The ethics of genome editing technologies in non-human animals: A systematic review of reasons reported in the academic literature

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Keywords: genome editing, CRISPR, animals, ethics, human health, environment

Proposed running head: The ethics of genome editing in animals

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Abstract

In recent years, new genome editing technologies have emerged that can edit the genome of non-human animals with progressively increasing efficiency. Despite ongoing academic debate about the ethical implications of these technologies, no comprehensive overview of this debate exists. To address this gap in the literature, we conducted a systematic review of the reasons for and against the development and use of genome editing technologies in animals reported in the academic literature. Most included articles were written by academics from the biomedical or animal sciences. The reported reasons related to seven themes: human health, efficiency, risks and uncertainty, animal welfare, animal dignity, environmental considerations and public acceptability. Our findings illuminate several key considerations about the academic debate, including the underrepresentation of animal interests, a lack of disciplinary diversity in the contributing academics, a scarcity of systematic comparisons of potential consequences of using these technologies, and a disjunction between the public and academic debate on this topic. As such, this article can be considered a call for a broad range of academics to get increasingly involved in the discussion about genome editing, to incorporate animal interests and systematic comparisons, and to further discuss the aims and methods of public involvement.

Media summary

Our systematic review of the academic literature on the timely and important topic of genome editing in animals reveals that the academic debate on this topic is predominantly shaped by scientists. It also shows that the academic literature has a strong focus on the consequences of (not) using these technologies and pays relatively little attention to animal interests and certain public concerns. It invites other academics to contribute to the debate, to engage in systematic comparisons of potential consequences, and to address increasing attention to animal interests and the aims and methods of involving citizens in this debate.

Introduction

In the last two decades, a host of genome editing technologies has emerged that can edit the genome with progressively increasing efficiency and ease of use. These technologies are based on the use of sequence-specific engineered nucleases, such as Zinc Finger Nucleases [1], meganucleases [2], and Transcription Activator-Like Effector Nucleases (TALENs) [3]. In more recent years, genome editing was revolutionized by the emergence of Clustered Regularly Interspaced Palindromic Repeat (CRISPR) and the CRISPR-associated protein Cas9 (CRISPR associated protein 9) [4]. In parallel, new applications of these genome editing technologies have emerged, such as gene drives, which allow the rapid and dominant spread of gene alterations within a population or even a species [5,6].

Overall, this new generation of genome editing technologies allows scientists to modify the genomes of non-human animals (from here on: 'animals') more precisely than classical transgenesis [7] with comparably fewer off-target effects [8]. Furthermore, engineered nucleases can introduce genetic changes without the use of foreign DNA [9]. These genome editing technologies have a broad range of possible applications in animals, including to increase livestock productivity and disease resistance [10], create new animal models to study human disease [11], protect native species by eradicating invasive species, decrease or even eliminate vector-borne diseases such as malaria, and perhaps even resurrect extinct species [5,12]. Comprehensibly, these technologies and their applications have sparked both excitement and apprehension, raising new questions on ethics and governance and generating significant debate in both academic and public spaces.

Despite this ongoing debate, to our knowledge no comprehensive overview of the arguments raised in the academic discourse on genome editing in animals exists. Such an overview is a valuable contribution to the academic literature, as it provides insights into patterns of argumentation in the expert debate and can help uncover arguments that go unmentioned or are insufficiently conceptualized. It is particularly salient to study the academic debate since academic experts can have a strong influence on related policy and governance decisions [13,14]. Moreover, insight into the academic debate is important for understanding whether it differs from the public debate and arguments. For technologies that have high societal impact, such as genome editing, it is important to bridge potential gaps between the public and academic discourse in the early phases of development.

In this article, we present such a comprehensive overview by reporting the reasons for and against the development and use of genome editing technologies in animals as these have been mentioned in the academic literature. Subsequently, we critically assess the academic debate and identify perspectives, issues and arguments that are underrepresented in the existing literature.

Methods

A systematic review of the reasons that have been given for and against the development and use of new-generation genome editing technologies in animals was conducted. This review was based on the method developed by Strech & Sofaer [15], which can be used to systematically identify reasons and arguments in favour of or against particular (normative or descriptive) positions or claims. This method does not assess the adequacy, quality or normative weight of the reported reasons [15], but enables a systematic collection of all the relevant literature in which an opinion, point of view, or position is put forward. Subsequently, it allows for an equally systematic extraction and synthesis of the reasons. It incorporates relevant items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [16] as well as thematic analysis typical of qualitative research [15].

Search strategy

A literature search of the PubMed, Web of Science, Scopus, CAB Abstracts and Philosopher's Index databases was conducted to find relevant articles. The choice for databases was discussed with experienced librarians; these five databases were selected as they cover a comprehensive area of biomedical, veterinary, and ethics research journals and articles. A search strategy that combined search terms for genome editing, animals (adapted from Hooijmans, Tillema, Leenaars & Ritskes-Hoitinga [17]), and ethics was used (Supplementary Table 1).

Article selection and inclusion criteria

Academic articles or book chapters written in English or Dutch, published in 2010 or later, were eligible for inclusion. Publications that did not contain a reason for or against the development or use of new-generation genome editing technologies in animals were excluded. Publications that specifically focused on older techniques (e.g. classical transgenesis) were also excluded.

Two researchers independently screened the titles and abstracts and, if applicable, the full texts of the articles. In case of disagreement about inclusion or exclusion, differences were discussed until consensus was reached. The reference lists of included articles were subsequently screened for additional relevant articles.

Data extraction and analysis

The full text of the selected articles was analysed using a data extraction document (Supplementary Table 2) that was designed prior to starting the data extraction to extract data in a systematic way. The contextual data of the included articles, including the discipline of the author(s) and the specific technologies and applications discussed, were also included. Subsequently, all the reasons for and against the development and use of new-generation genome editing technologies in animals were extracted. The reasons that were mentioned in the included articles ('reason mentions') were subsequently compared. If different articles mentioned the same reason these were bundled under the same 'narrow reason'. Next, a list of narrow reasons was generated: for each narrow reason, we noted which article included that reason and the number of times it was mentioned.

Additionally, the narrow reasons were used to generate an overview of broader themes to which the narrow reasons related. If a narrow reason applied to two themes, the narrow reason was listed under the most applicable theme, as determined by consensus amongst the researchers. The formulation of both the narrow reasons and themes was an iterative process in which the categories were re-evaluated amongst all researchers several times to bundle similar narrow reasons together, categorize them and define the themes that best encompassed the narrow reasons.

Finally, an overview of the themes and narrow reasons was created by listing these in a table under the overarching classifications of 'human-related', 'animal-related', or 'environment-related' reasons in order of frequency of appearance. Within each theme, the narrow reasons mentioned in the literature were subcategorized as reasons for or against genome editing in animals; these subcategories were similarly listed in order of frequency of appearance. Where applicable, rebuttals of reasons in favour of genome editing were listed in the subcategory 'against' and vice versa.

Results

The database searches resulted in a total of 760 unique records. After title/abstract screening, full text screening, and cross-referencing, 133 articles were included for data extraction and analysis (**Figure 1**).

Author affiliation

The included articles were written by professionals working primarily in academic institutions, in a variety of different departments or divisions: biomedical or biological sciences (n=77/133), animal sciences (n=30/133), ethics (n=20/133), philosophy (n=14/133), biotechnology companies (n=8/133), governmental organisations (n=6/133), law (n=5/133), (bio)engineering (n=4/133), nutritional or food sciences (n=3/133), agricultural sciences (n=3/133), consultancy (n=2/133), epidemiology (n=2/133), political sciences (n=2/133), bioinformatics or computational biology (n=2/133), psychology (n=1/133), mathematics (n=1/133) and a private foundation (n=1/133). In 10/133 articles no author affiliation was listed (**Table 1**).

Reasons for and against new-generation genome editing in animals

In total, 115 different reasons were mentioned in the reviewed articles; 67 reasons of these reasons were in favour and 48 against the development and use of new-generation genome editing in animals. The included articles contained from 1 up to 13 different reasons. The reasons were in response to a broad range of potential applications of genome editing in animals (**Table 2**).

These narrow reasons were subsequently categorized into seven broad themes: (1) human health; (2) efficiency; (3) risks & uncertainty; (4) public acceptability; (5) animal welfare; (6) animal dignity and species-specific capacities; (7) environmental considerations (**Table 3**). In the following sections, the different broad and narrow reasons are discussed in more detail.

Human-related reasons

Human health

Most reasons in favour of genome editing in animals concerned its potential to improve human health. First, these hoped-for improvements include using gene drives to reduce the burden of vector-borne diseases [5,6,18–49], either by suppressing or eradicating insect populations [44,45] or inducing vector resistance to disease pathogens [45,46]. At the same time, however, some authors noted that gene drives could pose risks to human health if they disrupted ecosystems on which humans are dependent [39], or if modified mosquitoes did not confer resistance — or if they actually reduced instead of increased resistance to the target infection [42,48].

Second, various authors note that genome editing in animals could enhance research in animal systems by creating better animal models of human disease [3,4,7,11,24,26,28,30,32,50–76], which could ultimately benefit human health, for example by leading to the creation of new medicines and therapies [26,32,40,70]. At the same time, it was argued that there is a lack of reproducibility of animal findings in humans [77–79], which could put human research participants at risk at a later stage of the research [78].

In a similar way, authors argued that genome editing could expedite research in other species, including non-human primates, which could provide more accurate models for human (neurological) disease [40,51,61,80–88]. The permissibility of this approach was questioned, however, given available alternatives such as using organoids or stem cell models of disease [78] or using animal models of smaller animals such as mice [40]. It was mentioned that although genome editing in non-human primates could be considered ethically problematic, it would be even more ethically problematic to let humans die who could be saved [84].

Third, genome editing in animals could provide a solution to the long-standing shortage of human organ donors by facilitating xenotransplantation from pigs into humans [23,24,26,32,55,65,66,70,72,73,89–104], either by reducing the chance of immune rejection in xenotransplantation

[30,33,38,55,65,66,70,72,73,87,89,90,93,94,97–99] or by decreasing the risk of transmission of porcine pathogens such as porcine endogenous virus (PERV) [23,26,32,55,73,89,91,93,99–101,103,104]. It was mentioned that this solution should be compared to alternative solutions to this problem in terms of resource allocation and prioritization [21].

Fourth, genome editing could help to meet the challenge of producing more food more sustainably to ensure that the future human population can be fed [76,105–108], for example by increasing skeletal muscle mass and thereby meat production. Concurrently, it was mentioned that little is known about the effects these modified organisms would have on humans when consumed [50] and that it could be undesirable to increase meat production given the negative impact of meat consumption on human health [19].

Finally, authors noted that genome editing could be used to create a chicken strain with low allergenicity, which could benefit humans with egg allergies [40]. On the other hand, authors mentioned that there may not be a compelling need to produce such chickens since the allergy usually only occurs in children, and because alternatives and egg substitutes are available [109]. Finally, some authors noted that if genome editing were used to 'de-extinct' species, the re-created species could potentially be harmful to humans if it became a vector or reservoir for viruses [110].

Efficiency

Many reasons in favour of genome editing in animals mentioned the efficiency of these techniques. First, it was argued that genome editing could be a potentially efficient and rapid tool to improve important traits in livestock [26,111,112], which could increase production efficiency [24,28,67,70,95,111,113], for example by achieving a higher meat yield [24,28,67,95,111]. Various authors argued that genome editing using engineered nucleases (ZFN, TALEN or CRISPR) was more efficient, versatile, precise, easy to use, or accurate than previous genetic technologies [3,4,6,7,9,21,25,32,40,41,50,52,57–61,64,68,70,72,73,76–78,81,83,89, 94,102,106,108,114–120]. On the other hand, it was argued that genome editing technologies could still have inadequate gene targeting efficiency and cause off-target effects or mosaic mutations [103], particularly in non-human primates [59,66,71,79,81,82,85–87,121]. Other authors mentioned that these off-target effects could be identical to those of natural processes that continually create variation in the genomes of food animals [122], and that they could be fewer and more controlled compared with the mutations caused by generally accepted technologies such as conventional breeding [106,109]. Finally, it was suggested that off-target effects could be minimized by careful design [122].

Second, authors compared the efficiency of these technologies to alternative strategies in which genome-editing was not used. It was argued that genome editing could facilitate quicker or more effective trait improvement than classic breeding [10,32,66,69,106,108,122,123]. For gene drives, it was mentioned that this technology could be more efficacious than other approaches to eliminate vector-borne diseases [33,34] or than other pest management methods such as pesticides [39,42].

Third, it was argued that these technologies could lead to advances in scientific understanding [12,26,41,44,48,94,102,110,117] or to technological advances [12]. Authors also mentioned that genome editing could reduce the overuse of antibiotics in farm animals by providing these animals with disease resistance [24,114].

Fourth, issues of cost were addressed. It was mentioned that CRISPR could be relatively inexpensive in comparison to both previous genetic technologies [9,25,26,76,78,106,124], other pest management techniques such as insecticides [18,39] and traditional sterile insect methods [18], and that it could increase economic productivity in animals bred for human consumption [112,125]. Moreover, authors mentioned that genome editing could save costs for the farming industry by providing animals with disease resistance [40,95,102,114,126] or by transferring polled genes to horned cattle, obviating the need for expensive dehorning [28,108,111,127]. Finally, gene drives could be a cost-effective strategy for controlling the transmission of vector-borne diseases [6,33,42].

Risks & uncertainty

Other reasons given for or against the use of genome editing technologies concerned their potential risks and uncertainties.

For gene drives, the risks addressed primarily related to accidental or deliberate release of gene drive organisms. It was mentioned that the genes drive could spread beyond their target population [50,118] due to accidental release [18,27,34,39,47,115,128,129], horizontal transfer [34,42], cross-breeding [39], or gene flow [39], with unpredictable ecological consequences. Authors noted that it could be impossible to rule out breaches of containment, which would constitute a non-negligible risk as release of just a few gene drive organisms could cause the transgenes to spread on a global scale [46]. Authors also mentioned that gene drive organisms could be released deliberately, exposing the public and the environment to risk [21,130], particularly if these organisms were engineered to carry diseases rather than prevent them [21]. The potential for off-target mutations affecting the gene drive was mentioned as another risk [7,39,50,118]; a guide RNA could, for example, mutate over time and consequently target an unintended part of the genome [7].

Several authors mentioned potential ways to mitigate these risks. Various designs of the gene drive and other containment measures could mitigate unintended consequences or spread beyond the target population [5,18,21,22,26,28,31,37,38,48,116,128,129]. Authors also suggested that gene drives could be researched in a phased approach, allowing sufficient time to evaluate the efficacy and safety of gene drive organisms before regulatory decisions are made about whether they are suitable for widespread use [23,38]. Furthermore, it was argued that these potential negative consequences are not in themselves a sufficient reason not to use gene drives; the magnitude and likelihood of these risks ought to be analysed thoroughly and balanced against the potential benefits [45] as well as the risks and harm caused by the unmodified wild-type animal [18].

For genome editing in general, the uncertainty involved in assessing potential consequences of genome editing technologies was stressed. It was argued that the risks or consequences of genome editing technologies could be difficult or even impossible to characterize beforehand, given their novel features [39,48,130] and our incomplete knowledge and understanding of the genetic background of complex traits [111]. With respect to applications of genome editing in animal farming, on the other hand, it was argued that genome editing could be considered similar to conventional breeding since the created modifications are comparable to natural mutations and no transgenes are involved [66,67,109,122]. Although genome editing could result in off-target effects with potential negative effects, it was argued that genome editing is more precise and consequently has fewer risks than conventional breeding and therefore should be generally regarded as safe [108]. Some authors also argued that it is generally more difficult to prove that something is safe than to find potential risks; the damage of not using a new technique may exceed its potential risks [111].

Finally, it was mentioned that genome editing could be used to serve the (economic) interests of particular groups, such as the agriculture or food industry [39], with little concern for the public interest [39,113].

Public acceptability

Other human-related reasons in favour or against genome editing in animals concerned public acceptance or rejection of the technologies. Some authors argued that the new generation of genome editing technologies might be more acceptable to the public than previous technologies because no foreign DNA is introduced into the animal [9,41,111,112]. It was mentioned that this could consequently increase the chance of a publicly justified policy [9]. It was also mentioned that the public might consider gene drive applications in agriculture less controversial than using pesticides for pest control [39].

In contrast, it was argued that some uses of genome editing could generate public resistance to the technologies [12,30,40,46,48,129] , for example if public funds were used to bring back extinct species [12] or if genetically modified mosquitoes were to cross borders to other countries that did not support their release [46,48,129]. Other authors asserted that the latter concern could be mitigated by using gene drive designs that could enable local communities to make decisions concerning their own local environments [37]. While authors acknowledged that it would not be possible to seek consent from all humans who could potentially be impacted by the release of genome edited mosquitoes, it was argued that release could nonetheless be justified if the public health benefits of the trial are important enough for the community [48]. It was suggested that one way to conduct field trials with genetically modified animals whilst respecting the interests of community members is to use community advisory boards and a community authority [29].

<u>Animal-related reasons</u>

Animal welfare

Reasons that related to animal welfare were used to argue both in favour of and against genome editing in different types of animals.

First, it was argued that genome editing could decrease the suffering of farm animals. For example, genome editing could be used to prevent the killing of day-old male chicks [40,131] by enabling the production of poultry in which the embryo's sex can be recognized in the egg, in which genetic males become phenotypical females or in which male embryos die during early development. Authors also suggested that genome editing could be used to repair accumulated damage in the genome of breeding animals by removing harmful recessive alleles that impair animal fertility and health [111]. Additionally, genome editing could be used to create hornless cattle, which would not require the painful dehorning that is commonly performed in the farming industry to protect both cows and farmers from injury [9,24,28,32,40,107–109,111,122]. At the same time, it was mentioned that this goal could be accomplished in other ways too; instead of creating polled animals, the rearing environment of cattle could be improved to prevent accidents, horn covers could be used, or dehorning could be performed under anaesthesia [109,132].

Other authors emphasized the potential use of genome editing to increase animal health and welfare by making animals resistant to diseases [23,24,40,70,107,109,111,114] or better able to adapt to environmental conditions [28,125]. In contrast, it was argued that such uses of genome editing would enable even greater intensification of farming, for example by generating polled or disease resistant animals that could be kept at higher density [19,51,121]. While these authors noted that any intensification of farming would decrease animal welfare, others questioned the likelihood of this outcome given recent trends of companies improving animal welfare [107].

Some authors considered the possible use of genome editing to counter welfare problems of farm animals by creating so-called 'diminished animals' with an impaired ability to sense pain

[107,113,121,125,133–136]. In response, authors noted that there is no proof of concept experiment for such an application in farm animals and argued that conducting these experiments would itself cause suffering [121]. Lastly, authors noted that if farm animals were edited to improve production efficiency, some of these genome modifications could result in secondary complications that are bad for animal welfare [19,109,111]; increased muscle growth, for example, could lead to increased rates of Caesarean sections, leg problems, or breathing complications.

Second, it was argued that genome editing could be used to decrease the suffering of research animals, for example by decreasing the occurrence of unwanted genetic effects [77] and reducing the number of animals [78] used to create animal model systems compared to traditional methods [78]. On the other hand, it was argued that, if genome editing were to be widely used, this decrease in suffering per experiment would be offset by the overall increase in the numbers of transgenic animals used in research [51,77]; in this way, genome editing could contribute to animal suffering by perpetuating their continued use in research [9,30,51,77]. Moreover, it was mentioned that genome editing could bring routine genome editing of non-human primates within reach, which could substantially diminish these organisms' welfare and quality of life [78].

Third, it was mentioned that genome editing might decrease the suffering of many species of wild animals, for example by changing the reproductive behaviour of prey animals in ways that reduce their high infant mortality rate [25]. It was argued that the harm that would be prevented by doing so would outweigh the harm inflicted on animals during development and testing of these strategies [25]. On the other hand, authors argued that scientists cannot be confident enough that this strategy will successfully decrease wild animal suffering given the complexity of ecosystems, the unpredictability of climate change, and the indeterminacy of human behaviour [137]. With regards to reviving extinct species, it was mentioned that these animals could end up suffering as a result of the processes used or because of their genomic variations [12], and that revived species could threaten other animals if they become a vector or reservoir for viruses [110].

Finally, it was also argued that genome editing could affect animal welfare in several other ways. 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 [71,112]. Authors also mentioned that genome editing could result in off-target mutations or unintended effects, which could negatively affect animal health [9,19,24,109,138]. Others argued that genome editing using engineered nucleases could result in fewer off-target effects than previous techniques [9]. Furthermore, the so-called 'non-identity problem' was raised in the context of creating genetically modified animals; if these animals have a life worth living, one cannot conclude that they are worse off, even if they have welfare problems, for they would not have existed if they had not been genetically modified [113,132].

With regards to gene drives, it was mentioned that this technology could be a humane method to eliminate invasive species [6]. On the other hand, it was argued that such applications could lead humans to ignore the predicament of the animal and to accept negative effects on animal welfare for the sake of other goals [9], although this risk could be prevented by using less drastic gene drive designs and using them to promote animal welfare (for instance by driving disease resistance into wild populations) [9].

Animal dignity and species-specific capacities

Several authors argued that (applications of) genome editing are undesirable not because they might harm the welfare of these animals, but because they were harmed in other ways. First, it was argued that genome editing instrumentalises animals by using them as mere objects to serve human purposes [19,51,89,110,113], whereas these animals have intrinsic value [19], and in any case prospective human benefits should not be used to justify harm to animals [51]. For particular applications such as reviving extinct species or creating genome edited pets, authors argued that it could be in appropriate to alter physiological limits [40,53] or to exploit the animals for unimportant human purposes like entertainment [12]. Additionally, it was mentioned that genome editing could be viewed as the initiation of increasingly imbalanced power distribution between humans and animals [109]. On the other hand, some authors argued that genome editing could prevent additional violations to animal rights, which should be considered preferable to the status quo, even on an account that considers raising animals for human consumption to be impermissible [107].

Second, it was argued that genome editing could be an affront to an animal's dignity [111] and could prevent the animal from living according to its instincts [98]. On the other hand, it was argued that the Kantian concept of dignity cannot be applied to animals, for it is tied to prerequisites conditions, such as the ability to exert self-determination or to be a moral agent, that animals do not possess [139]. Likewise, it was argued that it does not make sense to propose that genome editing could impinge on an animal's dignity and thereby harm that animal even if its welfare is improved, because what is good for an individual must in some way resonate with that individual [107]. Similarly, it was argued that dignity-related arguments ultimately cannot justify an objection that is based on a species norm rather than on respect for individual animals, as is the case in the discussion on enhancement [113,132]. Finally, authors noted that because genome editing could determine which individual comes into existence, it could be hard to say that its rights were infringed, its dignity violated, or even that it was wrongly instrumentalised since it would otherwise not exist [133].

Third, it was argued that genome editing could affect the telos (the essence and purpose) of an animal [109] if they are genetically altered to the point where they lose the behaviour that makes them that particular animal [134], for example if genome editing were used to create diminished animals [125]. In response, it was argued that the idea that there is a 'true essence' of a species is mistaken, as behaviours and tendencies change over time [107]; furthermore, the telos of a creature could still be respected by providing it with an environment that fits its altered genetic predispositions [107]. Moreover, it was argued that it could be morally acceptable to modify an animal's telos if the animal was made less miserable or indeed happier since only an individual animal, not its telos, can be harmed [135].

With regards to species-specific considerations, it was argued that genome editing could expedite transgenesis in non-human primates, which likely occupy a level of moral status that would obligate us to protect them from being used in this way [78] or to allow it only in extremely exceptional circumstances [77]. It was also mentioned that genome editing could only be rightfully done if its permissibility was evaluated for each species on its own merits [51]. With regards to mosquitoes, it was mentioned that extincting them through gene drives could breach the sanctity of their lives, however, it was argued that neither existing mosquitoes (that will not die nor suffer, but merely fail to reproduce), nor the species holistically (for which it could not be considered clear that they possess relevant cognitive capacities) bear a significant degree of moral status [45].

Finally, objections were given to specific applications of genome editing. It was argued that although genome editing could increase animal welfare by facilitating diminishment, this result would be an inappropriate response to the systematic wronging [133] or inappropriate valuation [121] of agricultural animals, whereas we have a duty of reparation to members of this historically wronged group [133]. Authors also mentioned that genome editing could also facilitate xenotransplantation, which might be considered ethically untenable because it compromises species boundaries and treats animals as re-designable systems for human use [89]. On the other hand, it was argued that species norms (which could also be breached if genome editing was used for animal diminishment) are only indirectly morally significant, as a generally useful guide to evaluating animal welfare [132,133]. Similarly, it was mentioned that 'disabilities' caused by diminishment, which could affect the species-typical essence of these animals, would not necessarily make these animals worse off, as the literature on human disabilities has taught us [107,136].

<u>Environmental-related reasons</u>

Environmental considerations

Environmental considerations were mostly used to argue against genome editing. One line of argument pursued the potential impacts of genome edited animals on ecosystems. Authors argued that both genome edited organisms [24,34] and gene drive organisms [6,7,24,27,30,34,39,40,50,76,115,118] could have unknown negative effects on ecosystems. It was mentioned that gene drive organisms could be more transformative, uncontrollable and ecologically damaging than other genome edited organisms that contain self-limiting genes [29], particularly if gene drives were used to eradicate species [7,24,30,50,76,118]. By eradicating a species, gene drives could disrupt the positive contributions of these species in native ecosystems [129], for example by eliminating the food source of another species [7,76,118] or promoting the proliferation of invasive pests [7,76]. In contrast, it was argued that genome editing could enable ecological conservation [44] and save endangered native species [5,47,49] if used to eradicate invasive species [5,37,47,49] or revive ecological proxies of extinct species [12,140]

Authors also argued that genome editing could impact the environment in other ways. On the one hand, it was reasoned that that using genome editing to increase the productivity of livestock could be undesirable given the negative impact of farming on the environment, for example through greenhouse gas production and water and land pollution [19]. On the other hand, genome editing could perhaps contribute to reducing the environmental impact of animal production, for example by decreasing the amount of phosphate pollution [111]. Similarly, authors noted that using gene drives to control agricultural pests could be a more environmentally sound control method than using insecticides [18] and that gene drives could help scientists to develop and support more sustainable agricultural models [5,21,37,38], for example by editing populations of resistant species to become vulnerable to pesticides and herbicides again [5,21,38].

Authors raised several environmental considerations in response to specific proposed applications of genome editing, in particular de-extincting species. On the one hand, it was argued that de-extincting species could be just; since humans caused the extinction and have the power to revive them, they may have a duty to do so [12]. On the other hand, it was mentioned that in some cases there may no longer be a niche for a particular de-extincted species [12,110], and as a result the de-extincted species may do substantial environmental damage if it is released or escapes into the environment. De-extincting animals could also diminish the desire to protect existing species [12,110]. Finally, it was mentioned that genome editing will fail to genuinely recreate species because there would not be a reproductive nor spatiotemporal relation between the resurrected animal and other members of its species [12,141]. In response to the ecological damage that could result from using genome editing to change the reproductive behaviour of wild animals to prevent suffering, it was mentioned that such damage could be offset by modifying other features of the ecosystem, too [25].

Finally, it was argued that genome editing could cross moral limits if humans were to use it to breach natural boundaries or to act out of hubris [12,51,113,130], as nature and life should not be completely manufactured or planned and we should acknowledge their unpredictability [12,113]. Some authors noted that genome editing might in itself constitute an unnatural interference with nature [113,131]. Authors also argued that while the natural order might not hold an intrinsic moral value, deleting genetic diversity risks eliminating advantageous traits [21]. In response, authors noted that it is unclear what is meant by 'naturalness' [98,107]. Furthermore, the natural is not necessarily good and the unnatural is not necessarily bad [98,107]. Similarly, it was argued that although it could be said that using genome editing could amount to 'playing God' or displaying hubris, there may be sufficient reasons – such as saving many lives – to justify improving the given [45]. For gene drives, it was mentioned that the use of this technology to control certain invasive species, if successful, could become a Trojan horse to legitimize the eradication of other species without questioning to whom or what they are harmful [39].

Discussion

To the best of our knowledge, this review constitutes the first systematic review of reasons for and against development and use of new-generation genome editing technologies in non-human animals as reported in the academic literature. Our review shows that a wide and diverse range of reasons is brought forward and provides a descriptive overview of these reasons, offering a starting point for subsequent further research and normative analysis [15].

Importantly, many reasons mentioned in this review are not reasons for or against all uses of genome editing in animals. Instead, they point to possible conditions for responsible use of these technologies. For example, the fact that genetically modified mosquitoes could potentially have negative consequences by spreading the modified gene beyond the target population, could lead to the requirement that a first trial site be geographically isolated, such as an island [48]. Our review also underlines that different ethical considerations may apply to different applications of genome editing in animals. From this point of view, the question to ask is not whether genome editing in general is ethically acceptable but under which conditions it could be.

In what follows, we make four additional observations about the academic debate, and suggest areas for future research and analysis. In particular, we note a lack of disciplinary diversity in the authors shaping the academic debate, an underrepresentation of animal interests, a scarcity of systematic comparisons of potential consequences of using these technologies, and a disjunction between the public and academic debate on this topic. We will elaborate on these observations below.

Critical appraisal of the academic literature

Our findings provide insight into who is shaping the academic debate on the use of gene editing technologies in non-human animals. As Table 1 illustrates, while authors of different backgrounds are involved in this debate, the large majority are (mostly biomedical or veterinary) scientists, investigating the technical feasibility of different applications of genome editing in animals. Authors working in ethics, philosophy, and the social sciences are underrepresented. This lack of disciplinary diversity is particularly problematic as the debate moves from discussions of technical feasibility to (potential) real-world applications, in which academic experts will likely influence policy and regulatory decisions [13,14]. To critically assess the applications of genome-editing in animals from different perspectives, a multidisciplinary and proactive evaluation of the technologies and their ethical and societal implications – for example through ethics parallel research [142,143] – is essential.

Our findings also illuminate characteristics of the specific reasons addressed in the literature. Given that this review concerns genome editing in animals, it is remarkable how few animal-related reasons have been put forward; most reasons for or against the use of genome editing in animals rest on human-related grounds. So far, little of the biomedical literature considers the welfare of (research) animals; for example, articles that mention off-target effects seldom consider whether these effects could have an impact on animal welfare. Similarly, both biomedical and ethical literature provide little reflection on species-specific considerations. Although the moral status and interests of non-human primates were raised [40,77,78], the moral status of other animals was rarely mentioned. Given that accounts of moral status are generally founded in sentience [144] and consciousness, the interests of other animals appear worthy of more attention within this debate. And while the relationship between humans and animals was brought up in several reasons, particularly those related to animal dignity, this relationship was never framed in terms of human virtues [145]. Such an analysis might ask, for example, who we become when we use and alter animals in certain ways. Indeed, when it comes to ethical theory, we note that the most frequently reported reasons – to a large extent originating from biomedical literature – were consequentialist in nature, i.e. focusing on potential (positive or negative) outcomes of using genome editing technology in animals on human health, animal welfare or ecosystems. While an initial emphasis on consequentialism is consistent with general argumentative patterns around new and emerging science and technologies [146], other ethical theories are relevant to this debate and will also be necessary to understand and engage with public attitudes and concerns.

Our third major observation is that surprisingly few articles engaged in a systematic comparison of the harms and benefits of the proposed application of genome editing compared to alternatives. This gap in the literature is noteworthy, as such systematic comparisons are necessary to draw conclusions about what would result in the best *overall* consequences. Such an analysis could draw on the principles of proportionality and subsidiarity. According to the principle of proportionality, potential benefits should be balanced against potential harms or risks; those that argue in favour or against (applications of) genome editing in animals ought to present an explicit comprehensive overview of the benefits, harms and risks in question and argue why the harms outweigh the benefits or vice versa. The principle of subsidiarity entails that a policy should only be used if there is no less harmful policy that would achieve the same result. This principle suggests that applications of genome editing ought to be compared to alternative policies in terms of potential harms and benefits, including the – often forgotten – benefits and harms of the status quo. In the case of gene drives, for example, potential ecological damage resulting from their use is a pressing concern, warranting a thorough inventory of related risks and harms. When weighing those risks and benefits, the principle of subsidiarity forces us – amongst other things – to balance the possible ecological damage of using gene drives to eradicate vector-borne diseases with the deaths that are now caused by these diseases and the ecological damage of using pesticides. This kind of analysis is consistent with calls from the scientific community to integrate *comparative* assessment of risks and benefits into the regulatory framework [147,148]. Yet where some scientific reports define benefits in narrow economic terms, the principle of subsidiarity requires a broad definition of and metric for benefits that extend beyond economics.

Finally, we observed a disjunction between the expert and public debate on this topic. Academic experts have made significant calls for public engagement with and debate about genome editing [4,34,40,95,149,150], particularly with regards to the possible use of gene drives [5,6,32,38,39,42,118,128]. A study commissioned by the United Kingdom's Royal Society explores public perceptions and the reasoning behind them [151]. In both this study and the academic debate more generally, considerable weight is given to the potential for genetically modified animals to improve human health or (negatively) impact ecosystems [151]. However, other public concerns regarding genome editing technologies are thus far underrepresented in or wholly absent from the academic literature, including the public concern for equity of access to genome editing technologies, questions about the just distribution of governmental funding of genome editing compared with other investments, and concerns about the commercialization of genome editing technologies. With regards to commercialization, members of the public have raised the worry that businesses could prioritize profit-making over the public good and could fail to provide a balanced representation of the benefits and risks of these technologies [151]. The fact that these concerns are largely absent from the academic debate on genome editing in animals is particularly problematic given ongoing calls for public engagement, and raises interesting questions that relate to a broader discussion about what the rationale, form, and aim of public engagement should be. If the goals of such engagement are not merely to inform the public, but also to address societal challenges and to allow the public to be involved in shaping technological developments together with other stakeholders, then issues regarding commercialisation, distributive justice, and access to genome editing technologies should also be studied in the academic literature.

Limitations

This systematic review provides a comprehensive overview of the reasons brought forward in the academic debate on genome editing in animals. The articles presented were included after thorough screening of the academic literature on the topic by two independent reviewers, based on a search strategy that guided by experienced librarians. Nonetheless, this review has several limitations.

First, given the focus on relatively new genome editing technologies and the large amount of literature on this topic, this review included articles published between 2010 and 2018. We recognize that some arguments raised previously, or in different contexts or in older but related debates, may be relevant for the current discussion of genome editing. Second, a systematic review of this kind always involves reporting bias; a different group of researchers could have selected or grouped the included reasons in a different way. Third, we could not systematically perform a quality assessment of the included literature, as there is no screening instrument to assess the quality of normative papers or the reasons mentioned.

Conclusion

Genome editing has a broad range of possible applications in research animals, farm animals and wild animals. Despite ongoing academic debate on this topic, this study is the first comprehensive overview of this debate. Our article provides a systematic review of the reasons for and against development and use of genome editing technologies in animals as reported in the academic literature. We identified 67 different reasons for and 48 different reasons against genome editing in animals, which related to human health, efficiency, risks and uncertainty, animal welfare, animal dignity, environmental considerations and public acceptability. Our findings illuminate several key features of the academic debate thus far, including a lack of disciplinary diversity in the contributing professionals, an underrepresentation of animal interests, a scarcity of systematic comparisons of potential consequences of using these technologies, and a disjunction between the public and academic debate on this topic.

As such, our article can be considered a call for professionals from a wide range of disciplines to become involved in the academic discussion about genome editing. We also suggest that this ongoing debate seek to incorporate animal interests, systematically compare applications of these technologies using the principles of proportionality and subsidiarity, and further research the range of concerns uncovered through public engagement. Proactive and multidisciplinary collaboration can both advance these technological developments and the academic discourse about them, allowing us to go beyond rhetoric of promises or fears and positioning their ethical analysis in real world practices [152,153].

Competing interests

We have no competing interests.

Authors' contributions

NG, KJ and AB were responsible for designing the article concept. NG and KJ performed the data collection and analysis. NG was responsible for drafting and revision of the manuscript, to which KJ, SH, JJ and AB provided critical intellectual input and revisions. All authors approved the manuscript.

Acknowledgements

We would like to thank prof. dr. Niels Geijsen for his comments on this work.

Funding

This project was supported by the division of Applied and Engineering Sciences of the Netherlands Organisation for Scientific Research (NWO; project no. 15804). JJ's work is funded by a grant from the John Templeton Foundation; SH's work is funded by a grant from the British Academy.

Figure 1: Flow chart of study selection and inclusion

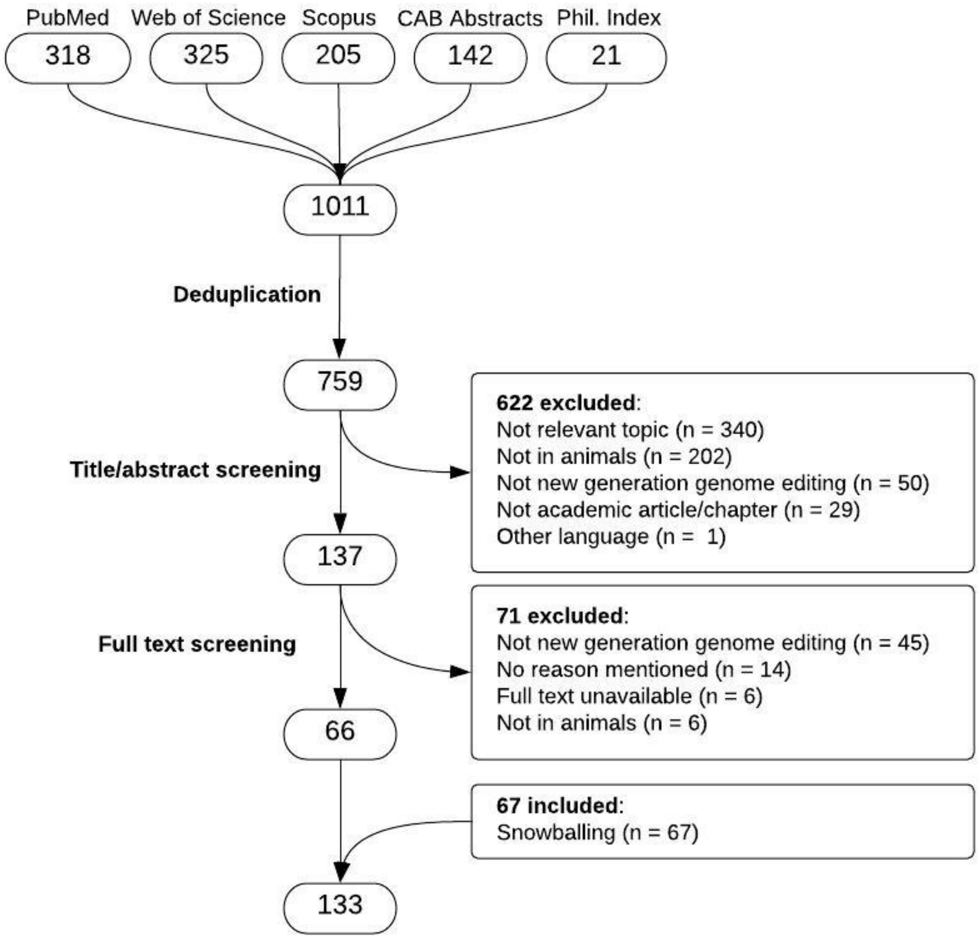

Table 1: Author affiliation

Author affiliation or discipline	N	References[1]
Biological or (bio)medical sciences	77	[3–6,18,20,22,26,28,33–39,41,44,46,50–52,54,55,57–59,61–64,66–68,72–74,76,77,79–97,99,100,102–104,107-110,115,118,119,122,126–129,138,140]
Veterinary medicine or animal sciences	30	[10,11,18,20,33,54,56,65–67,69,71,72,79,80,88,92,96,99,104,108,111,112,114,122,123,126–128,131]
Ethics	20	[6,19,21,22,27–30,42,45,48,49,76,78,89,98,107,109,136,139]
Philosophy	14	[9,25,39,76,110,113,121,130,132–135,137,141]
No affiliation or no author listed	10	[7,31,40,43,47,53,60,101,116,124]
Biotechnology company	8	[10,20,70,99,100,104,108,117]
Governmental organization	6	[18,23,38,118,128,131]
Law	5	[12,22,120,125,137]
(Bio)engineering	4	[68,72,75,104]
Nutritional or food sciences	3	[24,32,105]
Agricultural sciences	3	[70,106,131]
Consultancy	2	[77,113]
Epidemiology	2	[18,98]
Political sciences	2	[24,38]
Bioinformatics or computational biology	2	[38,68]
Psychology	1	[26]
Private foundation	1	[6]
Mathematics	1	[37]

Table 2: Potential applications of genome editing in animals mentioned in the literature

Potential application of genome editing in animals	*(Potential) aim*
Genome editing in general	
Create an animal model of Parkinson's disease [11]	Create animal models of human disease
Delete an antigen that causes hyperacute rejection in pig-to-human transplantation [73] or inactivating porcine endogenous retroviruses (PERV) to prevent transmission of these viruses to humans [99]	Facilitate xenotransplantation from pigs to humans by reducing the chance of immune rejection
Increase skeletal muscle mass and thereby meat production [67]	Increase nutritional value for humans; increase production efficiency in animal farming
Create a chicken strain with low allergenicity [40]	Decrease allergic reactions in humans
Increase disease resistance to Porcine Reproductive and Respiratory Syndrome in livestock [114]	Decrease suffering of farm animals; increase production efficiency; reduce use of antibiotics
Create polled (hornless) cattle [108]	Decrease suffering of farm animals (by preventing painful dehorning); decrease costs; increase production efficiency; decrease moral distress of farmers.
Produce poultry in which the of which the embryo's sex can be recognized in the egg, in which genetic males become phenotypical females, or in which male embryos die during early development [131]	Decrease suffering of farm animals by preventing the killing of male chicks
Create so-called 'diminished' animals in which the ability to sense pain is impaired [107]	Decreasing suffering of animals in research and farming
Revive the woolly mammoth as a major grazing animal in the Arctic [110,140]	Curiosity; advance scientific understanding; restore an Arctic steppe in the place of the less ecologically rich tundra [33]
Gene drives	
Induce mosquito resistance to malaria parasites [35]; induce infertility in mosquitos [45]	Reduce the burden of vector-borne diseases
Reduce fertility or biasing sex towards males in invasive species, creating a population that is not reproductively viable [118]	Control or eradicate invasive species
Increase genetic gain in breeding programs [10]	Increase economic productivity in animal farming
Change reproductive behaviour of wild animals that give birth to large numbers of offspring, many of whom do not survive to adulthood, by decreasing the number of offspring they produce per cycle [25]	Prevent wild animal suffering

Table 3: Reasons for and against the development and/or use of genome editing technologies in animals

		n	References	Technologies
Human-related reasons				
Human health				
For (n=115)	Could enhance research by creating better animal model systems of human disease	35	[3,4,7,11,24,26,28,30,32, 50–73,75,76]	Various (ZFN, TALEN, CRISPR); genome editing
	Could improve human health by reducing the burden of vector-borne diseases such as malaria	34	[5,6,18–49,74]	Gene drives; genetic modification; genome editing
	Could facilitate xenotransplantation, which could be a solution to the human donor shortage	23	[30,31,33,38,55,65,66, 70,72,73,86–101]	Various (ZFN, TALEN, CRISPR)
	Could expedite research in other species, including non-human primates, which provide more accurate models for human (neurological) disease	12	[40,51,61,80–88]	CRISPR
	Could help to meet the challenge of producing more food more sustainably to ensure the future global population can be fed	5	[76,105–108]	Various (ZFN, TALEN); genetic modification)
	Could improve human health through the provision of new medicines and therapies	4	[26,32,40,70]	Various (TALEN, CRISPR)
	Could enable genome engineering in non-human primates; this could be considered ethically problematic, but it is much more ethically problematic to watch people die who could be saved	1	[84]	CRISPR
	Could be used to create a chicken strain with low allergenicity	1	[40]	CRISPR
Against (n=13)	Re simplifying and speeding up the production of new transgenic animal models of human disease: most of such models fail to directly benefit humans; this lack of reproducibility may put human research participants at risk at a later stage	3	[77–79]	CRISPR
	Re bringing routine genome engineering of non-human primates within reach, which could help identify genetic underpinnings of disease or develop therapies: the moral permissibility of this approach is questionable given available alternatives	2	[40,78]	CRISPR
	Could pose risks to human health if genetic modification is not successful in creating mosquitoes resistant to infections, but instead confers no resistance or actually reduces resistance to the target infection	2	[42,48]	Genetic modification; gene drives
	Could be used to re-created species, which may become a vector or reservoir for viruses that can be harmful for human beings	1	[110]	Genetic engineering
	Could disrupt ecosystems, which could be harmful to human populations depending on them	1	[39]	Gene drives
	Re use to create a chicken strain with low allergenicity: there may not be a compelling need for doing so since allergy usually only occurs in children, and alternatives and egg substitutes are available	1	[109]	Various (ZFN, TALEN, CRISPR)
	Re use to produce better quality food: little is known about the effects these modified organisms would have on humans when consumed	1	[50]	CRISPR
	Could increase productivity of the livestock sector: this is an undesirable outcome given the negative impact of meat consumption on human health	1	[19]	Various (ZFN, TALEN, CRISPR)
	Re use to reduce the chance of immune rejection in xenotransplantation, which could provide a solution to the longstanding problem of shortage of organs: such use should be compared to alternatives in terms of resource allocation & prioritization	1	[21]	CRISPR

Efficiency				
For (n=98)	Could be more efficient, versatile, precise, easy to use or accurate than previous editing technologies	39	[3,4,6,7,9,21,25,32,40,41,50,52,57–61,64,68,70,72,73,76–78,81,83,89,94,102,106,108,114–120]	Various (ZFN, TALEN, CRISPR)
	Could lead to advances in scientific understanding or technological advances	9	[12,25,40,43,47,91,99,110,118]	Various (ZFN, TALEN, CRISPR; genetic modification; active genetics*)
	Could be relatively inexpensive in comparison to previous approaches	9	[9,17,24,25,38,73,75,103,119]	CRISPR, gene drives
	Could save costs for the farming industry	9	[27,39,92,99,105,107,114,120,121]	Various (ZFNs, TALEN, CRISPR)
	Could accelerate and/or enhance the trait improvement currently accomplished by classic breeding	8	[10,38,66,69,103,105,113,116]	Various (ZFN, TALEN, CRISPR, gene drives)
	Could increase production efficiency	7	[17,31,67,70,92,114,117]	Various (ZFNs, TALEN, CRISPR); genetic modification
	Could be a potentially efficient and rapid tool to improve important traits in livestock	3	[26,111,112]	Various (ZFNs, TALEN, CRISPR)
	Could be a cost-effective strategy to control the transmission of vector-borne diseases	3	[6,33,48]	Genetic modification, gene drives
	Could increase economic productivity in animals bred for human consumption	2	[112,125]	Various (ZFNs, TALEN, CRISPR); genetic engineering
	Could provide animals with disease resistance, which could reduce the overuse of antibiotics	2	[24,114]	Various (TALEN, CRISPR)
	Could be used to eradicate vector-borne diseases in a more efficacious and/or logistically less complex way than other efforts to eliminate these diseases	2	[33,34]	Gene drives
	Could be used for pest control, being more precise or effective than other pest management methods such as pesticides	2	[39,42]	Gene drives
	Re the possibility of off-target effects: these are fewer and more controlled compared with the mutations that are caused by generally accepted technologies such as conventional breeding	2	[106,109]	Various (ZFNs, TALEN, CRISPR)
	Re the possibility of off-target effects: these can be minimized by careful design and testing, and their effects are largely identical to those of the natural processes that continually create variation in the genomes of food animals	1	[122]	Various (ZFNs, TALEN, CRISPR
Against (n=10)	Could still have inadequate gene targeting efficiency, off-target effects, or cause mosaic mutations	10	[59,66,71,79,81,82,85–87,121]	Various (ZFN, TALEN, CRISPR)
Risks & uncertainty				
Against (n=24)	Could spread beyond its target population due to accidental release, cross-breeding, or gene flow; this release could have unpredictable ecological consequences	11	[18,27,34,39,42,47,50,115,118,128,129]	Gene drives
	Could introduce off-target mutations into the gene pool and spread these across a species	4	[7,39,50,118]	Gene drives
	Could have novel features that are unprecedented and unexpected, so the risks and consequences are difficult or even impossible to characterize beforehand	3	[39,48,130]	Various (synthetic biology, gene drives, genetic modification)
	Could involve risks of deliberate release of (disease carrying [27]) genetically modified mosquitoes to the environment	2	[21,130]	Synthetic biology (incl. genome editing), gene drives
	Could be used to serve the (economic) interests of particular groups with little concern for the general interest	2	[39,113]	Various (ZFNs, TALEN, CRISPR, gene

				drives)
	Could have unexpected effects since our knowledge & understanding of the genetic background of complex traits is incomplete	1	[111]	Various (ZFNs, TALEN, CRISPR)
	Could have non-negligible risks because breaches of containment are impossible to rule out and, once released, just a few escaped genetically modified mosquitoes could be capable of spreading transgenes on a global scale	1	[46]	Gene drives
For (n=23)	Re the potential to spread beyond its target population or have unintended consequences: various designs of the gene drive and other containment measures may mitigate these risks	13	[5,18,21,22,26,28,31,37, 38,48,116,128,129]	Gene drives
	Re novel features: could be considered similar to conventional breeding due to the similarity to natural mutations and absence of transgenes	4	[66,67,109,122]	Various (ZFNs, TALEN, CRISPR)
	Re potential risks: could be researched in a phased approach, allowing sufficient time to evaluate the efficacy and safety of gene drives before regulatory decisions are made on whether they will be suitable for use	2	[23,38]	Gene drives
	Re potential for off-target effects with negative effects: genome modification is more precise and consequently has far fewer risks than conventional breeding	1	[108]	Various (ZFN, TALEN)
	Re potential risks: it is generally more difficult to prove that something is safe than to find potential risks; the damage of not using a new technique may exceed its potential risks	1	[111]	Various (ZFNs, TALEN, CRISPR)
	Re uncertain consequences: these are not in itself a sufficient reason not to use the technology; the magnitude and likelihood of these risks ought to be thoroughly analysed and balanced against the potential benefits	1	[45]	Gene drives
	Re potential risks: these ought to be balanced with the risks and harm caused by the unmodified wild-type	1	[18]	Gene drives
Public acceptability				
For (n=9)	Could be more acceptable to the public than previous technologies, as no foreign DNA is introduced	4	[9,41,111,112]	Various (ZFNs, TALEN, CRISPR)
	Could increase the chance of a publicly justified policy permitting genome editing	1	[9]	CRISPR
	Could be less controversial than using pesticides for pest control	1	[39]	Gene drives
	Could impact community members who have not consented to the release of genetically modified mosquitoes, however this may be justifiable if the public health benefits of the trial for the community are important enough	1	[48]	Genetic modification
	Could be used in field trials with genetically modified animals whilst respecting the interests of community members if community advisory boards and a community authorization process are used	1	[29]	Gene drives
	Re public resistance: could lead to resistance when modified mosquitoes cross borders to communities who did not agree with this, however various designs of the gene drive may prevent this, enabling local communities to make local decisions	1	[37]	Gene drives
Against (n=6)	Could lead to public resistance	6	[12,30,40,46,48,129]	Gene drives; genetic modification; genome editing, genetic engineering
Animal-related reasons				
Animal welfare				
For (n=39)	Could decrease animal suffering in dairy farming by creating dehorned cattle, preventing invasive and painful dehorning	10	[9,24,28,32,40,107–109,111,122]	Various (ZFNs, TALEN, CRISPR)
	Could counter welfare problems by creating so-called ‘diminished animals’ in which the ability to sense pain is impaired	8	[107,113,121,125,133–136]	Genome editing (CRISPR); genetic engineering/modification
	Could increase animal health and welfare by providing animals with disease resistance	8	[23,24,40,70,107,109, 111,114]	Various (ZFNs, TALEN, CRISPR)
	Could increase adaptations to different environmental conditions	2	[28,125]	Various (ZFNs, TALEN, CRISPR); genetic engineering

	Could be used to prevent the killing of day-old male chicks	2	[40,131]	CRISPR; genetic modification
	Re the possible creation of animals with welfare problems: if they have a life worth living we cannot say that they are worse off due to the genetic modification, for if they had not been created with genetic modification, they would not have existed at all	2	[113,132]	Genetic modification
	Re off-target effects: could result in fewer off-target effects than previous techniques, which could improve welfare of genetically modified animals	1	[9]	CRISPR
	Could reduce the numbers of animals used to create model organisms compared to traditional methods, which typically sacrifice many animals before achieving the desired genotype and phenotype	1	[78]	CRISPR
	Could remove known harmful recessive alleles that impair fertility or health and in that sense repair accumulated damage in the genome of breeding animals	1	[111]	Various (ZFNs, TALEN, CRISPR)
	Could prevent wild animal suffering by using genome editing to change reproductive behaviour; the harm that would be prevented by doing so would outweigh the harm of developing and testing these strategies	1	[25]	CRISPR
	Could lead us to ignore the predicament of the animal and to accept negative effects on animal welfare for the sake of other goals, however this concern may be addressed by using less drastic gene drive designs and using these promote animal welfare	1	[9]	Gene drives
	Re applications that would permit even greater intensification of farming resulting in decreased animal welfare: this seems unlikely given recent trends of companies to improve animal welfare	1	[107]	Various (ZFNs, TALEN, CRISPR)
	Could be a humane method to eliminate invasive species	1	[6]	Gene drives
Against	Could result in off-target mutations or unintended effects, which could negatively affect animal health	5	[9,19,24,109,138]	Various (ZFNs, TALEN, CRISPR)
(n=25)	Could contribute to animal suffering by perpetuating the use of animals in research	5	[9,30,51,77,78]	Genome editing; CRISPR
	Could result in secondary complications that are bad for animal welfare (e.g. increased muscle growth could lead to increased rates of Caesarean sections, leg problems, or breathing complications)	3	[19,109,111]	Various (ZFNs, TALEN, CRISPR)
	Could be used for applications that would permit even greater intensification of farming; this outcome would be undesirable	3	[19,51,121]11,20,118	Various (ZFNs, TALEN, CRISPR); genome engineering
	Could be used to decrease animal suffering (by creating polled cattle or diminished animals), however there are alternatives to doing so (e.g. by improving animals' environments)	2	[109,132]	Various (ZFNs, TALEN, CRISPR)
	Could be combined with somatic cell nuclear transfer cloning to deliver the nuclease-mediated genetic alterations, which is associated with embryonic losses, postnatal death, and birth defects	2	[71,112]	Various (ZFNs, TALEN, CRISPR)
	Could bring routine genome editing of non-human primates within reach; this use of the technologies may substantially diminish these organisms' welfare and quality of life	1	[78]	CRISPR
	Re use to preventing wild animal suffering: the complexity of ecosystems, the unpredictability of climate change and the indeterminacy of human behaviour leaves us with too little confidence that this aim will be successful	1	[137]	Genome editing
	Re use to create diminished animals who lack the affective dimension of pain: no proof of concept experiment has been done on farm animals and conducting these experiments would itself cause suffering	1	[121]	Genetic engineering
	Re use to de-extinct species: the de-extincted animals may end up suffering either as a result of the processes used or because of their particular genomic variations	1	[12]	Genetic engineering
	Re use to 'de-extinct' species: the re-created species may become a vector or reservoir for viruses that can be harmful for other animals	1	[110]	Genetic engineering
Animal dignity & species-specific characteristics				
Against	Could be objectionable since it instrumentalises animals by using them as mere objects to serve human purposes	5	[19,51,89,110,113]	Various (ZFNs, TALEN, CRISPR);
(n=21)	Could be used to de-extinct species or create gene-edited pets, but it is questionable if physiological limits should be altered or	3	[12,40,53]	Various (TALEN, CRISPR)

	animals should be exploited for unimportant human purposes like entertainment			
	Could impinge on animal's dignity as altering the genome of an animal is a failure to acknowledge its dignity or prevents the animal from living its instinct	3	[51,98,111]	Various (ZFNs, TALEN, CRISPR)
	Could affect the 'telos' (the essence and purpose of a creature) if they are genetically altered to the point where they lose the behaviour that characterizes that animal	3	[109,125,134]	Various (ZFNs, TALEN, CRISPR); genetic modification
	Could expedite transgenesis in other species, including non-human primates, which likely occupy a level of moral status that would obligate us to protect them from being used in this way or to allow it only in extremely exceptional circumstances	2	[77,78]	CRISPR
	Could create diminished animals to decrease animal suffering, but this is an inappropriate response to the historical wronging of agricultural animals; we have a duty to repair these wrongs	2	[121,133]	Genome editing (CRISPR mentioned)
	Could only be rightfully done if the permissibility of genome editing in research is evaluated for each species on its own merits	1	[51]	CRISPR
	Could be used to facilitate xenotransplantation, which could be considered ethically untenable as it compromises species boundaries	1	[89]	CRISPR
	Could be viewed as the initiation of increasingly imbalanced power distribution between humans and animals	1	[109]	Various (ZFNs, TALEN, CRISPR)
For (n=14)	Re breaching species norms if used for animal diminishment: species norms are only indirectly morally significant, as a generally useful guide to evaluating animal welfare	2	[132,133]	Genome editing (CRISPR)
	Re violating animal dignity or integrity: such arguments focus only on respect for individual animals, they ultimately cannot justify an objection that is based on a species-norm, as is the case in the discussion on enhancement	2	[113,132]	Genetic modification
	Re use to create diminished animals, which could be said to harm these animals as their species-typical essence would be changed: as the literature about human disability has taught us, we should not assume that 'disabilities' caused by diminishment make animals worse off	2	[107,136]	Various (ZFNs, TALEN, CRISPR; genetic engineering
	Re violating rights, violating dignity or wrongly instrumentalising: genome editing determines which individual will come into existence rather than modifying existing individuals, making it hard to say how its rights could have been infringed, its dignity violated, or even that it has been wrongly instrumentalised	1	[133]	Genome editing (CRISPR mentioned)
	Re breaching the sanctity of the lives of mosquitoes by making them go extinct: neither existing mosquitoes nor the species holistically bear a significant degree of moral status	1	[45]	Gene drives
	Re impinging on an animal's dignity by making them serve better as objects for human use: the Kantian concept of dignity cannot be applied to animals, for this concept is tied to prerequisite conditions that animals do not possess	1	[139]	Genetic engineering
	Re use to modify an animal's telos or nature: this could be morally acceptable if the animals are made less miserable or happier as one does not morally wrong the telos by changing it; only individuals can be wronged	1	[135]	Genetic engineering
	Could be used to prevent additional violations to animal rights, which would be preferable to the status quo, even on an account that considers raising animals for human consumption impermissible	1	[107]	Various (ZFNs, TALEN, CRISPR
	Re impinging on an animal's integrity or dignity and thereby harming him even if welfare is improved: what is good for an individual must in some way resonate with that individual; what is good for him cannot diverge from his welfare	1	[107]	Various (ZFNs, TALEN, CRISPR)
	Re impact on the 'telos' of an animal: the animal's telos can still be respected if it is provided with an environment that fits its altered genetic predispositions	1	[107]	Various (ZFNs, TALEN, CRISPR)
	Re impact on the 'telos' of an animal: the idea that there is some 'true essence' of a species is mistaken as behaviours and tendencies change over time, making it hard to see why this should be seen as morally problematic	1	[107]	Various (ZFNs, TALEN, CRISPR)

Environment-related reasons				
Environmental considerations				
Against (n=28)	Could have unknown negative effects on ecosystems	12	[6,7,24,27,30,34,39,40,50,76,115,118]	Gene drives
	Could cross moral limits by exceeding the extent to which humans breach natural boundaries or act out of hubris; nature/life cannot be completely manufactured or planned and we ought to acknowledge their unpredictability	4	[12,51,113,130]	Various (ZFNs, TALEN, CRISPR, biology)
	Could constitute an unnatural interference with nature	2	[113,131]	Various (ZFNs, TALEN, CRISPR); genetic modification
	Could be used to de-extinct species, for which there may no longer be a niche	2	[12,110]	Genetic engineering
	Could be used to de-extinct species, which might diminish the desire to protect existing species	2	[12,110]	Genetic engineering
	Re use to de-extinct species: genome editing will fail to genuinely recreate species while preserving their species identity	2	[12,141]	Genome editing; genetic engineering
	Could disrupt the natural order; although this order should not hold an intrinsic moral value, deleting genetic diversity could carry risks by deleting traits that are advantageous	1	[21]	Gene drives
	Could lead to increased productivity of the livestock section, which is not desirable given the negative impact of this sector on the environment (e.g. greenhouse gas production & water and land pollution)	1	[19]	Various (ZFNs, TALEN, CRISPR)
	Could be used to control certain invasive species; if this succeeds, this could become a Trojan horse to legitimate the eradication of other species without questioning to whom or what they are harmful	1	[39]	CRISPR, gene drives
	Could be more transformative, uncontrollable and ecologically damaging than organisms modified to contain self-limiting genes	1	[29]	Gene drives
For (n=18)	Could enable ecological conservation by eradicating invasive species or reviving extinct species	7	[5,12,37,44,47,49,140]	Active genetics*; gene drives; genetic engineering
	Could help to develop and support more sustainable agricultural models	4	[5,21,37,38]	Gene drives
	Re potential to be considered unnatural or alike 'playing God': it is unclear what is meant by naturalness; furthermore, there is no reason to accept that the natural is necessarily good and the unnatural necessarily bad	2	[98,107]	Various (ZFNs, TALEN, CRISPR); genetic engineering
	Could contribute to reducing the environmental impact of animal production	1	[111]	Various (ZFNs, TALEN, CRISPR)
	Re potential of extincting mosquitoes to be considered 'playing God' or displaying hubris: there may be sufficient reasons – such as saving many lives - that may justify improving the given	1	[45]	Gene drives
	Could be used to control agricultural pests; this may be a more environmentally sound control method than using insecticides	1	[18]	Gene drives
	Could be used to de-extinct species, which would be just; since humans killed extinct species and have the power to revive them, there is a duty to do so	1	[12]	Genetic engineering
	Re ecological risks created by using gene drives to prevent wild animal suffering by using genome editing to change reproductive behaviour: these risks may be offset by modifying other features of the ecosystem, too	1	[25]	CRISPR, gene drives

* Genetic manipulations in which a "genetic element is copied from one chromosome to the identical insertion site on the sister chromosome using cas9 and guide RNA elements" [44]

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Supplementary Table 1: Search strategy

Search strategy for Pubmed/MEDLINE:

	Search string	*# results*
Genome editing	“Genetic Engineering”[Mesh] OR “Clustered Regularly Interspaced Short Palindromic Repeats”[Mesh] OR “CRISPR-cas Systems”[Mesh] OR “Zinc fingers”[Mesh] OR “Transcription Activator-Like Effector Nucleases”[Mesh] OR ((Gene[tiab] OR genetic[tiab] OR genome[tiab]) AND (Engineering[tiab] OR edit[tiab] OR editing[tiab] OR enhancing[tiab] OR enhancement[tiab] OR modification[tiab] OR therapy[tiab])) OR “Zinc finger”[tiab] OR “Zinc fingers”[tiab] OR meganucleases[tiab] OR TALEN[tiab] OR “Transcription Activator-Like Effector Nucleases”[tiab] OR “Transcription Activator Like Effector Nucleases”[tiab] OR “Clustered Regularly Interspaced Short Palindromic Repeats”[tiab] OR “CRISPR”[tiab] OR “gene drive” [tiab] OR “gene drives”[tiab]	380.201
Animals*	“Animal experimentation”[MeSH] OR “models, animal”[MeSH] OR “animal population groups”[MeSH] OR Animals[MeSH] OR animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR pan[Tiab] OR paniscus[Tiab] OR "pan paniscus"[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR troglodytes[Tiab] OR "pan troglodytes"[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimians[Tiab] OR "bush baby"[Tiab] OR prosimian[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae[Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR pongo[Tiab] OR pygmaeus[Tiab] OR "pongo pygmaeus"[Tiab] OR orangutans[Tiab] OR pygmaeus[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR pongo[Tiab] OR equus[Tiab] OR cow[Tiab] OR calf[Tiab] OR bull[Tiab] OR chicken[Tiab] OR chickens[Tiab] OR gallus[Tiab] OR quail[Tiab] OR bird[Tiab] OR birds[Tiab] OR quails[Tiab] OR poultry[Tiab] OR poultries[Tiab] OR fowl[Tiab] OR fowls[Tiab] OR reptile[Tiab] OR reptilia[Tiab] OR reptiles[Tiab] OR snakes[Tiab] OR snake[Tiab] OR lizard[Tiab] OR lizards[Tiab] OR alligator[Tiab] OR alligators[Tiab] OR crocodile[Tiab] OR crocodiles[Tiab] OR turtle[Tiab] OR turtles[Tiab] OR amphibian[Tiab] OR amphibians[Tiab] OR amphibia[Tiab] OR frog[Tiab] OR frogs[Tiab] OR bombina[Tiab] OR salientia[Tiab] OR toad[Tiab] OR toads[Tiab] OR "epidalea calamita"[Tiab] OR salamander[Tiab] OR salamanders[Tiab] OR eel[Tiab] OR eels[Tiab] OR fish[Tiab] OR fishes[Tiab] OR pisces[Tiab] OR catfish[Tiab] OR catfishes[Tiab] OR siluriformes[Tiab] OR arius[Tiab] OR heteropneustes[Tiab] OR sheatfish[Tiab] OR perch[Tiab] OR perches[Tiab] OR percidae[Tiab] OR perca[Tiab] OR trout[Tiab] OR trouts[Tiab] OR char[Tiab] OR chars[Tiab] OR salvelinus[Tiab] OR "fathead minnow"[Tiab] OR minnow[Tiab] OR cyprinidae[Tiab] OR carps[Tiab] OR carp[Tiab] OR zebrafish[Tiab] OR zebrafishes[Tiab] OR goldfish[Tiab] OR goldfishes[Tiab] OR guppy[Tiab] OR guppies[Tiab] OR chub[Tiab] OR chubs[Tiab] OR tinca[Tiab] OR barbels[Tiab] OR barbus[Tiab] OR pimephales[Tiab] OR promelas[Tiab] OR "poecilia reticulata"[Tiab] OR mullet[Tiab] OR mullets[Tiab] OR seahorse[Tiab] OR seahorses[Tiab] OR mugil curema[Tiab] OR atlantic cod[Tiab] OR shark[Tiab] OR sharks[Tiab] OR catshark[Tiab] OR anguilla[Tiab] OR salmonid[Tiab] OR salmonids[Tiab] OR whitefish[Tiab] OR whitefishes[Tiab] OR salmon[Tiab] OR salmons[Tiab] OR sole[Tiab] OR solea[Tiab] OR "sea lamprey"[Tiab] OR lamprey[Tiab] OR lampreys[Tiab] OR pumpkinseed[Tiab] OR sunfish[Tiab] OR sunfishes[Tiab] OR tilapia[Tiab] OR tilapias[Tiab] OR turbot[Tiab] OR turbots[Tiab] OR flatfish[Tiab] OR flatfishes[Tiab] OR sciuridae[Tiab] OR squirrel[Tiab] OR squirrels[Tiab] OR chipmunk[Tiab] OR chipmunks[Tiab] OR suslik[Tiab] OR susliks[Tiab] OR vole[Tiab] OR voles[Tiab] OR lemming[Tiab] OR lemmings[Tiab] OR muskrat[Tiab] OR muskrats[Tiab] OR lemmus[Tiab] OR otter[Tiab] OR otters[Tiab] OR marten[Tiab] OR martens[Tiab] OR martes[Tiab] OR weasel[Tiab] OR badger[Tiab] OR badgers[Tiab] OR ermine[Tiab] OR mink[Tiab] OR minks[Tiab] OR sable[Tiab] OR sables[Tiab] OR gulo[Tiab] OR gulos[Tiab] OR wolverine[Tiab] OR wolverines[Tiab] OR minks[Tiab] OR mustela[Tiab] OR llama[Tiab] OR llamas[Tiab] OR alpaca[Tiab] OR alpacas[Tiab] OR camelid[Tiab] OR camelids[Tiab] OR guanaco[Tiab] OR guanacos[Tiab] OR chiroptera[Tiab] OR chiropteras[Tiab] OR bat[Tiab] OR bats[Tiab] OR fox[Tiab] OR foxes[Tiab] OR iguana[Tiab] OR iguanas[Tiab] OR xenopus laevis[Tiab] OR parakeet[Tiab] OR parakeets[Tiab] OR parrot[Tiab] OR parrots[Tiab] OR donkey[Tiab] OR donkeys[Tiab] OR mule[Tiab] OR mules[Tiab] OR zebra[Tiab] OR zebras[Tiab] OR shrew[Tiab] OR shrews[Tiab] OR bison[Tiab] OR bisons[Tiab] OR buffalo[Tiab] OR buffaloes[Tiab] OR deer[Tiab] OR deers[Tiab] OR bear[Tiab] OR bears[Tiab] OR panda[Tiab] OR pandas[Tiab] OR "wild hog"[Tiab] OR "wild boar"[Tiab] OR fitchew[Tiab] OR fitch[Tiab] OR beaver[Tiab] OR beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) OR wildlife [tiab] OR cattle [tiab] OR livestock [tiab] OR bovine[tiab]	6.613.079

	NOT (humans[mh] NOT animals[mh:noexp])	
Ethics	Ethics [Mesh] OR ethics [Subheading] OR "Morals"[Mesh:NoExp] OR "Moral Obligations"[Mesh] OR moral [tiab] OR morals [tiab] OR ethic* OR bioethic*	248.177
Combined	Genome editing AND animals AND ethics	968
	Language: English and Dutch Publication dates: 01-01-2010 – 27-02-2018	**318**

Search strategy for Web of Science

	Search string	*# results*
Genome editing	(TS=(Gene OR genetic OR genome)) AND (TS=(Engineering OR edit OR editing OR enhancing OR enhancement OR modification OR therapy)) OR TS=("Zinc finger" OR "Zinc fingers" OR meganucleases OR TALEN OR "Transcription Activator-Like Effector Nucleases" OR "Transcription Activator Like Effector Nucleases" OR "Clustered Regularly Interspaced Short Palindromic Repeats" OR "CRISPR" OR "gene drive" OR "gene drives")	579.482
Animals*	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR "mugil curema" OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR wildlife OR cattle OR livestock OR bovine)	6.782.389

Ethics	TS=(moral OR morals OR ethic* OR bioethic*)	241.750
Combined	Genome editing AND animals AND ethics	676
Filters	Language: English and Dutch Publication dates: 01-01-2010 – 27-02-2018	**325**

Search strategy for Scopus

	Search string	*# results*
Genome editing	(TITLE-ABS-KEY(Gene OR genetic OR genome)) AND TITLE-ABS-KEY (Engineering OR edit OR editing OR enhancing OR enhancement OR modification OR therapy) OR TITLE-ABS-KEY (“Zinc finger” OR “Zinc fingers” OR meganucleases OR TALEN OR “Transcription Activator-Like Effector Nucleases” OR “Transcription Activator Like Effector Nucleases” OR “Clustered Regularly Interspaced Short Palindromic Repeats” OR “CRISPR” OR “gene drive” OR “gene drives”)	708.028
Animals*	TITLE-ABS-KEY (animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR “bush babies” OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR “mugil curema” OR “atlantic cod” OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR “xenopus laevis” OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR wildlife OR cattle OR livestock OR bovine)	9.320.350
Ethics	TITLE-ABS-KEY(moral OR morals OR ethic* OR bioethics*) OR SRCTITLE (moral OR morals OR ethic* OR bioethics*)	459.070
Combined	Genome editing AND animals AND ethics	1869

Filters	**AND NOT index(medline)** Language: English and Dutch; Publication dates: 01-01-2010 – 27-02-2018	**205**

Search strategy for CAB Abstracts

Search string for	*Search string*	*# results*
Genome editing	Exp genetic engineering/ or gene therapy/ or transgenic animals/ OR ((Gene.ti,ab OR genetic.ti,ab OR genome.ti,ab) AND (Engineering.ti,ab OR edit.ti,ab OR editing.ti,ab OR enhancing.ti,ab OR enhancement.ti,ab OR modification.ti,ab OR therapy.ti,ab)) OR Zinc finger.ti,ab OR Zinc fingers.ti,ab OR meganucleases.ti,ab OR TALEN.ti,ab OR Transcription Activator-Like Effector Nucleases.ti,ab OR Transcription Activator Like Effector Nucleases.ti,ab OR Clustered Regularly Interspaced Short Palindromic Repeats.ti,ab OR CRISPR.ti,ab OR gene drive.ti,ab OR gene drives.ti,ab.	61.743
Ethics	Exp ethics/ OR moral values/ OR moral.ti,ab OR morals.ti,ab OR ethic*.ti,ab OR bioethics*.ti,ab OR ethical.ti,ab OR moral.jw OR morals.jn OR ethic*.jn OR bioethics*.jn	19.141
Combined	Genome editing AND ethics	769
Filters	Language: English and Dutch Publication dates: 01-01-2010 – 27-02-2018	**142**

Search strategy for Philosopher's Index

	Search string	*# results*
Genome editing	((Gene.ti,ab OR genetic.ti,ab OR genome.ti,ab) AND (Engineering.ti,ab OR edit.ti,ab OR editing.ti,ab OR enhancing.ti,ab OR enhancement.ti,ab OR modification.ti,ab OR therapy.ti,ab)) OR Zinc finger.ti,ab OR Zinc fingers.ti,ab OR meganucleases.ti,ab OR TALEN.ti,ab OR Transcription Activator-Like Effector Nucleases.ti,ab OR Transcription Activator Like Effector Nucleases.ti,ab OR Clustered Regularly Interspaced Short Palindromic Repeats.ti,ab OR CRISPR.ti,ab OR gene drive .ti,ab OR gene drives.ti,ab	712
Animals*	animals.ti,ab OR animal.ti,ab OR mice.ti,ab OR mus.ti,ab OR mouse.ti,ab OR murine.ti,ab OR woodmouse.ti,ab OR rats.ti,ab OR rat.ti,ab OR murinae.ti,ab OR muridae.ti,ab OR cottonrat.ti,ab OR cottonrats.ti,ab OR hamster.ti,ab OR hamsters.ti,ab OR cricetinae.ti,ab OR rodentia.ti,ab OR rodent.ti,ab OR rodents.ti,ab OR pigs.ti,ab OR pig.ti,ab OR swine.ti,ab OR swines.ti,ab OR piglets.ti,ab OR piglet.ti,ab OR boar.ti,ab OR boars.ti,ab OR "sus scrofa".ti,ab OR ferrets.ti,ab OR ferret.ti,ab OR polecat.ti,ab OR polecats.ti,ab OR "mustela putorius".ti,ab OR "guinea pigs".ti,ab OR "guinea pig".ti,ab OR cavia.ti,ab OR callithrix.ti,ab OR marmoset.ti,ab OR marmosets.ti,ab OR cebuella.ti,ab OR hapale.ti,ab OR octodon.ti,ab OR chinchilla.ti,ab OR chinchillas.ti,ab OR gerbillinae.ti,ab OR gerbil.ti,ab OR gerbils.ti,ab OR jird.ti,ab OR jirds.ti,ab OR merione.ti,ab OR meriones.ti,ab OR rabbits.ti,ab OR rabbit.ti,ab OR hares.ti,ab OR hare.ti,ab OR diptera.ti,ab OR flies.ti,ab OR fly.ti,ab OR dipteral.ti,ab OR drosphila.ti,ab OR drosophilidae.ti,ab OR cats.ti,ab OR cat.ti,ab OR carus.ti,ab OR felis.ti,ab OR nematoda.ti,ab OR nematode.ti,ab OR nematoda.ti,ab OR nematode.ti,ab OR nematodes.ti,ab OR sipunculida.ti,ab OR dogs.ti,ab OR dog.ti,ab OR canine.ti,ab OR canines.ti,ab OR canis.ti,ab OR sheep.ti,ab OR sheeps.ti,ab OR mouflon.ti,ab OR mouflons.ti,ab OR ovis.ti,ab OR goats.ti,ab OR goat.ti,ab OR capra.ti,ab OR capras.ti,ab OR rupicapra.ti,ab OR chamois.ti,ab OR haplorhini.ti,ab OR monkey.ti,ab OR monkeys.ti,ab OR anthropoidea.ti,ab OR anthropoids.ti,ab OR saguinus.ti,ab OR tamarin.ti,ab OR tamarins.ti,ab OR leontopithecus.ti,ab OR hominidae.ti,ab OR ape.ti,ab OR apes.ti,ab OR	12.815

	pan.ti,ab OR paniscus.ti,ab OR "pan paniscus".ti,ab OR bonobo.ti,ab OR bonobos.ti,ab OR troglodytes.ti,ab OR "pan troglodytes".ti,ab OR gibbon.ti,ab OR gibbons.ti,ab OR siamang.ti,ab OR siamangs.ti,ab OR nomascus.ti,ab OR symphalangus.ti,ab OR chimpanzee.ti,ab OR chimpanzees.ti,ab OR prosimians.ti,ab OR "bush baby".ti,ab OR prosimian.ti,ab OR bush babies.ti,ab OR galagos.ti,ab OR galago.ti,ab OR pongidae.ti,ab OR gorilla.ti,ab OR gorillas.ti,ab OR pongo.ti,ab OR pygmaeus.ti,ab OR "pongo pygmaeus".ti,ab OR orangutans.ti,ab OR pygmaeus.ti,ab OR lemur.ti,ab OR lemurs.ti,ab OR lemuridae.ti,ab OR horse.ti,ab OR horses.ti,ab OR pongo.ti,ab OR equus.ti,ab OR cow.ti,ab OR calf.ti,ab OR bull.ti,ab OR chicken.ti,ab OR chickens.ti,ab OR gallus.ti,ab OR quail.ti,ab OR bird.ti,ab OR birds.ti,ab OR quails.ti,ab OR poultry.ti,ab OR poultries.ti,ab OR fowl.ti,ab OR fowls.ti,ab OR reptile.ti,ab OR reptilia.ti,ab OR reptiles.ti,ab OR snakes.ti,ab OR snake.ti,ab OR lizard.ti,ab OR lizards.ti,ab OR alligator.ti,ab OR alligators.ti,ab OR crocodile.ti,ab OR crocodiles.ti,ab OR turtle.ti,ab OR turtles.ti,ab OR amphibian.ti,ab OR amphibians.ti,ab OR amphibia.ti,ab OR frog.ti,ab OR frogs.ti,ab OR bombina.ti,ab OR salientia.ti,ab OR toad.ti,ab OR toads.ti,ab OR "epidalea calamita".ti,ab OR salamander.ti,ab OR salamanders.ti,ab OR eel.ti,ab OR eels.ti,ab OR fish.ti,ab OR fishes.ti,ab OR pisces.ti,ab OR catfish.ti,ab OR catfishes.ti,ab OR siluriformes.ti,ab OR arius.ti,ab OR heteropneustes.ti,ab OR sheatfish.ti,ab OR perch.ti,ab OR perches.ti,ab OR percidae.ti,ab OR perca.ti,ab OR trout.ti,ab OR trouts.ti,ab OR char.ti,ab OR chars.ti,ab OR salvelinus.ti,ab OR "fathead minnow".ti,ab OR minnow.ti,ab OR cyprinidae.ti,ab OR carps.ti,ab OR carp.ti,ab OR zebrafish.ti,ab OR zebrafishes.ti,ab OR goldfish.ti,ab OR goldfishes.ti,ab OR guppy.ti,ab OR guppies.ti,ab OR chub.ti,ab OR chubs.ti,ab OR tinca.ti,ab OR barbels.ti,ab OR barbus.ti,ab OR pimephales.ti,ab OR promelas.ti,ab OR "poecilia reticulata".ti,ab OR mullet.ti,ab OR mullets.ti,ab OR seahorse.ti,ab OR seahorses.ti,ab OR mugil curema.ti,ab OR atlantic cod.ti,ab OR shark.ti,ab OR sharks.ti,ab OR catshark.ti,ab OR anguilla.ti,ab OR salmonid.ti,ab OR salmonids.ti,ab OR whitefish.ti,ab OR whitefishes.ti,ab OR salmon.ti,ab OR salmons.ti,ab OR sole.ti,ab OR solea.ti,ab OR "sea lamprey".ti,ab OR lamprey.ti,ab OR lampreys.ti,ab OR pumpkinseed.ti,ab OR sunfish.ti,ab OR sunfishes.ti,ab OR tilapia.ti,ab OR tilapias.ti,ab OR turbot.ti,ab OR turbots.ti,ab OR flatfish.ti,ab OR flatfishes.ti,ab OR sciuridae.ti,ab OR squirrel.ti,ab OR squirrels.ti,ab OR chipmunk.ti,ab OR chipmunks.ti,ab OR suslik.ti,ab OR susliks.ti,ab OR vole.ti,ab OR voles.ti,ab OR lemming.ti,ab OR lemmings.ti,ab OR muskrat.ti,ab OR muskrats.ti,ab OR lemmus.ti,ab OR otter.ti,ab OR otters.ti,ab OR marten.ti,ab OR martens.ti,ab OR martes.ti,ab OR weasel.ti,ab OR badger.ti,ab OR badgers.ti,ab OR ermine.ti,ab OR mink.ti,ab OR minks.ti,ab OR sable.ti,ab OR sables.ti,ab OR gulo.ti,ab OR gulos.ti,ab OR wolverine.ti,ab OR wolverines.ti,ab OR minks.ti,ab OR mustela.ti,ab OR llama.ti,ab OR llamas.ti,ab OR alpaca.ti,ab OR alpacas.ti,ab OR camelid.ti,ab OR camelids.ti,ab OR guanaco.ti,ab OR guanacos.ti,ab OR chiroptera.ti,ab OR chiropteras.ti,ab OR bat.ti,ab OR bats.ti,ab OR fox.ti,ab OR foxes.ti,ab OR iguana.ti,ab OR iguanas.ti,ab OR xenopus laevis.ti,ab OR parakeet.ti,ab OR parakeets.ti,ab OR parrot.ti,ab OR parrots.ti,ab OR donkey.ti,ab OR donkeys.ti,ab OR mule.ti,ab OR mules.ti,ab OR zebra.ti,ab OR zebras.ti,ab OR shrew.ti,ab OR shrews.ti,ab OR bison.ti,ab OR bisons.ti,ab OR buffalo.ti,ab OR buffaloes.ti,ab OR deer.ti,ab OR deers.ti,ab OR bear.ti,ab OR bears.ti,ab OR panda.ti,ab OR pandas.ti,ab OR "wild hog".ti,ab OR "wild boar".ti,ab OR fitchew.ti,ab OR fitch.ti,ab OR beaver.ti,ab OR beavers.ti,ab OR jerboa.ti,ab OR jerboas.ti,ab OR capybara.ti,ab OR capybaras.ti,ab OR wildlife.ti,ab OR cattle.ti,ab OR livestock.ti,ab OR bovine.ti,ab	
Combined	Genome editing AND animals	76
Filters	Language: English and Dutch Publication dates: 01-01-2010 – 10-04-2018	**21**

***** The search string for 'animals' was adapted from Hooijmans, Tillema, Leenaars & Ritskes-Hoitinga [17].

Supplementary table 2: Data extraction sheet

General information	
Authors, country & background author	
Full reference	
Which technology?	
Which application?	
Scope?	*E.g. only animals / also other species (plants/humans) mentioned in the paper? If only animals, specific animals mentioned?*
Aim(s)/general conclusion drawn	

Data extraction			
Narrow reasons mentioned	**Page no.**	**Theme**	**Other comments**
1. …			
2. …			
Etc. …			