by CRISPR-Cas9 in the female mouse germline*, Nature, 566, 105–109, https://doi.org/10.1038/s41586-019-0875-2

Gutman Argemí, C., 2019, *Renowned philosopher Martha Nussbaum addresses animal ethics*, The Brown Daily Herald, https://www.browndailyherald.com/2019/04/10/renowned-philosopher-martha-nussbaum-addresses-animal-ethics/

Harris, J., 2010, *Enhancing Evolution: The Ethical Case for Making Better People, Princeton University Press*, https://press.princeton.edu/books/paperback/9780691148168/enhancing-evolution

Heller, C., 2013, *Food, Farms, and Solidarity: French Farmers Challenge Industrial Agriculture and Genetically Modified Crops*, Duke University Press, https://doi.org/10.1007/s10460-015-9635-6

Heo, Y.T., Quan, X., Xu, Y.N., Baek, S., Choi, H., Kim, N.H. & Kim, J., 2015, *CRISPR/Cas9 Nuclease-Mediated Gene Knock-In in Bovine-Induced Pluripotent Cells*, Stem Cells and Development 24(3), 393-402, https://doi.org/10.1089/scd.2014.0278

Herrmann, K. & Jayne, K. (eds), 2019, *Animal Experimentation: Working Towards a Paradigm Change*, Brill, https://doi.org/10.1163/9789004391192

High Level Group of Scientific Advisors, 2017, *New Techniques in Agricultural Biotechnology*, https://doi.org/doi:10.2777/17902

Holtman, L. & Gersbach, C.A., 2018, *Editing the Epigenome: Reshaping the Genomic Landscape*, Annual Review for Genomics and Human Genetics 19, 43-7, https://doi.org/10.1146/annurev-genom-083117-021632

Hurlbut, J. B., Jasanoff, S., Saha, K., Ahmed, A., Appiah, A., Bartholet, E., Baylis, F., Bennett, G., Church, G., Cohen, I. G., Daley, G., Finneran, K., Hurlbut, W., Jaenisch, R., Lwoff, L., Kimes, J. P., Mills, P., Moses, J., Park, B. S., Parens, E., Salzman, R., Saxena, A., Simmet, H., Simoncelli, T., Snead, O.C., Rajan, K.S., Truog, R.D., Williams, P., Woopen, C., 2018, *Building Capacity for a Global Genome Editing Observatory: Conceptual Challenges*, Trends in biotechnology, 36(7), 639–641, https://doi.org/10.1016/j.tibtech.2018.04.009

International Commission on the Clinical Use of Human Germline Genome Editing, 2020, *Release of heritable human genome editing*, https://www.nationalacademies.org/our-work/international-commission-on-the-clinical-use-of-human-germline-genome-editing#sectionPublications

Isasi, R., Kleiderman, E. & Knoppers, B.M., 2016, *Editing policy to fit the genome?* Science (80), 351, 6271, https://doi.org/10.1126/science.aad6778

Italian Committee for Bioethics, 2017, *Ethical Issues in gene-editing using CRISPR/CasX*, http://bioetica.governo.it/en/opinions/opinions-responses/ethical-issues-in-gene-editing-using-crisprcas9/

Kang, X., He, W., Huang, Y., Yu, Q., Chen, Y., Gao, X., Sun, X. & Fan, Y., 2016, *Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing*, Journal of Assisted Reproduction and Genetics 33(5), 581-588, https://doi.org/10.1007/s10815-016-0710-8

Kang, Y., Zheng, B., Shen, B., Chen, Y., Wang, L., Wang, J., Niu, Y., Cui, Y., Zhou, J., Wang, H., Guo, X., Hu, B., Zhou, Q., Sha, J., Ji, W. & Huang, X., 2015, *CRISPR/Cas9-mediated Dax1 knockout in the monkey recapitulates human AHC-HH*, Human Molecular Genetics 24(25), 7255-7264, https://doi.org/10.1093/hmg/ddv425

Keulartz, J. & van den Belt, H., 2016, *DIY-Bio – economic, epistemological and ethical implications and ambivalences*, Life Sciences, Society and Policy, 12, 7, https://doi.org/10.1186/s40504-016-0039-1

Kirksey, E., 2016, *Who is Afraid of CRISPR Art?* Somatoshpere, http://somatosphere.net/2016/03/who-is-afraid-of-crispr-art.html

Knoepfler, 2015, *Gmo Sapiens: The Life-Changing Science of Designer Babies*, WSPC.

Korsgaard, C., 2018, *Fellow Creatures: Our Obligations to the Other Animals*, Oxford University Press.

Kosicki, M., Tomberg, K., Bradley, A., 2018, *Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements*, Nature Biotechnology 36(8), 765, https://doi.org/10.1038/nbt.4192

Lai, L., Kolber-Simonds, D., Park, K.W., Cheong, H.T., Greenstein, J.L., Im, G.S., Samuel, M., Bonk, A., Rieke, A., Day, B.N., Murphy, C.N., Carter, D.B., Hawley, R.J., Prather, R.S., 2002, *Production of α-1,3-Galactosyltransferase Knockout Pigs by Nuclear Transfer Cloning*, Science, 295, 5557, 1089-1092, https://doi.org/10.1126/science.1068228

Lakoff, G. & Johnson, M., 2008, *Metaphors we live by*, University of Chicago Press.

Ledford, H., 2015, *CRISPR, the disruptor*, Nature 522, 20–24, https://doi.org/10.1038/522020a

Li, F., Upadhyaya, N., Sperschneider, J., Matny, O., Nguyen-Phuc, H., Mago, R., Raley, C., Miller, M.E., Silverstein, K.A.T., Henningsen, E., Hirsch, C.D., Visser, B., Pretorius, Z.A., Steffenson, B., Schwessinger, B., Dodds, P.N., Figueroa, M., 2019, *Emergence of the Ug99 lineage of the wheat stem rust pathogen through somatic hybridization*, Nature Communications in press, https://doi.org/10.1038/s41467-019-12927-7

Li, H., Yang, Y., Hong, W. et al, 2020, *Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects*. Signal Transduction and Targeted Therapy 5, 1, https://doi.org/10.1038/s41392-019-0089-y

Liang, P., Xu, Y., Zhang, X., et al., 2015, *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, Protein & Cell 6(5), 363-372, https://doi.org/10.1007/s13238-015-0153-5

Liu, H., Chen, Y., Niu, Y., et al., 2014, *TALEN-Mediated Gene Mutagenesis in Rhesus and Cynomolgus Monkeys*, Cell Stem Cell 14(3), 323-328, https://doi.org/10.1016/j.stem.2014.01.018

Liu, Z., Zhou, X., Zhu, Y., Chen, Z.F., Yu, B., Wang, Y., Zhang, C.C., Nie, Y.H., Sang, X., Cai, Y.J., Zhang, Y.F., Zhang, C., Zhou, W.H., Sun, Q. & Qiu, Z., 2014, *Generation of a monkey with MECP2 mutations by TALEN-based gene targeting*, Neuroscience Bulletin 30(3), 381-386, https://doi.org/10.1007/s12264-014-1434-8

Long, C., McAnally, J.R., Shelton, J.M., Mireault, A.A., Bassel-Duby, R. & Olson, E.N., 2014, *Prevention of muscular dystrophy in mice by CRISPR/Cas9-mediated editing of germline DNA*, Science, 345(6201), 1184-1188, https://doi.org/10.1126/science.1254445

Louwaars, N., 2019, *Food Safety and Plant Breeding: why are there no problems in practice?* Chapter 5, in: Urazbaeva, A., Szajkowska, A., Wernaart, B., Tilkin Franssens, N. & Spirovska Vaskoska, R. (eds), *The functional Field of food law*, Wageningen Academic Press, European Institute of Food Law Series, 11, 89-101, https://doi.org/10.3920/978-90-8686-885-8_5

Ma, H., Marti-Gutierrez, N., Park S.W., et al., 2017, *Correction of a pathogenic gene mutation in human embryos*, Nature, 548(7668), 413-419, https://doi.org/10.1038/nature23305

Ma, X., Mau, M. & Sharbel, T.F., 2017, *Genome Editing for Global Food Security*, Trends in Biotechnology, 36, 2, 123-127, https://doi.org/10.1016/j.tibtech.2017.08.004

Maclaurin, J. & Sterelny, K., 2008, *What is Biodiversity?* Chicago, University of Chicago Press.

Macpherson, I., Roqué, M.V. & Segarra, I., 2019, *Ethical Challenges of Germline Genetic Enhancement*, Frontiers in Genetics, 10, https://doi.org/10.3389/fgene.2019.00767

May, R., 1973, *Stability and Complexity in Model Ecosystems*, Princeton University Press, Princeton.

McLeod, C. & Nerlich, B., 2017, *Synthetic biology, metaphors and responsibility*, Life sciences, society and policy, 13(1), 13, https://doi.org/10.1186/s40504-017-0061-y

Nagashima, H., Matsunari, H., 2016, *Growing human organs in pigs-A dream or reality?* Theriogenology, 86(1), 422-6, https://doi.org/10.1016/j.theriogenology.2016.04.056

National Academies of Sciences, Engineering, and Medicine, 2017, *Human Genome Editing: Science, Ethics, and Governance*, Washington, DC: The National Academies Press, https://doi.org/10.17226/24623

National Centre for the Replacement, Refinement and Reduction of Animals in Research, *The 3Rs*, https://nc3rs.org.uk/the-3rs

National Public Health Partnership, 2006, *The Language of Prevention*, http://www.health.vic.gov.au/archive/archive2014/nphp/publications/language_of_prevention.pdf

Neuhaus, C.P., 2017, *Ethical issues when modelling brain disorders in non-human primates*, Journal of Medical Ethics, 44, 323-327, https://doi.org/10.1136/medethics-2016-104088

Niu, D., Wei, H.J., Lin, L., George, H., Wang, T., Lee, I.H., Zhao, H.Y., Wang, Y., Kan, Y., Shrock, E., Lesha, E., Wang, G., Luo, Y., Qing, Y., Jiao, D., Zhao, H.,

Zhou, X., Wang, S., Wei, H., Güell, M., Church, G.M., Yang, L., 2017, *Inactivation of porcine endogenous retrovirus in pigs using CRISPR/CasX*, Science, https://doi.org/10.1126/science.aan4187

Niu, Y., Shen, B., Cui, Y., et al, 2014, *Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos*, Cell 156(4), 836-843, https://doi.org/10.1016/j.cell.2014.01.027

Nuffield Council on Bioethics, 2018, *Genome Editing and Human Reproduction: social and ethical issues*, https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction

Nuffield Council on Bioethics, 2016, *Genome Editing – An Ethical Review*, https://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf

Nussbaum, M., 2006a, *Frontiers of justice: Disability, nationality, species membership*, The Belknap Press; 2006b, *The moral status of animals*, The Chronicle Review, 52.

O'Keefe, M., Perrault, S., Halpern, J., Ikemoto, L., Yarborough, M. & UC North Bioethics Collaboratory for Life & Health Sciences, 2015, *"Editing" genes: A case study about how language matters in bioethics*, The American Journal of Bioethics, 15(12), 3-10, https://doi.org/10.1080/15265161.2015.1103804

Oye, K., Esvelt, K., Appleton, E., Catteruccia, F., Church, G., Kuiken, T., Lightfood, S.B.Y., McNamara, J., Smidler, A., Collins, J.P., 2014, *Regulating gene drives*, Science, 345, 6197, https://doi.org/10.1126/science.1254287

Patience, C., Takeuchi, Y. & Weiss, R., 1997, *Infection of human cells by endogenous retrovirus of pigs, Nature Medicine*, 3, 282-286, https://doi.org/10.1038/nm0397-282

Prainsack, B. & Spector, T.D., 2006, *Twins: A cloning experience*, Social Science & Medicine, 63, 10, 2739-2752, https://doi.org/10.1016/j.socscimed.2006.06.024

Preamble to the Constitution of WHO as adopted by the International Health Conference, 1946/1948 (Official Records of WHO, no. 2, p. 100)

Qasim, W., et al, 2017, *Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells*, Science Translational Medicine 9 (374), https://doi.org/10.1126/scitranslmed.aaj2013

Reardon, S., 2020, *Step aside CRISPR, RNA editing is taking off*, Nature 578, 24-27, https://10.1038/d41586-020-00272-5

Reardon, S., 2015, *New life for pig-to-human transplants*, Nature, 527, 152–154, https://doi.org/10.1038/527152a

Regalado, A., 2019, *Don't change your DNA at home, says America's first CRISPR law*, MIT Technology Review, https://www.technologyreview.com/2019/08/09/65433/dont-change-your-dna-at-home-says-americas-first-crispr-law

Regulation (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC, http://data.europa.eu/eli/reg/2003/1830/oj

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, http://data.europa.eu/eli/reg/2007/1394/2019-07-26

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, http://data.europa.eu/eli/reg/2014/536/2014-05-27

Report from the Commission to the European Parliament and the Council, 2019, *Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017*, https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1581689520921&uri=CELEX:52020DC0016; and the accompanying Staff Working Document, https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1581689520921&uri=CELEX:52020SC0015

Ruan, J., Xu, J., Chen-Tsai, R.Y. & Li, K., 2017, *Genome editing in livestock: Are we ready for a revolution in animal breeding industry?* Transgenic Research, 26(6), 715-726, https://doi.org/10.1007/s11248-017-0049-7

Sachs, D.H., & Galli, C., 2009, *Genetic manipulations in pig*, Current Opinion in Organ Transplantation, 14(2), 148–153, https://doi.org/10.1097/MOT.0b013e3283292549

Saha, K., Hurlbut, J.B., Jasanoff, S., Ahmed, A., Appiah, A., Bartholet, E., Baylis, F., Bennett, G., Church, G., Cohen, I.G., Daley, G., Finneran, K., Hurlbut, W., Jaenisch, R., Lwoff, L., Kimes, J.P., Mills, Moses, J., Park, B.S., Parens, E., Salzman, R., Saxena, A., Simmet, H., Simoncelli, T., Snead, O.C., Rajan, K.S., Truog, R.D., Williams, P., Woopen, C., 2018, *Building Capacity for a Global Genome Editing Observatory: Institutional Design*, Trends in Biotechnology, 36, 8, 741-743, https://doi.org/10.1016/j.tibtech.2018.04.008

Sandel, M.J., 2007, *The Case Against Perfection: Ethics in the Age of Genetic Engineering*, Harvard University Press.

Sarkar, S., 2010, *Diversity: A Philosophical Perspective*, Diversity 2, no. 1: 127-141, https://doi.org/10.3390/d2010127

Savulescu, J. & Kahane, G., 2017, *Understanding Procreative Beneficence*, The Oxford Handbook of Reproductive Ethics, https://10.1093/oxfordhb/9780199981878.013.26

Schroder, K., 2018, *CRISPR has already revolutionized genetics, Why not the obviousness standard too?* 87 University of Cincinnati Law Review 1191, https://scholarship.law.uc.edu/uclr/vol87/iss4/9

Schweitzer, A., 1987, *The Philosophy of Civilization*, Prometheus Books.

Seyfried, G., Pey, L. & Schmidt, M., 2014, *European do-it-yourself (DIY) biology: beyond the hope, hype, and horror,* Bioessays, 36(6), 548–51, https://doi.org/10.1002/bies.201300149

Shapiro, B., 2015, *Mammoth 2.0: will genome engineering resurrect extinct species?* Genome Biology 16, 228, https://doi.org/10.1186/s13059-015-0800-4

Singer, P., 1975, *Animal Liberation: A New Ethics for Our Treatment of Animals*, HarperCollins.

Singh, P., Schimenti, J.C., Bolcun-Filas, E., 2015, *A Mouse Geneticist's Practical Guide to CRISPR Applications*, Genetics, Volume 199, 1, 1–15, https://doi.org/10.1534/genetics.114.169771

Skarnes, W.C., 2015, *Is Mouse Embryonic Stem Cell Technology Obsolete?* Genome Biology, 16, 109, https://doi.org/10.1186/s13059-015-0673-6

Smalley, E., 2018, *FDA warns public of dangers of DIY gene therapy*, Nature Biotechnology 36, 119–120, https://doi.org/10.1038/nbt0218-119

Spanish Bioethics Committee, 2019, *Declaración del Comité de Bioética de España sobre la edición genómica en humanos*, http://assets.comitedebioetica.es/files/documentacion/es/CBE%20Declaracion%20sobre%20edicion%20genomica%20en%20humanos.pdf

Standing Committee on plants, animals, food and feed, 2015, Summary report, https://ec.europa.eu/food/sites/food/files/safety/docs/reg-com_toxic_20150623_sum.pdf

Steen, G.J., Reijnierse, W. G., & Burgers, C., 2014, *When do natural language metaphors influence reasoning? A follow-up study to Thibodeau and Boroditsky (2013)*. PloS One, 9(12), https://doi.org/10.1371/journal.pone.0113536

Strecker, J., Ladha, A., Gardner, Z., Schmid-Burgk, J.L., Makarova, K.S., Koonin, E.V., Zhang, F., 2019, *RNA-guided DNA insertion with CRISPR-associated transposases*, Science, 365, 6448, 48-53, https://doi.org/10.1126/science.aax9181

Suntsova, M.V. & Buzdin, A.A., 2020, *Differences between human and chimpanzee genomes and their implications in gene expression, protein functions and biochemical properties of the two species*, BMC Genomics 21, 535, https://doi.org/10.1186/s12864-020-06962-8

Tague, G.F., 2020, *An Ape Ethic and the Question of Personhood*, Lexington Books.

Taylor, P.W., 1981, *The Ethics of Respect for Nature*, Environmental Ethics 3/3: 197- 218, https://doi.org/10.5840/enviroethics19813321.

Taylor, P.W., 1986, *Respect for Nature*, Princeton University Press.

The Cartagena Protocol on Biosafety to the Convention on Biological Diversity, 2020, https://www.cbd.int/doc/legal/cartagena-protocol-en.pdf

The Convention on Biological Diversity, 1992 (1760 U.N.T.S. 69), https://www.cbd.int/convention/text/

The Netherlands Commission on Genetic Modification (COGEM), 2018, *CRISPR & Animals: Implications of Genome Editing for Policy and Society*, https://cogem.net/en/publication/crispr-animals-implications-of-genome-editing-for-policy-and-society/

The Rio Declaration on Environment and Development, 1992, The United Nations Conference on Environment and Development, https://www.cbd.int/doc/ref/rio-declaration.shtml

UK Home Office, 2016, *Statistics of Scientific Procedures on Living Animals: Great Britain 2015*, http://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2015

UNESCO, *Declaration on the Responsibilities of the Present Generations Towards Future Generations*, 1997, http://portal.unesco.org/en/ev.php-URL_ID=13178&URL_DO=DO_TOPIC&URL_SECTION=201.html

USA Federal Register, Vol. 82, No. 12, 19 January 2017, Proposed Rules, p. 7015, https://thefederalregister.org/82-FR/Issue-12

Van der Meer, P., Angenon, G., Bergmans, H., Buhk, H., Callebaut, S., Chamon, M., Eriksson, D., Gheysen, G., Harwood, W., Hundleby, P., Kearns, P., McLoughlin, T., Zimny, T., 2021, *The Status under EU Law of Organisms Developed through Novel Genomic Techniques*, European Journal of Risk Regulation, 1-20, https://doi.org/10.1017/err.2020.105

Waldron, J., 2017, *One Another's Equals: The Basis of Human Equality*, The Belknap Press of Harvard University.

Wang, D., Wang, K. & Cai, Y., 2020, *An overview of development in gene therapeutics in China*, Gene Therapy 27, 338–348, https://doi.org/10.1038/s41434-020-0163-7

Warner, E., 2017, *Goodbye Glybera! The World's First Gene Therapy will be Withdrawn*, Labiotech.eu, https://www.labiotech.eu/more-news/unique-glybera-marketing-withdrawn/

Wellcome Sanger Institute, *Animals in research*, https://www.sanger.ac.uk/about/who-we-are/research-policies/animals-in-research/

WHO, 2018, *Natural toxins in food*, https://www.who.int/news-room/fact-sheets/detail/natural-toxins-in-food

WHO, 2010, *Progress and prospects for the use of genetically modified mosquitoes to inhibit disease transmission*, https://www.who.int/tdr/publications/training-guideline-publications/gmm-report/en/

Wu, Y., Liang, D., Wang, Y., Bai, M., Tang, W., Bao, S., Yan, Z., Li, D. & Li, J., 2013, *Correction of a Genetic Disease in Mouse via Use of CRISPR-Cas9*, Cell Stem Cell, 13(6), 659-662, https://doi.org/10.1016/j.stem.2013.10.016

Yang, W., Tu, Z., Sun, Q. & Li, X.J., 2016, *CRISPR/CasX: Implications for Modeling and Therapy of Neurodegenerative Diseases, Frontiers in Molecular Neuroscience*, 9, 30, https://doi.org/10.3389/fnmol.2016.00030

Yoshimi, K., Kaneko, T., Voigt, B. & Mashimo, T., 2014, *Allele-specific genome editing and correction of disease-associated phenotypes in rats using the CRISPR–Cas platform*, Nature Communications 5(1), 4240, https://doi.org/10.1038/ncomms5240

Zaidi, S.S.-A., Vanderschuren, H., Qaim, M., Mahfouz, M.M., Kohli, A., Mansoor, S., Tester, M., 2019, *New plant breeding technologies for food security*, Science (80) 363:1390–1, https://doi.org/10.1126/science.aav6316

Zubașcu, F., 2021, *Horizon Europe to fund research on genome editing in agriculture*, https://sciencebusiness.net/framework-programmes/news/horizon-europe-fund-research-genome-editing-agriculture

THE MEMBERS OF THE EGE

Christiane Woopen

Chair of the EGE

Herman Nys

Vice-Chair of the EGE

Siobhán O'Sullivan

Vice-Chair of the EGE

Emmanuel Agius

Anne Cambon-Thomsen

Ana Sofia Carvalho

Eugenijus Gefenas

Julian Kinderlerer

Andreas Kurtz

Jonathan Montgomery

Laura Palazzani

Barbara Prainsack

Carlos Maria Romeo Casabona

Nils-Eric Sahlin

Marcel Jeroen Van den Hoven

ON THE DEVELOPMENT OF THE OPINION

The EGE develops its Opinions upon requests from the Commission, as stipulated in Commission Decision 2016/835. The request for advice on the ethics of genome editing was communicated to the EGE in a letter from Carlos Moedas, Commissioner for Research and Innovation, in 2018. The Commissioner expressed "tremendous need for your advice both on the bigger picture of this issue and on specific aspects of concern," including "the dividing lines which otherwise limit the ethical analysis: human and non-human; somatic and germline; research and therapeutic and enhancement purposes; agricultural, health, environmental and further areas; existing and future technologies and implications," and specific aspects such as "gene editing applied to animals as well as gene editing in the context of biodiversity and ecosystems."

The EGE collectively worked towards this Opinion and its recommendations, with Anne Cambon-Thomsen, Julian Kinderlerer, Barbara Prainsack and Christiane Woopen as rapporteurs for its core chapters. Detailed discussions took place in the EGE's regular meetings, directing the drafting of the rapporteurs.

At the same time, the EGE also responded to the pressing need for advice on the broader ethical and societal dimensions of the Covid-19 pandemic and issued a *Statement on European solidarity and the protection of fundamental rights in the COVID-19 pandemic* at the outset of the crisis (in April 2020), a *Joint Statement on scientific advice to European policy makers concerning the COVID-19 pandemic* (in June 2020) and a *Joint Opinion on improving pandemics preparedness and management* (in November 2020).

The development of the present Opinion involved several relevant services of the European Commission and a wide range of stakeholders and experts, many of whom presented their expertise and views to the EGE in dedicated hearings. A central part of this, pursuant to Commission Decision 2016/835, was also the Open Round Table, which took place on 16 October 2019, together with the International Dialogue on Bioethics and Ethics of Science and New Technologies (ID-BEST), which took place on 17 October 2019. These events emphasised awareness raising and the importance of structural public engagement on genome editing and on all its cognate ethical questions, with the manifold perspectives arising from them having informed the preparation of this Opinion.

The close and fruitful cooperation with the teams in the sister international organisations tasked with the ethics and governance of emerging technologies (notably: UNESCO, WHO, FAO, ILO, OHCHR, WTO, WIPO, UNEP, ICGEB as well as Council of Europe and OECD) is gratefully acknowledged, as is the crucial role in that regard of the UN Inter-Agency Committee on Bioethics, in which the European Commission is represented by Jim Dratwa.

Furthermore, all of the people who participated in the different phases of this process, be it physically or online or in writing, are most gratefully acknowledged. Notably: Lluis Montoliu (Centro Nacional de Biotecnologia), Kevin Esvelt (Massachusetts Institute of Technology), Mark Prescott and Romina Aron-Badin (Scientific Committee on Health, Environmental and Emerging Risks), Janusz Bujnicki (Group of Chief Scientific Advisors), John Harris (University of Manchester), Peter Dabrock (German Ethics Council), George Gaskell (London School of Economics), Pierre Jouannet (Université Paris Descartes), Kathy Niakan (Francis Crick Institute), Hervé Chneiweiss (WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing), J. Patrick Clarke (European Disability Forum), Ian Ragan (UK National Centre for the Replacement, Refinement and Reduction of Animals in Research), Tsutomu Sawai (Institute for the Advanced Study of Human Biology at KUIAS Kyoto University), Ana Granados (European Forum of Farm Animal Breeders, Farm Animal Breeding & Reproduction Technology Platform), Penny Hawkins (RSPCA Science and Policy Group, Eurogroup for Animals), Brian Wynne (European Network of Scientists for Social and Environmental Responsibility), Sheila Jasanoff (Harvard Kennedy School of Government), Max Schulman (MTK, Finnish Farmers' Union, Copa and Cogeca), Nina Holland (Corporate Europe Observatory), Joanna Dupont-Ingliss (EuropaBio), the members of the WHO expert advisory committee on developing global standards for governance and oversight of human genome editing, Susanna Louhimies (DG ENV), Diana Herold (DG SANTE), Chantal Bruetschy (DG SANTE), Sirkku Heinimaa (DG SANTE), Ilaria Ciabatti (DG SANTE), Johannes Klumpers (DG R&I), Jeremy Bray (DG R&I), Wolfgang Burtscher (DG R&I), Renzo Tomellini (DG R&I), Lisa Diependaele (DG R&I), Louiza Kalokairinou (DG R&I), Jean-Eric Paquet (DG R&I) and Commissioner Carlos Moedas.

THE EGE TEAM

Jim DRATWA
Head of the EGE Team

Barbara GIOVANELLI
Policy Officer

Marta JASINSKA
Policy Assistant

Joanna PARKIN
Policy Officer

Ann ARO
Administrative Assistant

Contact: ec-ethics-group@ec.europa.eu

With thanks to former members of the EGE team: Maija Locane, Florence Dose and Carolina Polito.

Getting in touch with the EU

IN PERSON

All over the European Union there are hundreds of Europe Direct information centres.
You can find the address of the centre nearest you at:
https://europa.eu/european-union/contact_en

ON THE PHONE OR BY EMAIL

Europe Direct is a service that answers your questions about the European Union.
You can contact this service:

– by freephone: **00 800 6 7 8 9 10 11** (certain operators may charge for these calls),

– at the following standard number: **+32 22999696**, or

– by email via: **https://europa.eu/european-union/contact_en**

Finding information about the EU

ONLINE

Information about the European Union in all the official languages of the EU is available on the Europa website at: **https://europa.eu/european-union/index_en**

EU PUBLICATIONS

You can download or order free and priced EU publications from:
https://op.europa.eu/en/publications. Multiple copies of free publications may be obtained by contacting Europe Direct or your local information centre (see **https://europa.eu/european-union/contact_en**).

EU LAW AND RELATED DOCUMENTS

For access to legal information from the EU, including all EU law since 1952 in all the official language versions, go to EUR-Lex at: **http://eur-lex.europa.eu**

OPEN DATA FROM THE EU

The EU Open Data Portal (**http://data.europa.eu/euodp/en**) provides access to datasets from the EU. Data can be downloaded and reused for free, for both commercial and non-commercial purposes.

The advent of new genome editing technologies such as CRISPR/CasX has opened new dimensions of what and how genetic interventions into our world are possible. In this Opinion, the European Group on Ethics in Science and New Technologies (EGE) addresses the profound ethical questions raised and revived by them.

The Opinion analyses various domains of application, from human health to animal experimentation, from livestock breeding to crop variety, and to gene drives. With its wide view across areas, the Opinion identifies underlying and overarching issues that deserve our concerted attention, among them, the different meanings that ought to be attributed to humanness, naturalness or diversity. It also formulates recommendations, including inclusive societal deliberation of global scope about genome editing, a call for the development of international standards for its ethical and safe use, warnings about narrow conceptualisations of the ethical issues at stake, the establishment of a platform for exchange and debate on heritable human genome editing, and more, also domain-specific, propositions.

Research and Innovation policy

Publications Office
of the European Union