Joint INRA–CIRAD–IFREMER
Ethics Advisory Committee

OPINION 12

ON THE use of genome-editing technologies in animals

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Ethics Advisory Committee

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President of INRA
President of CIRAD
President of IFREMER

For the attention of:

The President of the Joint INRA–CIRAD–IFREMER Ethics Advisory Committee

Paris, 4 November 2016

Subject: *Referral to the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee regarding issues raised by new biotechnologies (such as CRISPR-Cas9 genome editing) when used to perform research and develop innovations focused on plant and animal production.*

Dear Committee President,

The scientific community is undergoing a technological revolution driven by novel methodologies that allow researchers to make easy, inexpensive, precise, reliable, and rapid modifications to genomes. Although these techniques are first and foremost powerful research tools that reflect a breakthrough in our ability to engineer and control living organisms, there also exist potentially valuable industrial applications for these new technologies, notably in plant and animal breeding. However, at the same time, society remains focused on the debate surrounding genetically modified organisms (GMOs), polyploid organisms, and mutants.

Among such tools, the best known is the CRISPR-Cas9[1]genome-editing system. Other technologies have recently become available, including knockdown agents that can sterilise farmed fish by inhibiting gene expression or polyinosinic:polycytidylic acid (poly I:C), a synthetic double-stranded RNA analogue that can be injected into farmed fish or oysters to stimulate an antiviral response. Furthermore, the crop sciences have witnessed the emergence of new plant-breeding techniques (NPBTs).

There are diverse environmental, economic, and ethical considerations associated with these new technologies. Their use in plants and animals, and notably in farm animals, raises concerns about the following issues:

(1) the transmissibility and effects of the genes involved, as well as the possibility of irreversible impacts on biodiversity

(2) the risk of environmental damage, especially since certain experiments can only be performed under natural conditions

(3) the lens through which stakeholders—such as industry representatives (e.g., in aquaculture), consumers, and everyday citizens—view these technologies as a result of their use in research contexts

(4) intellectual property rights, particularly when such technologies are used in innovative applications

1 *See the letter of referral to the INSERM Ethics Committee on issues related to the development of this technology*

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Past experiences have shown us that differences in opinion exist among scientists, industrial stakeholders, and advocacy groups (e.g., NGOs) alike. It is thus crucial to encourage broadscale cultural adaptation to the life sciences and to promote debate of the ethical questions being raised, so that these new technologies and any resulting innovations are perceived as societal advances.

To date, two initiatives have begun to address ethical concerns related to new genome-editing technologies: (1) INSERM has elaborated an ethical approach to research utilising the CRISPR-Cas9 system, where the focus has been placed on the tool's therapeutic potential for humans and its ecological impacts on species that negatively affect humans (e.g., "pests" and pathogens) and (2) the French High Council for Biotechnology has examined the effects of the crop biotechnologies (i.e., NPBTs) used to improve plants and, in particular, seeds.

We propose that the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee espouse a complementary approach when considering the diverse ethical issues that arise in research, notably those that involve sectors creating animal-based products for human consumption.
Moreover, given that the Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research issued an opinion on synthetic biology in 2013, it would be ideal to structure the opinion(s) requested here (on genome-editing technologies such as CRISPR-Cas9) in such a way as to complement the opinion on synthetic biology. It is worth noting that the Committee for Ethics and Precautionary Principles in Agricultural Research (COMEPRA), jointly run by INRA and IFREMER from 2003 to 2007, issued two relevant opinions in October 2004: one on the use of biotechnologies in oyster farming and the other on genetically modified plants.

We leave it to the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee to decide whether plants, animals, and micro-organisms should be dealt with separately (i.e., in separate opinions), if this subdivision could facilitate the committee's work. Indeed, while some concerns may be shared, new genome-editing technologies could raise distinct questions depending on the field of application, whether that be crops, farm animals, "pests", or disease vectors. Thus, a first opinion could look at plants (a group for which work in this domain is already well underway). Algae, and perhaps fungi, could come next, laying the foundation for a discussion of genome-editing in animals.

Consequently, we propose that the committee first examine NPBTs, including those based on the CRISPR-Cas9 system. Any ethical issues not already addressed by prior studies could be tackled. Discussion could centre around the technologies themselves; the ways in which they are perceived and promoted by research stakeholders; and the ways in which they can be exploited. It is thus important to examine not only the place of such technologies within the genome-editing toolbox for plants, but also the role of plant improvement itself within the suite of potential strategic pathways for confronting the challenges of the 21st century, namely those related to climate change, the bioeconomy, and biodiversity.

Following its exploration of the above issues, the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee should be able to make concrete recommendations and direct the attention of the three research institutes towards specific points of concern that merit continued monitoring.

Building on this foundation, a more global analysis can be performed that draws upon the synthetic biology and COMEPRA opinions with a view to answering the following questions: To what degree are the previous recommendations still applicable? Which elements should be adjusted and/or further developed? Is there a need for the approaches to be brought up to date? Finally, what type of follow-up to these opinions does the committee recommend?

It would be ideal if the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee could produce an opinion focused on genome-editing in plants within a period of approximately 12–15 months (between now and summer 2017), so that the committee could then immediately begin its work on animal biotechnologies

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and, more specifically, on the precision editing of animal genomes, given the high stakes in this domain.

We are available should you require any additional information, and we greatly appreciate your attention to this matter.

Sincerely yours,

INRA President and CEO	CIRAD President and CEO	IFREMER President and CEO
Philippe Mauguin	Michel Eddi	François Jacq

CC: Christine Charlot, Philippe Feldmann and Philippe Goulletquer

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Opinion Summary

The use of genome-editing technologies in animals

In its 12th opinion, the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee (hereafter, the Committee) focused on the use of targeted genome-editing technologies, such as CRISPR-Cas9, in animals. The Committee continued the line of reflection begun in the opinion on genome editing in plants but shifted its attention to concerns related to farm animals and animals classified as "pests" (hereafter, simply "pests").

Farm animals

The Committee underscored that genome-editing methods help advance knowledge and are both more adaptable and precise than conventional genetics and random mutagenesis techniques. However, given that INRA, CIRAD, and IFREMER perform oriented research, it is important to explore how such knowledge and methods could ultimately be used to improve the welfare and productivity of farm animals.
The Committee expressed that social relevance and acceptability must be considered when choosing which genome-editing tools to apply to farmed species in both terrestrial and aquatic systems. The Committee also emphasised that breeding objectives should include clear benefits for farm animals, consumers, and society. It further recommended that the three research institutes and their research teams improve the accessibility of debates by disseminating high-quality information.

"Animal Pests"

The Committee specifically focused on the gene-drive technology used to control animals classified as pests, especially insect vectors of human diseases. Gene drives are employed to promote the transmission of a given trait via sexual reproduction, with a view to disseminating the trait as quickly as possible within a target population. In most cases, gene-drive technology is used to transmit deleterious traits that can lead to the elimination of local populations or entire species. The Committee examined the potential risks arising from gene drives based on genome editing and explored how such systems may eventually transform chemical and biological practices for controlling animal "pests", including insects. The following conclusion was reached: regardless of whether one is considering ecosystem threats, the potential for displacement, or the possibility that gene drives will exacerbate the very problems they are supposed to solve, risk analysis can only be carried out on a case-by-case basis. Notably, such analyses should evaluate the likelihood that dissemination will be broader than anticipated and that any resulting effects can be reversed.
The Committee highlighted the key factors that can shift the balance among the diverse positive or negative outcomes of gene drives. The Committee also stressed the importance of considering the scientific, ethical, political, and participatory dimensions of this issue in tandem.

Recommendations

Given the significance of the concerns raised, including those of a philosophical and ethical nature, the Committee counselled caution when applying genome editing in animals, particularly because it is difficult to establish firm scientific boundaries and place limits on technology usage. The Committee also developed some specific recommendations for INRA, CIRAD, and IFREMER in the following areas:

- Using genome editing to generate knowledge and targeted research
- Establishing priorities
- Accounting for animal welfare
- Pursuing basic research on gene drives
- Responding to society's need for information

See also: Opinion 11 of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee on New Plant Breeding Techniques

Preamble

Technologies, precautionary measures, and values

INRAE, CIRAD, and IFREMER share a common goal: to conduct oriented research that guides the sustainable use of natural resources by humans. Their joint ethics advisory committee examines and provides recommendations on ethical issues arising from the institutes' projects and practices, work that goes beyond economic and societal objectives. The approach is always consistent, whether the study system is aquatic or terrestrial. The target species is also irrelevant: the Committee lends its attention to animals, plants, and micro-organisms alike, whether the latter are soil dwellers, water dwellers, or symbionts found within plants or animals. In its work, the Committee considers the intrinsic value of its study subjects, weighing their worth to the diverse members of the global population in more than monetary terms. The Committee also maintains that humans should always act with caution and care, striving for environmental sustainability.

Hence, this opinion on the use of genome-editing technologies in animals begins by discussing the welfare of farm animals, legally protected sentient beings. This topic was previously addressed in 2015 by the Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research in its 7th opinion. Here, the Committee emphasises that the above technologies should not be used to adapt animals to horrendous living conditions in order to justify a disregard for their welfare.

In the field of biological control, the CRISPR-Cas9 system can be used to insert genetic constructs at specific sites in the genomes of crop "pests" and organisms that vector human and livestock diseases. The objective is to disseminate a trait within a population, via the sexual reproduction of its members, so that the population is exterminated or rendered harmless. In other words, the success of gene drives relies on the unimpeded spread of artificial genetic modifications. The Committee underscores that little is known about this strategy's effectiveness, its short- and long-term effects, and its impacts at the ecosystem level. The Committee therefore recommends that organisations and researchers espouse the precautionary principle and remain prudent in their adoption of this technology.

However, we have clearly reached a strategic crossroads in our use of biotechnology, given that our mastery of genome-editing techniques allows us to make targeted, precise modifications. It is thus important that researchers at INRA, CIRAD, and IFREMER assimilate and build upon the Committee's guidance. In this spirit, researchers are urged to adopt the following three core values in all their work: 1) complete mastery of their tools; 2) constant reflection on the non-monetary value of practices and programmes (e.g., their value to others); and 3) the prudent implementation of precautionary measures.

Axel Kahn, Committee President

Michel Badré, Committee Vice-President

Opinion on the use of genome-editing technologies in animals

Introduction

As its name implies, this opinion focuses on the use of new genome-editing technologies in animals. It builds upon the foundation laid in the opinion on plant genome-editing techniques[1] but turns its focus to animal production systems, examining current applications of CRISPR-Cas9 and similar tools. The opinion also addresses gene-drive technology, whose use in natural populations is controversial because modifications can spread in an unconstrained manner. The purpose of our work here is therefore to grapple with certain key issues and technological developments characteristic of the 21st century.

This opinion does not call into question genome editing itself. Instead, the objective is to explore the ethical concerns associated with possible applications of CRISPR-Cas9 technology. Whether we are dealing with domesticated or wild animals, genome editing gives rise to many questions that fuel debate, which may then hinder tool deployment.

For example, do limits exist on the genetic modifications that should be allowed in animals? Is it acceptable to use genome editing to adapt farm animals to their living conditions or to improve the welfare of farm animals by altering characteristic species traits? Is it ethical to introduce genes into natural populations, such as insect populations, with the goal of eliminating them? Should CRISPR-Cas9 technology be used for any and all purposes? At what level of uncertainty should a tool's deployment be disallowed?

This opinion does not profess to provide definitive answers to these questions. Instead, the intention is to present diverse perspectives on the use of new genome-editing technologies, discussing how they inform our understanding of the specificities and social relevance of non-human animal species. This text therefore seeks to foster discussion by highlighting some key concerns that INRA, CIRAD, and IFREMER should address when using genome editing for more than just the study of genes, namely when the technology forms the basis for commercial applications to be deployed outside the laboratory.

The opinion is divided into two parts, each focused on one of the major animal groups targeted by potential applications of genome editing: farm animals (II) and "pests" (III), mainly insects. This partitioning naturally arises from the different objectives underlying CRISPR-Cas9 usage in each group. In farm animals, the primary goal of genome-editing applications is to introduce adaptations. In "pests", the goal is to suppress or disarm certain populations (e.g., using pathogens) for any purpose, including to eliminate their negative effects on human health, the economy, and biodiversity.

Other realms of application will certainly emerge as the uses of genome editing expand. For example, the technology might eventually be used in efforts to adapt to climate change[2]. That said, any future applications will remain subject to certain types of more generalised criticism that have already been voiced with regards to genome editing in farm animals and "pests". It is therefore possible to lay the foundation for broader reflection on genome editing while simultaneously focusing on current paradigms for applying the technology.

[1] Joint INRA-CIRAD-IFREMER Ethics Advisory Committee (2018) *Opinion 11 on New Plant Breeding Techniques*

[2] See W. Cornwall "Researchers embrace a radical idea: engineering coral to cope with climate change" *Science* (March 21, 2019); available online at: https://www.sciencemag.org/news/2019/03/researchers-embrace-radical-idea-engineering-coral-cope-climate-change

1 ■ Genome editing in farm animals

Scientific background

Thanks to advances in molecular biology and the development of new tools, it is now relatively easy to sequence the genomes of living organisms. At present, we have characterised the genomes of most farmed species: cows, chickens, pigs, and horses, as well as dogs (for non-agricultural purposes). Analyses of genomic variability have clarified the relationships among different races of farm animals, the factors underlying such differences, and their taxonomic origins. These same analyses have guided the development of breeding strategies that utilise genomics approaches. Indeed, such strategies are routinely used in livestock species of high monetary value, such as cows. Gradually, the genomes of a wider variety of domesticated species have been published. For example, genomes are available for the cat, camel, duck, sheep, goat, salmon, sea bass, tilapia, carp, and oyster. In insects, the first genome to be described was that of the fruit fly, followed by those of the silkworm, various mosquito species, and the tsetse fly. Given this proliferation of genetic and genomic information, there is a range of potential applications for emerging genome-editing technologies.

The scientific basis for genome editing has repeatedly been described in scientific articles, reports written by experts, and media targeting the general public. Indeed, the Committee recently published an opinion on new plant-breeding techniques (NPBTs) in which the basic principles of targeted mutagenesis are summarised[3]. Targeted mutagenesis takes the same form in both plants and animals, although CRISPR-Cas9 is applied differently in animal cells. There may also be differences in the contexts in which the latter technology is employed.

However, the techniques for applying CRISPR-Cas9 in animals are essentially the same as those used to make genetic modifications to plants. Using microinjection, DNA is transferred into embryos via a gene construct that is associated with a suitable vector. In mammals, the embryos are implanted in the uterus of a host that may then give birth to genetically modified offspring. In chickens, alternative techniques are used to modify germ cell precursors, which are then re-injected into the circulatory system of embryos. Microinjection is also the technique employed in fish. Finally, in insects, transposable elements are frequently utilised as vectors. It is important to note that genome-editing techniques vary in efficiency among species.

Over time, the CRISPR-Cas9 system has grown in popularity and is progressively being applied in new species. For example, it is now used in fish, notably in model species such as the zebrafish and medaka as well as in aquaculture species, such as the salmon and tilapia, which have already been a target of transgenesis. Genome editing has also been successfully carried out in amphibians (e.g., frogs), invertebrates (e.g., crabs), crustaceans, coral, sea urchins, and sea anemones. Some studies have applied CRISPR-Cas9 in algae and micro-algae. In short, it appears that all living organisms, including plants, can undergo targeted mutagenesis via genome-editing technologies, and, chief among them, the CRISPR-Cas9 system. Also, compared to other techniques, genome editing has the advantage of allowing multiple genes to be modified in tandem.

Summary of non-biomedical applications of genome editing in farmed animals

Genome-editing technologies are first and foremost a powerful tool for making discoveries in the field of functional genomics. For example, the research network focused on CRISPR in molluscs and bivalves (CIBI) uses CRISPR-Cas9 to study gene regulation under different environmental conditions, with the objective of clarifying the phenomena behind resistance and/or mortality.

CRISPR-Cas9 targeted mutagenesis is much more adaptable and allows greater precision than conventional genetic techniques or random mutagenesis.

It is important to note that, although targeted mutagenesis is routinely used in many laboratories to study genes, research at INRA, CIRAD, and IFREMER is driven by the broader potential of scientific discoveries, as the primary objective of these three institutes is to develop applied solutions.

Genome editing is thus destined to become a tool for improving the traits[4], of farm animals in both terrestrial and aquatic production systems. In agricultural systems, it could be used to enhance both animal welfare and agricultural productivity. For example, it could be exploited to boost the feed conversion ratio and other performance-related traits; help animals cope with farming conditions; and increase disease resistance[5]. It is also possible to envision genetic modifications that reduce the environmental impacts of animal farming[6]. Table I summarises the different types of applications currently being developed for terrestrial and marine farming systems[7]. Applications focused on improving animal health seek to mitigate the increased susceptibility of animals that results from farming conditions.

[3] Joint INRA-CIRAD-IFREMER Advisory Ethics Committee (2018) *Opinion no.11 on New Plant Breeding Techniques for the genetic improvement of plants*: see p. 15–16.

[4] West and W.W. Gill "Genome editing in large animals" *Journal of Equine Veterinary Science* 41.1 (2016):1–6, 2.

[5] West and W.W. Gill "Genome editing in large animals" *Journal of Equine Veterinary Science* 41.1 (2016):1–6, 2.

[6] Researchers have investigated the possibility of reducing nitrate and phosphate levels in chicken and pig manure. A recent study has shown that methane emissions in ruminants have a genetic basis. Reducing these emissions is an important part of efforts to minimise the environmental impacts of cattle production. See J. Wallace et al. "A heritable subset of the core rumen microbiome dictates dairy cow productivity and emissions" *Science Advances* eaav8391 5.7 (2019).

Table I - Overview of agricultural applications of genome editing	
IMPROVING HEALTH	Research has validated a mastitis control strategy based on the production of human lysozyme and lactoferrin in the mammary gland; these two proteins have antimicrobial properties and are naturally secreted in saliva or milk. Transgenic pigs show a strong immune response (and, therefore, resistance) to porcine reproductive and respiratory syndrome[8]. Research has shown that creating transgenic poultry resistant to avian influenza can serve as a strategy for controlling the disease's spread within farms or local regions.
MODIFYING TRAITS RELATED TO ANIMAL REARING	A "hornless" gene has been introduced into valuable dairy cattle breeds to produce calves that naturally lack horns. A transgenic line of chickens has been produced in which individuals carry a gene encoding a fluorescent protein on the Z sex chromosome; this approach prevents the mass slaughter of male chicks, which have no commercial value for the egg-laying and broiler production industries.
MODIFYING TRAITS RELATED TO ANIMAL PRODUCTION	Researchers have turned off the genes encoding the proteins that cause allergies to cow's milk and eggs. In pigs, the gene encoding myostatin (mstn) has been inactivated. Myostatin is a protein that inhibits muscle growth. Pigs without it are "double-muscled" and thus produce more meat[9]. The dnd gene has been inactivated in salmon, which leads to the production of phenotypically normal females and males whose gonads contain no germ cells. As a result, they are sterile and thus cannot introduce genes into wild populations if they escape.

The use of modern genome-editing technologies is a new page in the history of animal domestication. Here, we present the major stages of the latter, the historical progression that has led to current methods of genetic improvement. The objective is not to assert that genome editing can be justified by an appeal to "tradition", but rather to highlight that the use of this tool falls squarely in line with other actions taken by humans to domesticate animals. Indeed, techniques for bringing about genetic improvements in animals have taken different forms over the ages, shaped by the state of knowledge at a given moment. Genome editing is simply another chapter in the story of domestication. Viewed through this lens, the purpose of these methods is quite old, even if the methods themselves are extremely novel.

For this reason, it is impossible to discuss genome editing without addressing animal domestication. Please note that the latter is not being called into question. Instead, we feel compelled to underscore that CRISPR-Cas9 technology has a wide range of possible uses and hence elicits questions that extend beyond the decision to use genome editing. Indeed, the broader issue is the control exerted by humans over the acquisition, loss, and/or development of new, heritable morphological, physiological, and/or behavioural traits in animals, regardless of the precise means used to achieve this end. These questions provoke reflection on the limits of genetic modification in animals and encourage us to establish boundaries. Thus, while exploring genome editing, we naturally end up considering the history of artificial selection in animals.

Key stages in the history of animal domestication

Humans have been domesticating animals via artificial selection for more than 100,000 years[10]. In fact, from the moment they encountered other animal species, humans have sought to shape the latter's traits and behaviours to obtain benefits for themselves.

Dogs provide a clear example of this process-they were originally domesticated wolves that lived alongside groups of humans. New archaeological evidence continues to push the origin of this relationship further

7 See A. Ducos *et al.* "Modifications ciblées des génomes: apports et impacts pour les espèces d'élevage» *INRA Productions animales* 30.1 (2017): 3–18, 8 et seq.; J. West and W.W. Gill "Genome editing in large animals" *Journal of Equine Veterinary Science* 41.1 (2016): 1–6, 4. Also see the table put together by Sovovà and colleagues, which includes biomedical applications in farm animals: T. Svovà et al. "Genome editing with engineered nucleases in economically important animals and plants: state of the art in research pipeline" *Current Issues in Molecular Biology* 21 (2017): 41–62, 48.

8 The genomes of pigs have also been modified to enhance resistance to African swine fever (S.A. Bhat *et al.* "Advances in genome editing for improved animal breeding: a review" *Veterinary World* [2017]: 1361–1366, 1361; S. Reardon "The CRISPR zoo—birds and bees are just the beginning for a burgeoning technology" *Nature* 531 [March 10, 2016]: 160–163, 161).

9 Furthermore, the mstn gene has been inactivated in cattle, sheep, goats, and fish (i.e., the yellow catfish) (T. Svovà et al. "Genome editing with engineered nucleases in economically important animals and plants: state of the art in research pipeline" *Current Issues in Molecular Biology* 21 [2017]: 41–62, 49).

10 R. Delort (1984) *Les animaux ont une histoire*, Paris, Éditions du Seuil.

back in time, revealing that our history of coexistence is much longer than suspected. It dates back tens of thousands of years, and the long-standing ties between humans and dogs have given rise to a vast diversity of dog breeds, whose size, coat colour, coat texture, head morphology, and personality differ dramatically. In certain modern breeds, these changes have been accompanied by significant effects on animal health and well-being.

Although humans began applying artificial selection to animals during the Palaeolithic, domestication played an essential role during the Neolithic, the most recent period of prehistory and the age during which agriculture emerged. From this point on, domestication efforts were greatly intensified to obtain animal breeds that could provide specific services, including the production of milk, meat, and eggs for consumption or the production of fibres, furs, and skins for clothing. Animals were also bred to transport people and heavy loads. That said, only a relatively small number of animal species have been domesticated overall. For the most part, they are what we call livestock-animals such as horses, camels, donkeys, cows, pigs, sheep, and goats. There are also poultry, namely chickens, ducks, and turkeys. The silkworm is a prime example of a domesticated insect.

Of all these species, the dog has experienced the most selective pressure. Next come the cow, the pig, and the chicken, which are primary sources of food for many human populations. The domestication process was unique for each of these species. For example, it is hypothesised that modern pigs resulted from a cross between wild boars domesticated in Europe and other wild boars domesticated in China. The ancestor of the cow was probably native to central Asia. As for the chicken, it likely originated in south-eastern China. However, in all cases, the wild ancestral populations have since disappeared. Domesticated animals have experienced constant selection for certain traits related to behaviour, docility, morphological characteristics (e.g., limb size and shape), and production capacity.

Fish, crustaceans, and molluscs long avoided domestication largely thanks to the wealth of fisheries. The peoples of Ancient China created the first fish farms (~1100 BCE) and, notably, developed systems for breeding carp; their techniques gradually spread throughout Asia. Around the same period, other ancient civilizations developed basic pond-based aquaculture methods. For example, the Greeks and Romans built complex fishponds, called vivariae piscinae, to generate a steady supply of fish and shellfish for consumption. Pond-based fish farming became more and more common over the centuries. Great changes took place around the time of the Industrial Revolution. Natural resources began to decline as both environmental conditions deteriorated and marine fisheries were overexploited via mechanised fishing vessels. Modern aquaculture was born in the 19th century, in 1852, when a team of French scientists developed a system for fertilising trout eggs. Since then, the number of fish hatcheries used for restocking purposes has rapidly grown across the globe. Early on, in the 1880s, marine aquaculture technologies were honed thanks to the emergence of a specialised scientific community, who helped manage the overexploited fisheries. Various programmes focusing on artificial genetic selection and domestication were launched in the 1930s but were utilised only sporadically. In the 1970s and 1980s, a more global framework for aquaculture began to be established, helped along by the founding of such institutions as the Food and Agriculture Organisation of the United Nations (FAO). In the decades that followed, aquaculture systems became thoroughly modern, incorporating new technologies (e.g., offshore cages, novel feed types) and expanding the diversity of farm species. The stated aim of modern aquaculture is to respond to the increased demand for seafood products, whose supplies are dwindling because of fishery declines. At present, the FAO believes that food security challenges can be tackled by tapping the large potential for genetic improvement in aquaculture systems. In this context, it is worth pointing out that the domestication of marine species has lagged far behind the domestication of terrestrial species: 45% of cultivated marine species do not differ from their wild counterparts. Only 10% of the world's aquaculture production is generated by organisms resulting from artificial selection[11].

When genetics became a distinct scientific discipline at the end of the 19th century, programmes were developed in which farm animals were subject to intense genetic improvement. They yielded dramatic results. For example, the volume of milk produced per cow increased tenfold within a century; chickens can now transform vegetable proteins into animal proteins with almost 100% efficiency; and a sow can produce up to thirty piglets per year. These are all examples of key traits subject to breeder focus in the 20th century because of their effects on yield and profitability. Genetic improvements were also made to traits related to disease resistance and product quality. Compared to traditional methodologies, molecular approaches have boosted the efficiency and precision of genetic selection. For certain farm species, it is now common practice to cryopreserve sperm, eggs, and embryos. In some contexts, cloning is used to produce

11 This historical background is based on the following sources: C. Nash (2011) *The history of aquaculture*, Wiley-Blackwell; FAO (2019) *The state of the world's aquatic genetic resources for food and agriculture assessments*, Rome, FAO Commission.

sport horses. Finally, although technically possible, the production of transgenic animals is extremely limited. At present, the only farmed transgenic animal is a line of salmon, which has been approved for human consumption in Canada. Commercial production of genetically modified salmon could begin in Canada in late 2020[12].

Based on this brief history of domestication, it appears that humans have continually sought to adapt animals to suit their own purposes; this process has included modifying animals to better fit within farming systems. In other words, artificial selection has always been driven by human needs. This observation is not necessarily a criticism-it simply clarifies that domestication represents a form of domination. Indeed, humans could have followed a different trajectory in their domestication efforts. The path taken by domestication has been shaped by numerous value-based choices made by breeders, and it can be said that artificial selection took some questionable turns well before the advent of industrial agriculture and science-based approaches. It must be stated that, over the long history of the artificial selection, including the modern era of genetic improvements, animals have not always experienced even-handed outcomes. This situation has sparked criticism and has led people to envision other possible trajectories. For example, there has been much debate about animal welfare in production systems.

Emergence of animal welfare as a concern within industrial production and breeding systems

Over the last fifty years, society has gradually become more aware of the conditions experienced by farm animals in intensive production systems. Following the publication of books such as *Animal Machines* by Ruth Harrison and *Animal Liberation* by Peter Singer[13], people began criticising the treatment of farm animals, denouncing the pain, suffering, and distress being caused to them. Indeed, it has become clear to everyone that industrial farming systems have only been able to increase production and decrease prices at the expense of animal welfare. The contemporary animal welfare movement also resulted in the creation of an impressive corpus of ethical and philosophical texts, which laid the groundwork for a new branch of ethics, animal ethics, that examines the moral obligations of humans towards animals.

This field of knowledge is fed by several currents of thought, both reformist and abolitionist in nature, and it has provided the intellectual basis for mounting an extremely effective and convincing social critique of industrial animal production systems. It has helped promote the passage of legislation in several countries that recognises animals as living, sentient beings and has propelled the adoption of welfare standards for farm animals.

In this regard, we should mention the *European Convention for the protection of animals kept for farming purposes* (ETS No. 87), adopted by the Council of Europe in 1976, which established common standards to protect farm animals from unnecessary harm or suffering stemming from housing, feeding, or transportation conditions. Twelve years later, the European Union passed the C*ouncil Directive 98/58/EC of 20 July 1998* concerning the protection of animals kept for farming purposes (OJ L 221 of 8.8.1998), a model piece of legislation that laid down common baseline standards for protecting livestock as well as specific regulations concerning certain farmed species and farming practices[14].

However, legal strategies for protecting farmed species will not satisfy all animal welfare advocates, particularly not members of the abolitionist movement. Such laws do, however, affirm that improved animal welfare is a socially recognised objective that has been validated by our political institutions. Indeed, the Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research (hereafter, the INRA-CIRAD Ethics Committee) recommended in its 2015 opinion on animal welfare (*Avis sur le bien-être des animaux d'élevage*)[15] that "animal welfare must be a key factor and target of animal husbandry".

Accounting for animal welfare

To date, breeding programmes have primarily focused on improving traits related to productivity, sometimes to the detriment of farm animals[16].

However, modern genetic improvements to farm animal traits have illustrated that artificial selection for higher productivity can simultaneously improve animal welfare in intensive farming systems. This result can clearly be seen in changes aimed at improving herd health. Thus, farm animal traits can be modified without trading off welfare for productivity; both can be improved in tandem. There are several CRISPR-Cas9 applications that align with this objective. One example is the introduction of the hornless gene into the genomes of dairy cattle and certain meat breeds, such as the Limousine, to produce calves that will thus be spared the painful dehorning process. CRISPR-Cas9 can also be employed to eliminate the "sex odour"

12 M. Ménard "Feu vert à l'élevage de saumon transgéniques" *La Terre de Chez Nous* (April 19, 2019); available online [in French] at https://www.laterre.ca/actualites/alimentation/feu-vert-a-lelevage-de-saumons-transgeniques

13 Harrison, R. 1964. *Animal Machines: An Expose of "Factory Farming" and Its Dangers to the Public.* New York: Ballantine Books; Singer, P. 1975. *Animal Liberation. A New Ethics of Our Treatment of Animals.* New York: Harper Collins.

14 See S. Brels (2017) *Le droit du bien-être animal dans le monde. Évolution et universalisation*, Paris, L'Harmattan: 167–175.

15 Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research (2015) *Opinion 7 on Farm Animal Welfare*

16 R.B. D'Eath *et al.*, "Breeding for behavioural change in farm animals: practical, economic and ethical considerations", (2010) 19(S) *Animal Welfare* 17-27, 21; Michael Greger, "Transgenesis in animal agriculture: addressing animal health and welfare concerns", (2011) 24 *Journal of Agricultural and Environmental Ethics* 451-472, 452-457.

of male pigs, which should help put an end to physical castration practices that cause suffering in piglets. Thus, genome editing has applications that could concurrently boost animal welfare and productivity. Such applications should be promoted because their underlying rationale is sound.

Indeed, breeding objectives are gradually shifting to better account for animal welfare[17]. These efforts must continue and even be intensified to more effectively protect animal welfare[18].

However, what exactly is meant by "animal welfare"? According to the standard definition, animal welfare comprises the following three elements:

- Biological functioning, which means animals do not experience illness or injury and have access to adequate levels of resources such as food, food supplements, water, and shelter
- Emotional state, which means animals live in conditions that promote a positive subjective experience from both an emotional and cognitive perspective
- Ability to express natural behaviours, which means that animals can engage in certain normal behaviours, which may differ depending on species-specific needs and capacities, social interactions, and environmental enrichment[19].

In general, experts and interprofessional organisations of farmers focus on biological functioning, emotional state, and their interactions when developing opinions or designing studies[20]. Good animal welfare is thus equated to the presence of an "acceptable" physiological status and the absence of any suffering. Consequently, if "improvements" (e.g., increased growth rate or productivity) introduced via targeted mutagenesis were found to cause adverse health effects, such as incapacitating pain or a predisposition to injury, they would be prohibited based on the above criterion.

There is more controversy surrounding the third element of animal welfare, which is the ability to express natural behaviours. For ethologists, good animal welfare exists when an individual can express the natural behaviours intrinsic to its species or when it can fulfil its desires[21]. Thus, if we subscribe to this principle for protecting animal welfare, CRISPR-Cas9 technology should not be used when it reduces an animal's natural capacity for living. However, this perspective is subject to debate.

People have proposed that allowing animals to live more natural lives should be an important criterion when designing farming systems. However, when this principle is applied in the context of genetic improvement, it leads to unacceptable conclusions, highlighting its inadequacy in these circumstances.

The specific case of altering the natural behaviour of farm animals

Conditions in industrial animal production systems are known to impede many natural behaviours. The result is often disorders characterised by high levels of aggression that are usually resolved via painful mutilation procedures. This state of affairs has been criticised by those adhering to the ethological definition of animal welfare, who support efforts to create farming systems that better account for natural behavioural needs.

As early as 1999, research conducted on a strain of congenitally blind chickens showed that such animals were less likely to exhibit signs of stress or agitation under overcrowded conditions. It was concluded that blindness in chickens could help solve some of the animal welfare challenges encountered in laying hen operations, notably the aggressive behaviour displayed by hens kept in cages (e.g., battery cages)[22]. Thus, the possibility was raised of eliminating certain natural functions, behaviours, capacities, and/or characteristics of animals because natural traits were seen as contributing to poor levels of animal welfare in intensive production systems. A similar rationale underlies efforts to breed featherless (i.e., "naked") chickens, that are better able to withstand farming conditions in warm climates. Such measures certainly have the potential to improve animal welfare under intensive farming conditions. However, should such conditions be acceptable? Should such changes to the natural lives of animals be allowed[23]?

There is widespread opposition to any genetic improvements aimed at changing the natural behaviours, needs, abilities, and/or characteristics of farm animals[24]. Framed by the ethological definition of animal welfare, this opposition is based on the presupposition that the different farmed species, subspecies, and breeds have a specific "nature" that human beings must not alter. Accordingly, it is asserted that livestock have the right to "remain intact" or, to employ the terms more commonly used by ethics experts, farm animals have a right to bodily integrity.

Apart from the fact that this demand is ambiguous and largely fails to hold up under critical analysis, it is also problematic because it grants farm animals such a degree of protection that it almost amounts to a condemnation of domestication. Indeed, it is crucial to recall that the behaviours, needs, abilities,

[17] See H.-W. Cheng "Breeding of tomorrow's chickens to improve well-being" *Poultry Science 89* (2010): 805–819.

[18] B.A. Rollin (1995) *The Frankenstein syndrome–ethical and social issues in the genetic engineering of animals*, New York, Cambridge University Press.

[19] D. Fraser "Science, values, and animal welfare: exploring the 'inextricable connection" *Animal Welfare* 4 (1995): 103-117; D. Fraser "Understanding animal welfare" *Acta Veterinaria Scandinavica* 50 (2008): S1

[20] R. Larrère "Justifications éthiques des préoccupations concernant le bien-être animal" *INRA Productions animales* 20.1 (2007): 11–16, 12.

[21] R. Larrère "Justifications éthiques des préoccupations concernant le bien-être animal" *INRA Productions animales* 20.1 (2007): 11–16, 12–13.

[22] P.R. Sandoe et al. "Staying good while playing God-The ethics of breeding farm animals" *Animal Welfare* 8 (1999): 313–328.

[23] It is possible that our current understanding of genes is insufficient, making it impossible to develop genome-editing applications of this type. However, it is likely that these or similar scenarios will one day become reality, assuming that we eventually acquire the requisite knowledge and that genome editing allows the simultaneous modification of several genes.

[24] For an overview and critique of the various positions taken, see R. De Vries "Genetic engineering and the integrity of animals" *Journal of Agricultural and Environmental Ethics* 19 (2006): 469–493; P.B. Thompson "The opposite of human enhancement: nanotechnology and the blind chicken problem" *Nanoethics 2* (2008): 305–316; P.B. Thompson "Why using genetics to address welfare may not be a good idea" *Poultry Science* 89 (2010): 814–821; M. Schultz-Bergin "The dignity of diminished animals: species norms and engineering to improve welfare" *Ethical Theory and Moral Practice* 20 (2017): 843–856.

and characteristics of farm animals are already quite different from those of their closest wild relatives. The "nature" of these animals has already been greatly shaped by the sustained interactions that took place between their ancestors and human communities. Given the control and artificial selection applied by humans over time, these animals no longer have much in common with their wild predecessors. As a result, it seems pointless to preserve the integrity of a specific "nature" that cannot even be clearly defined.

Thus, although intellectually attractive, the opposition to any genetic improvement of the natural behaviours, needs, capacities, and/or characteristics of farm animals misses the mark. It is not the practice of domestication itself that should be called into question, but rather the way it is implemented during animal breeding. If defined too broadly, the obligation to respect the bodily integrity of farm animals leaves us without any points of reference even as we face dramatic increases in the power of genome-editing technologies.

For example, if tomorrow we were able to combine our understanding of genes with genome editing to help relieve the suffering experienced by hundreds of millions of livestock, via modifications to their "natures", should we reject this option? As currently formulated, this question contains a logical fallacy, that is, we are faced with a false dilemma. Indeed, the choice is not binary: we do not need to choose between industrial production systems based on animals whose natural responses have been genetically inactivated (i.e., animals incapable of suffering) and industrial production systems based on animals whose natural responses are "intact" (i.e., animals capable of suffering). There is an alternative. Namely, we can modify the systems themselves to better respect the "nature", or bodily integrity, of farm animals[25].

It is important to note that a demonstrated preference for biotechnological solutions might indicate that there exists a profound ethical void when it comes to animal welfare, which underscores the need for us to re-evaluate our moral conduct[26]. However, we cannot dismiss out of hand that biotechnological approaches could be justified under certain sets of circumstances, considering that any proposed modifications to production systems themselves will likely face significant political and economic obstacles.

The Committee recognises that the ethical issues discussed herein are of a complexity that cannot be fully addressed in this text and that they must be debated at the societal level. Clearly, it is unacceptable to cite an improvement in animal welfare as a justification for employing genome editing in production systems if the objective is to allow abuses that inherently subject living animals to degrading conditions. However, it is difficult to provide a definitive judgment on the matter that would be universally valid in all potential situations. Although the Committee favours the choice to modify conditions in production systems, decisions must be made on a case-by-case basis given the push and pull among three key considerations-improving productivity, enhancing animal welfare, and respecting animal integrity. It is important to consider the specifics of each potential application, including consumer preferences. Because such applications can be troubling to some, it is necessary to arrive at a consensus of perspectives by fostering discussions that involve diverse stakeholders. In our opinion, this approach should help ensure that the issue receives social recognition and public support. In the case of aquaculture species, this concern is amplified because we must consider both the issue of animal welfare as well as the issue of containment. Notably, how do we limit the geographical and reproductive spread of fish or molluscs with modified genomes? Indeed, it is difficult, or even impossible, to fully contain aquatic species farmed in open, natural environments, a fact that has led to frequent criticism of the aquaculture industry. Escapees from fish farms pose a major problem because of their potential impacts on the health and diversity of wild fisheries. In the context described in this opinion, there is the additional worrisome uncertainty that arises from knowing that it is impossible to fully and effectively contain marine farm animals that have undergone genome editing[27].

Social acceptability

We must learn from the controversy that surrounded the development and commercialisation of genetically modified (GM) crops. More specifically, we must consider social relevance and acceptability when selecting the genome-editing tools to be applied in terrestrial and aquatic farm animals. This statement presupposes that the three research institutes behind this Committee, and their research teams, will foster awareness and debate by disseminating high-quality information.

To avoid the recent mistakes that occurred when plant transgenic technologies were rolled out, members of the scientific community and stakeholders in the breeding industry should move away from CRISPR-Cas9-based applications, whose sole beneficiaries are animal farmers. We are not rejecting the idea of economic profitability: it is important to recognise that farm animal breeding is a commercial activity that bolsters another commercial activity, farm animal production. However, genome-editing applications should

25 25See A. Ferrari "Animal disenhancement for animal welfare: the apparent philosophical conundrums and the real exploitation of animals. A response to Thompson and Palmer" *Nanoethics* 6 (2012): 65–75; R. Larrère "Justifications éthiques des préoccupations concernant le bien-être animal" *INRA Productions animales* 20.1 (2007): 11–16, 13.

26 P.B. Thompson "The opposite of human enhancement: nanotechnology and the blind chicken problem" *Nanoethics* 2 (2008): 305–316, 314–315.

27 See L. Létourneau (2011) "Aquaculture Ethics in the Biotechnology Century", G. Fletcher and M.L. Rise (eds.) *Aquaculture Biotechnology*, Ames IA, Wiley-Blackwell: 345–353; L.-E. Pigeon and L. Létourneau "The leading Canadian NGOs' discourse on fish farming: from ecocentric intuitions to biocentric solutions" *Journal of Agricultural and Environmental Ethics* 27.5 (2014): 767–785.

also furnish benefits to other parties, including farm animals (e.g., improved health), everyday consumers (e.g., hypoallergenic food products), and society as a whole (e.g., environmental protection). In this way, it is possible to establish a clean break, or at least a degree of distancing, with plant genome-editing technologies.

That said, we need to expect that controversy will arise over any applications of genome editing in farm animals and over the commercialisation of the resulting animals/animal products, regardless of the intended purpose. Believing that this biotechnology can be serenely deployed at the societal scale would require forgetting the persistent and active resistance to genetically modified organisms (GMOs) that we have witnessed. This spirit of resistance has been channelled into the debate regarding NPBTs, reviving discussion about GMOs[28].

To counter this opposition, we could adopt an argument based on semantics, putting forth the reasoning that genome-editing technologies do not always involve inserting novel genes created in the lab into the DNA of a regular organism (thus producing a GMO). Indeed, genome editing can be used to simply inactivate or modify genes, such that the resulting organism is not, strictly speaking, a GMO. However, it is clear from the debate within the European Union regarding the legal status of organisms and products created via new genome-editing technologies that this semantic argument will not suffice. Indeed, in its July 25, 2018 judgment, the European Court of Justice ruled that organisms whose genomes have been edited using recombinant-DNA-based techniques will be treated as GMOs under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

Consequently, we need to expect that the social relevance and acceptability of GMOs will remain important forces when seeking to commercialise products derived from animals with edited genomes because, under current European law, such organisms will be equated to GMOs by numerous advocacy groups and consumers. Unless genome editing is broadly and uniformly adopted by all the players in the animal industry, which seems highly unlikely, choosing to produce livestock with modified genomes or processing/selling products from such animals could have serious socio-economic consequences. In other words, exploiting biotechnological innovations is not a guarantee of commercial success[29]. That said, little is currently known about the social perception of genome editing and its potential applications[30].

2 ■ Genome editing in animals classified as pests

Scientific background

A specific genome-editing approach is taken in the case of animal “pests”, a group that includes insects. Indeed, targeted mutagenesis can be employed to develop what it is called gene drives. First proposed several years ago[31], this controversial technology seeks to "force" (i.e., propel with a ~100% success rate) gene transmission via sexual reproduction. Genome editing has expanded the range of possibilities for this general approach by allowing gene sequences to be targeted with great precision. In addition, the CRISPR-Cas9 system can be used to promote the preferential transmission of a trait to the members of a given population over the course of normal reproduction. Gene-drive technology thus ensures that the target population assimilates a given trait that, under normal circumstances, would never establish itself so quickly or spontaneously appear via natural selection. Gene drives thus increase our control over animal populations in nature, allowing us to take the future of a species in our own hands without having to wait for the outcomes of a "genetic lottery".

As previously discussed in multiple media and fora, there are two main visions for how gene drives can be applied in animal “pests”. First, they are viewed as a tool for spreading deleterious traits (e.g., sterility or lethality) that can eliminate entire target populations or species. Second, they are seen as a strategy for neutralising the direct and/or indirect pathogenicity of “pest” species. The best-known gene drive projects have been proposed to genetically modify mosquitoes, which vector human diseases like malaria[32]. Some people have also proposed using gene drives in the fight against invasive species that threaten native flora and fauna (e.g., rats, possums, or stray cats)[33]. In such contexts, they are presented as a strategy for controlling the presence of undesirable animals. The proposed use of gene-drive technology thus gives rise to two key concerns. First, we must reflect on how gene drives fit within the broader suite of control techniques deployed against animal “pests”. By comparing the risks and benefits associated with different techniques, we can identify the most appropriate tools for a given situation. Second, we must address a more philosophical concern that is related to how we perceive and deal with species that we deem to be undesirable. In short, it is essential to ponder the nature of our relationships with other species.

28 See Joint INRA-CIRAD-IFREMER Advisory Ethics Committee (2018) *Opinion no. 11 on New Plant Breeding Techniques*, Paris, INRA, CIRAD, and IFREMER.

29 A. Bruce "Genome-edited animals: learning from GM crops?" *Transgenic Research* 26 (2017): 385–398.

30 A. Shriver and E. McConnachie "Genetically modifying livestock for improved welfare: a path forward" *Journal of Agricultural and Environmental Ethics* 31 (2018): 161–180, 168.

31 See D. Brossard et al. "Promises and perils of gene drives: navigating the communication of complex, post-normal science" *Proceedings of the National Academy of Sciences* 116.16 (April 16, 2019): 7692–7697, 7692.

32 See S. Reardon "The CRISPR zoo-birds and bees are just the beginning for a burgeoning technology" *Nature* 531 (March 10, 2016): 160–163, 162. This example has been discussed extensively by several committees of experts, including the Scientific Committee within the High Council for Biotechnology. *Avis concernant l’utilisation de moustiques génétiquement modifiés dans le cadre de la lutte antivectorielle*. May 31, 2017. For a review of the different techniques used to control insects that transmit malaria, see A. Burt, M. Coulibaly, A. Crisanti, A. Diabate, and J.K. Kayondo “Gene drive to reduce malaria transmission in sub-Saharan Africa” *Journal of Responsible Innovation* 5 (January 24, 2018): S66 S80. A cohort of genetically modified mosquitoes was released for the first time in Burkina Faso on July 1, 2019: S. Douce “Au Burkina, un premier lâcher de moustiques génétiquement modifiés crée la polémique” *Le Monde* (July 4, 2019); available online at: https://www.lemonde.fr/afrique/article/2019/07/04/au-burkina-un-premier-lacher-de-moustiques-genetiquement-modifies-cree-la-polemique_5485432_3212.html

33 See K. M. Esvelt and N. J. Gemmell "Conservation demands safe gene drive" *PLoS Biology* e2003850 15.11 (2017); Royal Society Te Aparangi Gene Editing Panel (2017) The use of gene editing to create gene drives for pest control in New Zealand, Royal Society Te Aparangi.

Phrased another way, we need to ask ourselves how gene drives are transforming traditional control practices. More specifically, does gene-drive technology hone our ability to control animal populations in nature or does it increase the likelihood that we will cause irreparable damage to the natural environment? As we exploit new genome-editing technologies to create gene drives, we are forced to confront the broader ethical and philosophical issues that underlie the techniques we employ to control wild animal species. These issues have acquired additional weight as modern human societies are grappling with their vulnerability to the threats posed by climate change.

Consequently, the public will strongly question any actions that introduce artificial changes into the natural environment, seeking guarantees that no irreversible harm will occur. Can gene drives meet this requirement? To be able to answer this question, we must first revisit traditional chemical and biological control strategies and examine their strengths and weaknesses.

Role of gene drives in efforts to control animal "pests"

Humans have long sought to control wild animal species by various means. The primary objective has always been to provoke the decline or disappearance of populations with negative effects on the economy (e.g., because of impacts on crop farming, livestock farming, or fisheries), human health (e.g., because of pathogen transmission by insects), and/or the ecosystem (e.g., because of damage caused by invasive species). In tandem with ancient practices such as hunting, trapping, and the use of nets or spikes (e.g., against pigeons), efforts to control undesirable animal species have changed the landscape. During the 19th century, public health campaigns led numerous wetlands to be drained with a view to eradicating "pests". Today, some of these wetlands are undergoing restoration because of their rich biodiversity. Over the course of the 20th century, chemical and biological techniques were added to the arsenal of control methods used against insects and other animals classified as pests. Sulphur and pyrethrum have a long history as pesticides. The modern petrochemical industry began contributing many synthetic pesticides as agriculture become more industrialised. Biological control is an old idea[34] that was popularised towards the end of the 19th century via books written for the general public that provided lists of "useful insects". In the 20th century, researchers added to the suite of classical biological control methods by developing new techniques focused on sterilisation. The emergence of gene drives is another chapter in the history of human beings attempting to exert control over the environment. To properly understand this new technology, it is imperative to understand the broader context in which it is being deployed.

In chemical control, pesticides are used to fight "pests". In industrial agricultural systems, chemical control is largely synonymous with the use of synthetic pesticides. The latter have led to increased yields but have nonetheless progressively acquired a bad reputation.

Notably, conventional synthetic pesticides have, in some cases, caused significant damage to the environment, biodiversity, and farmer/farmworker health. These effects have been well documented and, after decades of conflict with the major players of the petrochemical industry, pesticide use is increasingly regulated[35]. Another issue is that the effectiveness of synthetic pesticides declines over time because the target species develop resistance. To deal with this challenge, replacement products or technologies must be developed, resulting in a frantic race for novel solutions that consumes vast quantities of energy and capital. In light of these concerns, gene drives may appear to be "cleaner", more reliable alternatives to chemical control strategies.

Biological control is also promoted as an alternative to chemical control. Because it exerts its influence via antagonistic relationships among living organisms, its effects on ecosystems would appear to be less pronounced. Traditional biological control methods eliminate unwanted insects and other animals by exploiting the presence of predators, competitors, micro-parasites, or macro-parasites. All biological control techniques are applied to populations found in nature. Briefly, there are two general types of techniques.

The first involves introducing a natural predator into a given environment. It is frequently used to control crop "pests" or to curb the expansion of populations that pose a threat to ecosystem dynamics. An example of the former is the introduction of ladybugs to control aphids, and an example of the latter is the introduction of wolves *(Canis lupus*) into Yellowstone Park to limit the proliferation of elk.

In contrast to chemical control strategies, this first biological control technique exploits a natural relationship between two living species to achieve an outcome desired by humans. Although this technique is presented as a tool that is largely local in scope, nothing prevents such introductions from escaping the control of those responsible for initiating them; indeed, interactions among species within ecosystems can never be perfectly controlled.

34 Ancient Egyptians used domesticated cats to control the rodents that ravaged grain supplies.

35 Pesticides can act as both a remedy and a poison, a dual function for which the ancient Greeks had a term: *pharmakon*. DDT illustrates this concept quite well. Widely used during the second half of the 20th century, DDT was criticised for the damage it caused to human health and the environment. However, malaria has been on the rise since DDT was banned.

The second type of technique exploits the mechanism of self-regulation, where some members of a given population are used to control others. A common method that has been used for decades involves introducing sterilised males into a population of their conspecifics. Most frequently, ionising radiation is employed as the sterilisation technique. These sterilised males then compete with wild males. Alternatively, it is possible to introduce individuals that carry lethal genes or that are infected with pathogens. Another option is to sterilise females of one species via the introduction of males from another species (e.g., the satyrisation of tsetse fly species). Finally, sometimes genetic modifications are elicited using a toxic protein (i.e., TIS 3.0)-males transmit the protein to females, causing them to die.

From an ecological point of view, techniques based on autocidal control can destroy populations by subverting natural reproductive mechanisms. To ensure the strategy's efficacy, the procedure is repeated over many generations within the target population. The effects of such techniques are thus constrained in space and time. As a result, they are unlikely to have irreversible effects and have been deemed to be relatively controllable.

Gene drives are similar to systems based on autocidal control because they seek to transmit a specific mutation. However, they have a more rapid rate of action because they do not rely on natural genetic crosses occurring over time. Moreover, gene drives, like the CRISPR-Cas9 technology they exploit, are biologically inspired to a certain extent. Indeed, their success is based on a mechanism similar to the so-called "selfish" genes, which increases the chances that the desired trait will be propagated, even if the survival of individual organisms declines as a result[36].

Compared to autocidal control systems, the clear advantage of gene drives is that they are self-propagating: genetic interventions need not be repeated over multiple generations. While gene drives provide clear advantages, much about them remains uncertain, including the risks they may pose.

Evaluating risks when knowledge is lacking

The unknown risks associated with gene drives are at the heart of many reports and articles evaluating the possible use of this technology in insects and other animal species. Most of these texts underscore the same key challenge: we simply lack information on the potential effects of artificially introduced mutations. This situation drastically limits our ability to carry out reliable risk analyses37. Furthermore, this gap in knowledge exists within a complex web of other issues that require clarification and that run from the molecular scale to the ecosystem scale[38].

For obvious reasons, research examining risks is more likely to be conducted in the laboratory, in confined spaces, or using modelling. It may be impossible to obtain the data needed for proper risk assessments from field experiments, which largely focus on insects and especially mosquitoes. Indeed, such studies are more often interested in evaluating a narrow definition of gene-drive efficiency as opposed to the technology's potential ecological effects[39].

As a result, the current consensus is that risk analysis should be performed on a case-by-case basis[40]. Indeed, each population is part of a unique network of relationships that are shaped by geography, climate, species endemicity, and even anthropogenic parameters, such as the regional structure of agricultural systems. It is therefore impossible to come up with generalised conclusions based on the results for a given gene drive within a given species. It is necessary to situate each potential application within its unique context, while simultaneously evaluating the risk of dissemination at a broader scale.

Could well-funded research programmes help fill these gaps in knowledge? It is important to acknowledge that, regardless of the level of research investment, some uncertainty will always remain. In some cases, the degree of uncertainty may be quite high[41]. That said, there are certain recurrent research themes: the risk of ecosystem imbalance and the likelihood that we will displace or exacerbate the problems that a gene drive was supposed to solve. It is thus clear that we must expand the breadth of our discussions on gene drive effectiveness and the reversibility of any adverse impacts[42].

Ecosystem risks: a vast field left to explore

We must remember that, in most cases, gene drives applied to natural populations of insects and other animals aim to limit or even eradicate species. We should be seriously concerned about possible disruptions to ecosystem balance and the subsequent chain reactions. At the same time, there is considerable uncertainty about potential outcomes.

What could happen if a link disappears from a trophic chain? Could this event threaten the persistence of certain animal populations? Could other populations end up proliferating as a result? These questions

36 N. Rode, A. Estoup, and D. Bourguet, Centre for Biology and the Management of Populations (CBGP), UMR INRA-CIRAD-IFREMER Montpellier SupAgro, July 9, 2018 hearing with the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee.

37 For example, as noted by the U.S. National Academies of Sciences, Engineering, and Medicine (p. 3): "There are considerable gaps in knowledge regarding a gene drive's effectiveness, both on the target organism and the environment, over time and across diverse genetic backgrounds. It is also essential to consider how gene drives will propagate throughout a population and affect not only the target species, but its entire ecological community." Quote from the following reference: Committee on *Gene Drive Research in Non-Human Organisms (2016) Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values*, Washington DC, National Academies Press.

38 See for example: K.R. Hayes et al. "Identifying and detecting potentially adverse ecological outcomes associated with the release of gene-drive modified organisms" *Journal of Responsible Innovation* 5 (2018): S139 58 or J. Kuzma et al. "A roadmap for gene drives: using institutional analysis and development to frame research needs and governance in a systems context" *Journal of Responsible Innovation* 5 (2018): S13 39, who writes (p. 10): "Not only do population and genetic characteristics matter for the impacts of gene drives, but so do biophysical attributes of weather and climate, geographies, and surrounding ecosystems. A significant challenge involves complexity in weather and climate and their effects on the spread of gene drives, reproduction of the host, and distribution of the host. Even if a field trial can be confined, it is unlikely to capture the range of physical conditions under which gene drives will be deployed and spread. These conditions will impact interactions with and potential risks to other species, such as predators and prey."

39 P.L.J. Rüdelsheim and G. Smets (2018) *Gene drives. Experience with gene drive systems that may inform an environmental risk assessment.* Bilthoven, COGEM.

40 See for example: Committee on Gene Drive Research in Non-Human Organisms (Ibid); Rüdelsheim et al. 2018 (Ibid); J. Baltzegar et al. "Anticipating complexity in the deployment of gene drive insects in agriculture" *Journal of Responsible Innovation* 5 (2018): S81 97; A. Burt et al. "Gene drive to reduce malaria transmission in sub-Saharan Africa" *Journal of Responsible Innovation* 5 (2018): S66 80; Royal Society (2018) Gene drive research-why it matters, London.

41 For example, as the Norwegian Biotechnology Advisory Board affirmed in its *Statement on gene drives* (2017): "In complex ecosystems, theconsequences of releasing a gene drive could be both so-called known unknowns (expected or foreseeable) and unknown unknowns (unexpected or unforeseeable)."

42 For a summary, see M. Scudellari "Self-destructing mosquitoes and sterilized rodents: the

already came up in the discussion of chemical and biological control methods. However, they are relevant in any situation where a species disappears, regardless of the cause. It is worthwhile pointing out that we are currently witnessing a massive and involuntary extinction of species. That said, the resistance that has been building and that has solidified around gene drives is highly reminiscent of the reaction to GMOs and other innovations stemming from genetic engineering. It is therefore important to acknowledge this sustained opposition when reflecting on the social acceptability of these applications.

Many of those reflecting on these issues make a clear distinction between endemic and invasive species. They hypothesise that, a priori, the disappearance of an invasive species is likely to cause less harm than that of an endemic species[43]. It should also be noted that some "pest" species have local relatives, which means that their disappearance may not much affect their predators.

The results of past eradication efforts are sometimes evoked to temper potential concerns. For example, campaigns to eliminate lice and fleas in Europe and the screwworm in the United States suggest that the disappearance of these groups has had minimal effects[44]. It remains unclear, however, whether these insects have truly vanished.

Imbalance can also occur because of the horizontal transmission of genes among species. While experts recognise that such transmission is possible, it is thought to be extremely infrequent and, even if it were to happen, it is unlikely to have functional consequences[45]. In contrast, vertical transmission could possibly occur among species capable of interbreeding. However, preventive measures can be taken. To counter this phenomenon, research can identify insertion sites that are specific to the target species or subspecies.

The risk of displacing and exacerbating pre-existing problems

In addition to ecosystem risks, there is also the risk that a pathogen could move from one species to another[46] or that a species deprived of its capacity to transmit one pathogen could end up transmitting another[47]. Various countermeasures have been proposed, such as building transgenes that would only be functional when inserted at a specific site and inactive anywhere else or creating combined systems in which sequences are inserted into several different genes, making it highly unlikely that natural mutations would arise that could circumvent the gene drive[48].

With regards to resistance, it is widely acknowledged that its appearance is inevitable. However, the problem of resistance is not unique to gene drives because it is also a concern for chemical control strategies[49]. In the case of gene drives, the development of resistance is unlikely to have catastrophic effects: in the worst-case scenario, there will be a reversion to the state that existed prior to the technology's usage. In this respect, gene drives display a unique and paradoxical feature: while the emergence of resistance may initially seem to constrain the long-term effectiveness of gene drives, some view it as a guarantee - ensuring that a species will not disappear completely, an outcome seen as desirable[50]. Thus, far from representing a disadvantage, the appearance of resistance can minimise the risks of gene drives, serving as a safety net and guaranteeing reversibility[51].

Effectiveness and reversibility

The lack of clarity regarding the limits of gene drives is not confined to the question of resistance. We see the same type of ambiguity in discussions about the technology's effectiveness. On the one hand, gene drives are presented as highly effective. On the other hand, when this level of effectiveness elicits concern - notably because the potential exists to eliminate entire species or to drastically reduce their genetic variability - the response is to assert that gene drives are only moderately effective. Indeed, for gene drives to be successful, various factors must operate correctly and a certain proportion of modified individuals must be released into the target population. Such requirements may initially appear to be disadvantageous. However, viewed from another angle, they are reassuring because they act as brakes on a technology that could escape our control[52].

Additionally, it has been argued that, even if gene drives elude these constraints, a second gene drive could be used to undo any negative effects. However, others have pointed out that such a response is largely theoretical at present. They also note that, even if the second gene drive were successful, it too could escape our control. Finally, they underscore that genetic reversibility is not the same as impact reversibility: the damage caused by the first gene drive might be impossible to repair[53].

We rediscover the same double-edged argument with regards to specificity[54]: gene drives make it possible to target a species or even a subpopulation with almost surgical precision, which should purportedly

promise of gene drives" *Nature* 571 (2019): 160–162.

43 See Committee on *Gene Drive Research in Non-Human Organisms (2016) Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values*, Washington DC, National Academies; R.F. Medina "Gene drives and the management of agricultural pests" *Journal of Responsible Innovation* 5 (2018): S255 62.

44 Norwegian Biotechnology Advisory Board (Ibid).

45 Scientific Committee of the High Council for Biotechnology (2017) A*vis en réponse à la saisine du 12 octobre 2015 concernant l'utilisation de moustiques génétiquement modifiés dans le cadre de la lutte antivectorielle*, Paris, High Council for Biotechnology.

46 Scientific Committee of the High Council for Biotechnology (Ibid)

47 Committee on Gene Drive Research in Non-Human Organisms (Ibid)

48 H. Godfray, J. Charles, A. North, and A. Burt "How driving endonuclease genes can be used to combat pests and disease vectors" *BMC Biology* 15 (2017): 81.

49 Both the *Plasmodium* parasites that cause malaria and their mosquito vectors have acquired resistance to commonly used insecticides, especially those applied to netting.

50 B. Borel "When evolution fights back against genetic engineering" The Atlantic (July 3, 2018). Available online at https://www.theatlantic.com/science/archive/2016/09/gene-drives/499574/

51 Unckless and colleagues have stated that resistance plays a positive role in such contexts, serving as a guarantee that the eradication of malaria will remain limited to one area. See R.L. Unckless, A.G. Clark, and P.W. Messer "Evolution of resistance against CRISPR/Cas9 gene drive" *Genetics* 205.2 (2017): 827–841.

52 P.L.J. Rüdelsheim and G. Smets (2018) *Gene drives. Experience with gene drive systems that may inform an environmental risk assessment.* Bilthoven, COGEM

53 R.F. Medina "Gene drives and the management of agricultural pests" J*ournal of Responsible Innovation* 5 (2018): S255 62; Committee on *Gene Drive Research in Non-Human Organisms (2016) Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values*, Washington DC, National Academies; INSERM Ethics Committee (2016) *Saisine concernant les questions liées au développement de la technologie CRISPR. Note du comité d'éthique.* Paris, INSERM.

54 Scientific Committee of the High Council for Biotechnology (2017) *Avis en réponse à la saisine du 12 octobre 2015 concernant l'utilisation de moustiques génétiquement modifiés dans le cadre de la lutte antivectorielle*, Paris, High Council for Biotechnology.

result in limited ecosystem disruption because there is no horizontal gene transfer. At the same time, this specificity represents a serious limitation because it means that the procedure would need to be repeated as many times as there are specific targets (e.g., species, subspecies).

All these characteristics of gene drives are supposed to ensure that genetic material will not spread in an uncontrolled manner. Indeed, even if the technology is applied to an island population, there is always a chance that one or more modified individuals will end up on some sort of transport vessel and then contaminate populations in other parts of the world[55]. This concern is particularly acute when gene drives are used in insects. That said, the mechanisms at play are relatively weak and should protect against the unlimited dissemination of modified genes. Significant efforts are required to launch and maintain functional gene drives. It should be possible to limit intergenerational transmission by adopting certain approaches, such as targeting highly specific sequences or employing a daisy-chain system. In other words, it is possible to adjust a gene drive's setting from self-sustaining to self-limiting[56].

Public health and socio-economic risks

To conclude this overview of the risks associated with gene drives, it is important to note that some people have drawn attention to consequences that stem not from the technology itself, but rather from its successful application.

Indeed, while some applications seek to eliminate diseases by blocking their transmission to humans, successfully accomplishing this goal could result in increased health risks to human populations over the longer term: new outbreaks could occur after the loss of population-level immunity[57]. Furthermore, Mitchell and colleagues[58], who are economists, have highlighted some of the socio-economic risks that could result from the "success" of gene drives, namely reduced mortality leading to increased demand for available resources, which could then result in environmental effects and social tension related to the potentially inequitable redistribution of resources. However, the same would be true for any of the scourges faced by humanity!

Of course, people will not be convinced of the credibility of such risks through simple statements underscoring their existence. Risks must be characterised and quantified using the criteria and methods regularly employed by the relevant fields of study. Indeed, remaining at the stage of conjecture does little to help identify and assess risks, which should be the greater goal. Furthermore, the process of evaluating risks must be objective and cannot ignore any issues that might be displeasing or disturbing.

As with any ethical dilemma, a trade-off will exist between multiple positive and negative outcomes that will be shaped by the different priorities established by different societies from among competing sets of values. This discussion highlights why is it is important to fully consider the choices presented to us by gene drives - or by any other genome-editing technology. As part of the process, it is also essential to address any gaps in science, ethics, politics, or participation.

In addition to risk analysis, philosophical perspectives will also inform the social relevance and acceptability of gene drive technology. Although seemingly antithetical to the latter, such schools of thought actually argue in favour of a precautionary approach on the basis of environmental concerns.

Philosophical perspectives on the application of gene drives in animal "pests"

The use of gene-drive technology is generally justified by citing the practical purposes it achieves. A common justification is that gene drives benefit humans, whether by protecting human health, the economy, or biological diversity. Insofar as human needs and interests are considered to have priority over other concerns, it is legitimate to establish a utilitarian relationship with the environment. Thus, using any means possible to fight species classified as pests is not only valid but can also be viewed as part of a moral responsibility to serve humanity.

However, it remains crucial to view any situation with a critical eye because technical solutions frequently fail to holistically address problems; while they may alleviate symptoms in the immediate term, their inadequacy quickly becomes apparent. For example, some people have envisioned exploiting gene drives to suppress acquired pesticide resistance in insects. This application has been criticised on the grounds that it encourages continued reliance on an agricultural model that is ecologically problematic and that reinforces the agricultural industry's dependence on technological tools[59]. More generally, this anthropocentric perspective can be seen as granting humans a superior metaphysical status, prompting them to readily sacrifice other living organisms to solve their problems[60].

55 C.M. Leitschuh et al. "Developing gene-drive technologies to eradicate invasive rodents from islands" *Journal of Responsible Innovation* 5 (2018): S121 38..

56 Scientific Committee of the High Council for Biotechnology (Ibid)

57 Scientific Committee of the High Council for Biotechnology (Ibid)

58 P.D. Mitchell, Z. Brown, and N. McRoberts "Economic issues to consider for gene drives" *Journal of Responsible Innovation* 5 (2018): S180 202.

However, ecological concerns need not be absent from this vision of the relationship between humans and nature. It is often the case that protecting the environment serves major human interests, primarily because environmental imbalance can have a negative effect on humans. Thus, our fundamental obligation to care for nature can be expressed in the form of humanistic environmentalism.

This movement calls on humans to change their behaviour, to eschew certain acts, and to preserve the natural environment as a way of defending their own best interests. The logical connection is as follows: if the exploitation or overexploitation of nature results in negative consequences, human beings are also harming themselves. We foster environmental consciousness when we realise that damaging the environment jeopardises our ability to satisfy our needs and protect our present and future interests.

When great uncertainty surrounds the possible ecological impacts of a technology, as in the case of gene drives, it makes sense to espouse the precautionary principle. This principle posits that, in situations of scientific uncertainty, risk prevention measures should be adopted, notably when serious or irreversible damage could result. As we have shown, far too many unresolved issues remain when it comes to gene-drive technology, which means we should avoid launching ourselves headlong into application development.

Similar conclusions can be drawn based on ecocentrism, which attributes intrinsic value to nature or, more specifically, to components of natural systems, such as ecosystems, regions, environments, habitats, or, stated another way, biotic communities and their abiotic features. Employing this lens demands revisiting the very concept of a "pest species". Indeed, because all populations in a given environment interact in dynamic ways, specific elements that humans perceive as harmful could actually benefit the entire system upon which human beings rely. As a result, the optimal response extends beyond simply defending direct human interests. It also encompasses the complete ecosystems upon which the future of humanity ultimately depends.

One of the first proponents of ecocentrism was the forester Aldo Leopold, who underscored the importance of preserving the integrity, stability, and beauty of natural areas[61]. Such ideas encourage us to view nature as a dynamic entity, whose individual and collective members cooperate and thrive based on natural cycles and processes. John Baird Callicot explained the foundation of this approach and its practical significance[62].

However, he did not provide any specific recommendations related to genetic engineering, so let us simply retain the key message that ecosystem functions should not be disrupted. This injunction is compatible with efforts to control insects and other animals classified as pests by humans. However, it also invites us to use caution in the case of gene-drive technology, given that its potential ecological impacts remain undefined.

In addition, this perspective promotes respect for the continuity of species and the beauty of historical biotic communities[63], calling for humans to consider the evolutionary trajectories of species, which extend beyond current, short-term, and longer-term human interests. It encourages us to explore ways of reducing anthropogenic impacts on living organisms to allow a certain degree of evolutionary spontaneity for all living creatures.

59 R.F. Medina "Gene drives and the management of agricultural pests" *Journal of Responsible Innovation* 5 (2018): S255 62.; P.D. Mitchell, Z. Brown, and N. McRoberts "Economic issues to consider for gene drives" *Journal of Responsible Innovatio*n 5 (2018): S180 202.

60 Critiques of technological solutions have both philosophical and practical components. Philosophically, the question arises: is it moral to hold the world view that humans have the right to dominate nature? From a practical perspective, criticism of technological solutions in the agricultural sciences mainly takes aim at the paradigm of productivity, which is seen as completely failing to consider alternative ways of framing agricultural issues. It highlights the fact that the solutions proposed do not solve the problems at hand and, indeed, often create new ones. It also asserts that technological solutions serve to maintain the current system instead of seeking better alternatives. Thus, from this point of view, technological solutions are the conservative choice. See D. Scott "The technological fix criticisms and the agricultural biotechnology debate" *Journal of Agricultural and Environmental Ethics* 24 (2011): 207–226.

61 A. Leopold (2000) *Sand County Almanac*, Paris, Flammarion.

62 J.B. Callicott (1999) *Beyond the land ethic*, Albany NY, State University of New York Press; J.B. Callicott (1989) In *defense of the land ethic*, Albany NY, State University of New York Press.

63 This concern, sometimes referred to as"evocentrism", has become central to debates on policies aiming to preserve biodiversity and, more specifically, now underpins the notion of ecological services (see F. Sarrazin and J. Lecomte "*Evolution in the Anthropocene*" Science 351 (February 26, 2016): 922–923; J. Lecomte and F. Sarrazin "Repenser l'innovation dans une perspective évocentrée de la biodiversité" *Biofutur* 378 (July-August 2016): 92.

3 ■ Recommendations

Establishing proper boundaries is a challenge that we immediately face when exploring the potential applications of genome editing in farm animals and animal "pests", especially insects. While CRISPR-Cas9 technology primarily poses a potential risk to animal welfare, gene drives can threaten ecosystem resilience. However, many questions, much uncertainty, and much ambiguity remain when it comes to this technology's possible impacts. For this reason, the opposition to gene drives is far less nuanced and far more technical. Indeed, it is the very idea of gene drives that is ardently rejected by its critics, not the specific ways in which it could be applied.

That said, both types of genome-editing technologies—targeted mutagenesis in farm animals and gene drives in "pest" species—raise important issues that must be carefully examined before we go ahead with research and development (R&D) programmes focused on potential applications. We thus recommend proceeding with caution when applying genome editing in animal species.

We also propose some specific recommendations that account for the purposes of these techniques and the difficulties inherent to any related research and development. When examining research options, it will be necessary to confront a key challenge shared by both technology types: establishing limits on research and technology usage.

RECOMMENDATION 1 - Using genome editing to generate knowledge and targeted research

Targeted mutagenesis is an excellent tool for advancing knowledge in functional genomics. It is thus important that researchers from the three institutes master genome-editing technologies and understand their limitations, both when conducting research in different animal species and when developing targeted research that will lead to commercial products.

RECOMMENDATION 2 - Establishing priorities

Before any work is initiated, it is necessary to consider the social relevance and acceptability of the proposed targeted and applied research. To this end, the Committee recommends that the three institutes submit for review any project using targeted mutagenesis that could potentially spark debate. The projects should be sent to a multidisciplinary committee comprising a variety of individuals: researchers and stakeholders from the fields concerned as well members of civil society (e.g., consumer associations and environmental advocacy groups).

In all cases, continued attention should be directed towards alternative techniques that could address identified needs and challenges without employing genetic modifications.

RECOMMENDATION 3 - Accounting for animal welfare

Livestock breeding objectives are already gradually shifting to better improve animal welfare[64]. Such efforts must be maintained and even intensified, as recommended by the Joint INRA-CIRAD Ethics Advisory Committee in its 2015 opinion[65]:

> "The ethics committee recommends that work to genetically improve farm animals should not focus solely on traits that influence productivity. Instead, it should also examine traits that affect animal welfare because such research could enhance understanding of the behaviour of farm animals, which are sentient beings. Regardless of the approach used, breeding must neither diminish animal welfare nor affect an animal's capacity to experience well-being" (pg. 21)

The Committee agrees with this recommendation and reaffirms its importance in this opinion. We want to particularly stress that when genome-editing technologies are used to improve farm animal production, they should not compromise animal welfare, regardless of any other considerations. We maintain that all three institutes must make a commitment to preserving animal welfare that guides all work on genetic improvements in farm animals. Furthermore, we feel that the sole aim of such improvements should not be to increase productivity or adapt animals to farming conditions.

RECOMMENDATION 4 - Pursuing basic research on gene drives

Gene-drive technology is radical for two reasons: there is no guarantee that conventional biosecurity measures can constrain the spread of its effects, and it has the potential to directly affect the fate of entire populations. While we can acknowledge that this technology holds promise, additional research must be undertaken to clarify the risks it could pose to ecosystems before it is applied to natural populations. At present, the use of this technology is justified exclusively in the case of severe threats

[64] See for example H.-W. Cheng "Breeding of tomorrow's chickens to improve well-being" *Poultry Science* 89 (2010): 805–819.

[65] See Joint INRA-CIRAD Ethics Advisory Committee for Agricultural Research (2015) *Avis 7 sur le bien-être des animaux d'élevage.*

to human, animal, or plant health. We should only perform field studies if we have clear evidence that they will not place ecological equilibria at risk, especially those in non-target populations.

When a gene drive is being considered for use as a control technique, it is crucial to make an informed decision based on comparisons with other "pest" control methods.

RECOMMENDATION 5 - Responding to society's need for information

The three institutes and their research teams must provide the public with the best possible information available about ongoing studies and their purposes, while accepting that said information will not necessarily lead to social acceptance. This responsibility is paramount and is part of the institutes' obligation to promote transparency and public debate.

PEOPLE WITH WHOM THE COMMITTEE MET

Meetings on July 9, 2018 in Paris with three INRA researchers in the Plant Health and Environment Division from the Centre for Biology and Management of Populations (CBGP) -a joint research unit of INRA-CIRAD-IRD-Montpellier SupAgro. The meetings focused on control methods for "pest" populations and, more particularly, on the issues and risks associated with gene drives.

- Denis BOURGUET, INRA, research director
- Arnaud ESTOUP, INRA, research director
- Nicolas RODE, a post-doctoral researcher at the time (funding: Mediterranean Centre for the Environment and Biodiversity [Labex CeMEB]) and now an INRA research scientist

Meetings during the Committee's visit to the Île-de-France - Jouy-en-Josas INRA Research Centre on September 17, 2018 with researchers from the Animal Physiology and Livestock Systems (PHASE), Animal Genetics (GA), and Animal Health (SA) Divisions (see the schedule for the day provided below)

Meetings on January 21, 2019 in Paris with one CIRAD researcher and two IFREMER researchers

- Jean-François BAROILLIER, CIRAD, Fish Evolution Research Team at the Institute of Evolutionary Sciences of Montpellier (ISEM), a joint research unit with which CIRAD fish researchers are affiliated (Description, Exploitation, and Preservation of Fish Biodiversity)
- Benjamin MORGA, IFREMER, pathologist and researcher at the Laboratory for Marine Mollusc Genetics and Pathology (La Tremblade)
- Rossana SUSSARELLU, ecotoxicologist and researcher at the Biogeochemistry and Ecotoxicology Research Unit in Nantes.

The latter two individuals jointly coordinate the internal network for CRISPR-Cas9 research in oysters.

Meetings during the Committee's visit to the Val-de-Loire - Tours - Nouzilly INRA Research Centre on March 18, 2019 with researchers from the PHASE, GA, SA Divisions (see the schedule for the day provided below)

COMMITTEE WORKING GROUP WHO WROTE THIS OPINION, DISCUSSED ITS CONTENTS DURING PLENARY SESSIONS, AND ADOPTED IT IN ITS FINAL FORM JULY 8, 2019

- Lyne LÉTOURNEAU (reporter)
- Madeleine AKRICH
- Bernadette BENSAUDE-VINCENT
- Jean-Louis BRESSON
- Pere PUIGDOMENECH

The composition of the full committee and the backgrounds of its members are provided in Appendix 3.

APPENDICES

Ile-de-France - Jouy-en-Josas INRA Research Centre
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Meeting of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee at the Ile-de-France - Jouy-en-Josas INRA Research Centre

Monday, September 17, 2018

Objectives of the visit

After having published a first opinion on NPBTs and, more specifically, genome-editing technologies in plants (e.g., CRISPR-Cas9), the Committee has entered the second phase of work mentioned in the referral. The Committee is now focusing on the use of new genome-editing technologies in animals. It intends to learn about INRA research in this area (e.g., its driving factors, type, purpose, and ethical issues).

Axel Kahn, President of the Committee, plans to hold two committee meetings focused on these topics at two INRA research centres:

- One will be held at the Île-de-France - Jouy-en-Josas INRA Research Centre on September 17, 2018. The Committee will meet with researchers whose work sheds light on the driving factors and potential uses of gene-based and/or genome-based selection in animals (based on criteria related to productivity, quality, health, robustness, etc.) as well as on genome-editing strategies and techniques, using examples from the range of species concerned.
- The other will be held at the Val-de-Loire - Tours - Nouzilly INRA Research Centre during the first half of 2019. This meeting will focus on the relationships between breeding outcomes and product quality, animal welfare, and other ethical issues.

Visitors

Members of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee *(see composition below)*

INRA welcoming committee

Thierry Pineau, President of the Île-de-France - Jouy-en-Josas INRA Research Centre and Regional Delegate for Île-de-France
Françoise Médale, Head of the Animal Physiology and Livestock Systems (PHASE) Division
Edwige Quillet, Head of the Animal Genetics (GA) Division

Objectives of the visit	
7:45 AM INRA headquarters rue de l'Université	**Meeting point for Committee members–8 am bus** providing transport between INRA headquarters and the Ile-de-France - Jouy-en-Josas INRA Research Centre
8:45-9:00 AM Building 156 2nd floor Conference room	**Welcome coffee**
Sequence 1	**Committee Meeting**
8:45-9:00 AM Building 156 2nd floor Conference room	**Work meeting for Committee members**
Sequence 2	**Introduction to the Ile-de-France - Jouy-en-Josas INRA Research Centre**
11:30-11:50 AM Building 156 2nd floor Conference room	**Presentation describing the centre and its work** (Thierry Pineau, President of the Île-de-France - Jouy-en-Josas INRA Research Centre and Regional Delegate for Ile-de-France, along with Françoise Médale, Head of the PHASE Division, and Edwige Quillet, Head of the GA Division)
Sequence 3	**Discussion among the Committee members, the president of the centre, and the two division heads**
11:50 AM-12:10 PM Building 156 2nd floor Conference room	**General questions about the principles related to genetic modifications in animals, carried out with artificial selection or biotechnological methods** (Thierry Pineau, President of the Île-de-France - Jouy-en-Josas INRA Research Centre and Regional Delegate for Ile-de-France; Françoise Médale, Head of the PHASE Division; and Edwige Quillet, Head of the GA Division)
Sequence 4	**Buffet lunch**
12:15-1:30 PM Building 200 Restaurant/ clubhouse area	*Sit-down meal* *A few additional guests attended the lunch to talk with Committee members* **Guests:** - **Françoise Médale**, Head of the PHASE Division - **Edwige Quillet**, Head of the GA Division - **Birte Nielsen**, President of the Committee for Ethical Animal Experimentation at the Île-de-France - Jouy-en-Josas INRA Research Centre and AgroParisTech - **Pascal Boireau**, ANSES, Scientific Coordinator of the DIM1Health project, Vice-President of the Scientific Board of the High Council for Biotechnology, and Director of the ANSES Animal Health Laboratory

[2]

	- **Laurent Journaux**, Head of the Genetics and Population Management Division at the French Livestock Institute (IDELE) - **Claire Rogel-Gaillard**, Director of the Joint Research Unit for Animal Genetics and Integrative Biology (INRA-AgroParisTech) - **Corinne Cotinot**, Director of the Joint Research Unit for Developmental Biology and Reproduction (INRA-ENVA) - **Olivier Sandra**, Researcher Director in the Joint Research Unit for Developmental Biology and Reproduction (INRA-ENVA) and Head of Research and Animal Experimentation for the president of the Île-de-France - Jouy-en-Josas INRA Research Centre
Sequence 5	**Meeting with researchers**
1:40–5:00 PM Building 156 2nd floor Conference room	Six presentations, given mostly by pairs of researchers (10 or 20 min per presentation with 20 min for questions). Other scientists were present to contribute to the discussion: - **Thierry Pineau**, President of the Île-de-France - Jouy-en-Josas INRA Research Centre and Regional Delegate for Ile-de-France - **Françoise Médale**, Head of the PHASE Division - **Edwige Quillet**, Head of the GA Division - **Olivier Sandra**, Researcher Director in the Joint Research Unit for Developmental Biology and Reproduction (INRA-ENVA) and Head of Research and Animal Experimentation for the president of the Île-de-France - Jouy-en-Josas INRA Research Centre - **Claire Rogel-Gaillard**, Director of the Joint Research Unit for Animal Genetics and Integrative Biology (INRA-AgroParisTech) - **Corinne Cotinot**, Director of the Joint Research Unit for Developmental Biology and Reproduction (INRA-ENVA) - **Rachel Rupp**, Research Director in the Joint Research Unit for Genetics, Physiology, and Livestock Systems (GenPhySE) in Toulouse and an expert in genome-based selection - **Stéphane Fabre**, Research Director in the Joint Research Unit for Genetics, Physiology, and Livestock Systems (GenPhySE) and an expert in genome editing - **Laurent Journaux**, Head of the Genetics and Population Management Division at the French Livestock Institute (IDELE) - **Christine Jez**, Head of Communications at the Île-de-France - Jouy-en-Josas INRA Research Centre **1. Principles, interests, and goals associated with the transition from gene-based to genome-based selection** (Didier Boichard, researcher in the Joint Research Unit for Animal Genetics and Integrative Biology [INRA-AgroParisTech])) **Detection of mutations that cause physiological disorders in**

	cattle. The importance of understanding rare human diseases (Aurélien Capitan, researcher in the Joint Research Unit for Animal Genetics and Integrative Biology [INRA-AgroParisTech]). *20 min presentation by the two speakers + 20 min for questions* **2. Project ReidSox. Use of genome-editing technology to demonstrate the effects of a causal mutation behind the high incidence of mammary tissue infections in ewes** (Laurent Boulanger, researcher in the Joint Research Unit for Developmental Biology and Reproduction [INRA-ENVA] and Gilles Foucras, professor at ENVT and researcher in the Joint Research Unit for Host-Pathogen Interactions [INRA-ENVT]). *10 min presentation by the two speakers + 20 min for questions* **3. Use of genome editing in model fish species** (Amaury Herpin and Julien Bobe, researchers in the Research Unit/Laboratory of Fish Physiology and Genomics - Brittany-Normandy INRA Research Centre) *10 min presentation + 20 min for questions* **4. Use of genome-editing technologies in animal stem cells** (Bertrand Bed'hom, researcher at Île-de-France - Jouy-en-Josas INRA Research Centre, the technology's uses and limitations; examples involving birds) *10 min presentation + 20 min for questions* **5. Using genome-editing technologies in mice to explore the effects of mutations hypothesised to underlie physiological disorders in cattle** (Jean-Luc Vilotte and Amandine Duchesne, researchers in the Joint Research Unit for Animal Genetics and Integrative Biology [INRA-AgroParisTech]) *10 min presentation + 20 min for questions* **6. Zinc-finger nuclease research in rabbits and goats and the creation of animal models that elicit specific ethical concerns** (Geneviève Jolivet and Eric Pailhoux, researchers in the Joint Research Unit for Developmental Biology and Reproduction [INRA-ENVA]) *10 min presentation + 20 min for questions*
Sequence 6	**Site visit** (for members of the Committee)
5:00-5:30 PM Xavier Leverve Building (442 - MICALIS)	**Equipment for performing protein analysis under anaerobic conditions** (Olivier Berteau, researcher in the Joint Research Unit for Food and Gut Microbiology [MICALIS]) **and the ANAXEM experimental facility for axenic, gnotoxenic mice and microbiota transfer studies, part of MICALIS** (Aurélie Balvay).
Sequence 7	**Return to Paris by bus**
5:00-5:30 PM Xavier Leverve Building (442 - MICALIS)	**Departure for Paris from the MICALIS Joint Research Unit car park**

Appendix 2

Meeting of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee

Monday, March 18, 2019

7:35 AM		8:39 AM	TGV trip - Arrival in Saint-Pierre-des-Corps at 8:39 am		
8:40 AM	50 min	9:30 AM	Trip from Saint-Pierre-des-Corps train station to Nouzilly		
9:30 AM	2 h	11:30 AM	Meeting of the Committee		Chenonceau Room (SDAR–basement)
11:30 AM	20 min	11:50 AM	Presentation describing the centre	Catherine Beaumont	
11:50 AM	20 min	12:10 AM	Presentation of how breeding is structured in different farm animals, role of cryobanking	Elisabeth Duval Elisabeth Blesbois Edwige Quillet Philippe Monget	
12:10 AM	20 min	12:30 PM	Discussion		
12:30 AM	10 min	12:40 PM	Summarising the possibilities and limits of genetic tools	Elisabeth Duval Sandrine Grasteau	
12:40 AM	10 min	12:50 PM	Discussion		
12:50 AM	1 h	1:50 PM	Buffet lunch with partners (ITAVI, SYSAAF, and ALLICE)		
1:50 PM	8 min	1:58 PM	Potential applications of biotechnology in poultry: studies on genome editing and in vitro meat, between dream and reality	Amélie Juanchich	Conference room
1:58 PM	8 min	2:06 PM		Bertrand Pain	
2:06 PM	24 min	2:30 PM	Discussion		
2:30 PM	8 min	2:38 PM	Muscle development and interactions with other functional elements	Pierre-Yves Rescan	
2:38 PM	8 min	2:46 PM		Cécile Berri	
2:46 PM	24 min	3:10 PM	Discussion		
3:10 PM	10 min	3:20 PM	Improving robustness: disease control and feed efficiency	Sandrine Grasteau	
3:20 PM	5 min	3:25 PM		Fabrice Laurent	
3:25 PM	25 min	3:50 PM	Discussion		
3:50 PM	15 min	4:05 PM	4:30 PM behaviour: the roles of olfaction and seasonality	Pablo Chamero	
4:05 PM		4:05 PM		Hugues Dardente	
4:05 PM	25 min	4:30 PM	Discussion		
4:30 PM	50 min	5:20 PM	Visit of the mass spectrometry facility, presentation describing the research carried out on horses (half the group)		UEPAO/PRC
5:20 PM	1 h	6:20 PM	Departure for the Saint-Pierre-des-Corps train station		
6:20 PM		7:28 PM	TGV trip		

Appendix 3

Composition of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee:

Axel KAHN	President of the Committee Medical doctor and PhD in the sciences INSERM research director
Michel BADRÉ	Vice-president of the Committee Engineer at the École Polytechnique - French National School of Rural Engineering, Water Resources, and Forestry Member of the Economic, Social, and Environmental Council, representing a group of environmental organisations
Madeleine AKRICH	Research director at the Mines ParisTech (in the Centre for the Sociology of Innovation) Engineer at Mines ParisTech PhD in the socio-economics of innovation
Bernadette BENSAUDE-VINCENT	Professor emeritus at the University of Paris 1 Panthéon-Sorbonne Associate professor of philosophy PhD in the humanities
Jean-Louis BRESSON	Physician specialising in nutritional medicine University professor Founder of the Necker-Cochin Centre for Clinical Investigation
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Appendix 5

Principles and values of the Joint INRA-CIRAD-IFREMER Ethics Advisory Committee:

•1 The Committee holds as a central tenet that human life has intrinsic dignity. When making recommendations, the Committee seeks to concretely reinforce human dignity by upholding the rights set out in the 1948 Universal Declaration of Human Rights.

•2 More generally, the Committee also strongly adheres to the values that have been expressed over the past several decades in the declarations and agreements established by the United Nations and other specialised organisations, including UNESCO. Chief among these values are the protection and promotion of biodiversity and cultural expression. The principles affirmed in these texts are implemented via international normative agreements.

•3 We must be stewards of the environment to ensure the well-being of future generations. We must also take care to not deplete natural resources or disrupt natural equilibria, as doing so could permanently jeopardise the planet's future. This commitment to sustainable development requires the Committee to consider not just the short term, but also the long term and the ultra-long term. At the same time, subscribing to a principle of total reversibility is utopian and impractical.

•4 The world is a system. An action that affects one system component will also have an impact on other components. It is thus necessary to explore the secondary effects of actions, any subsequent dynamics, and the strategic responses that emerge. While we must prioritise solutions at the global scale, global measures must be compatible with local measures, accounting for real-life conditions.

•5 The Committee views robustness and adaptability as two positive system attributes. Thus, even in an open society, a certain degree of autonomy in production systems is desirable at the national and regional levels.

•6 Progress occurs in societies that are open to technical and social innovations. It is nonetheless crucial to analyse and anticipate the effects of such innovations on human lifestyles and development. The benefits that arise must be shared equitably.

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