POLICY PAPER

POLICY PAPER FROM THE RUMIGEN CONSORTIUM

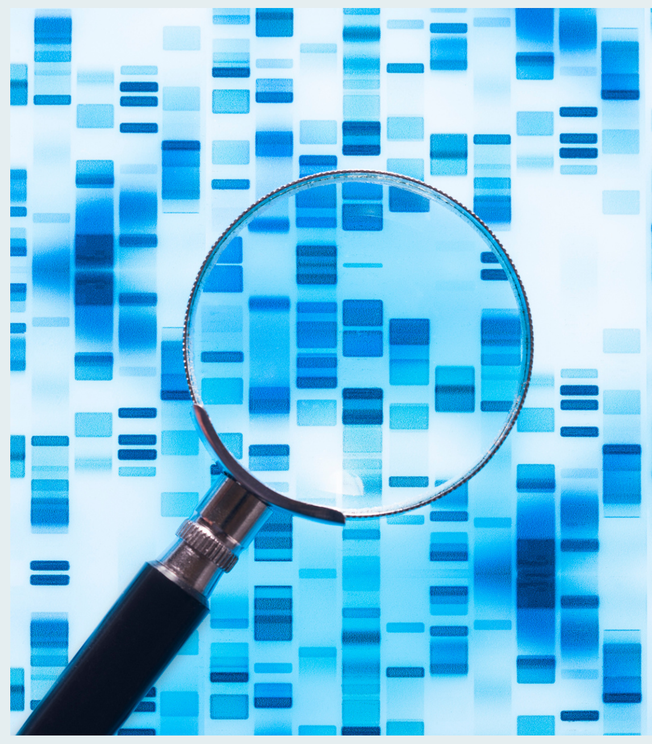
WHY GENOME EDITED ANIMALS SHOULD NOT BE CLASSIFIED AS GMOS

GENOME EDITING IS A NEW TECHNIQUE THAT HAS THE POTENTIAL TO CONTRIBUTE TO MAKING PROGRESS FOR MORE SUSTAINABLE FOOD SYSTEMS. THE EU GMO DIRECTIVE IS NOT FIT FOR PURPOSE. IT IS ESSENTIAL TO ESTABLISH AN AGILE AND PROPORTIONATE NEW EU LEGAL FRAMEWORK FOR FARMED ANIMALS.

BACKGROUND

Since settlement (around -11,000 years BC), humans have been selecting plant and animal species for their survival needs (farming, breeding, help with various agricultural tasks, etc.). In the animal world, species selection began even earlier with domestication (around 20,000 years ago for the canine species), when certain character traits (phenotypes), such as affability in the wolf/dog, were favoured and therefore selected. In the 19th century, genetic improvement of ruminant species for food production purposes moved on to breeding programs organized by Herd-books for pure breeds. The selection focus was mainly on milk and meat quantity and quality, such as protein, fatty acids, lactose and related traits.

With the discovery of the principles of Mendelian inheritance, the structure of DNA (1953), the development of high computational capacity, and the resulting advances in genetic and genomic knowledge, so-called "genomic" selection, it became possible to connect better the genetic constitution of animals (genotype) and their observable characteristics (phenotype). In the 21st century, adding new goals and traits in a more balanced way to breeding programs, such as improved animal health and welfare, better use of resources or reduced environmental footprint has become the norm.



The advent of new genome editing tools[1] (mainly the CrispR-Cas9 system) opens up the possibility of adding a new dimension to the selection process, allowing more precise generation and selection of particular and interesting characteristics (traits), such as the resistance of animals to a specific disease (e.g. bovine tuberculosis). However, at present, only traits for which the genotype-to-phenotype relationships are well established and for which one or few genes have a major impact are likely to be the subject of such approaches. Well-known examples are mutations in cellular receptors for certain viruses and the resistance of animals to infections by these same viruses. Furthermore, applying gene editing tools and associated research, such as the increasing knowledge of genome annotation[2] in farmed animals, will considerably help improve our understanding of the relationship between genetic information and its expression in animals and their descendants. This, in turn, will increase the number of cases where gene editing could be applied in precision livestock breeding processes.

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1 *Genome editing tools (mega-nucleases, ZFN, TALEN, CrispR-Cas9) are used to induce a cut in the two strands of the DNA molecule at a defined, chosen and predetermined point in the genome. This cut is then repaired by the host cell using its own DNA repair systems, in three ways known as SDN1, SDN2 and SDN3 (SDN for Site-Directed Nuclease). SDN1 and SDN2 produce new genetic variants, either random (SDN1) or predefined (SDN2). SDN3 enables the integration of exogenous DNA (transgenesis) at a targeted point in the genome, where the cut has been induced. Other editing methods, such as base editing, have been developed that do not require DNA cutting.*

2 *Genome annotation is the process of deciphering an organism's genetic code to identify genes, regulatory elements, and functional regions within its DNA (https://youtu.be/fg-t3S0YdOU)*

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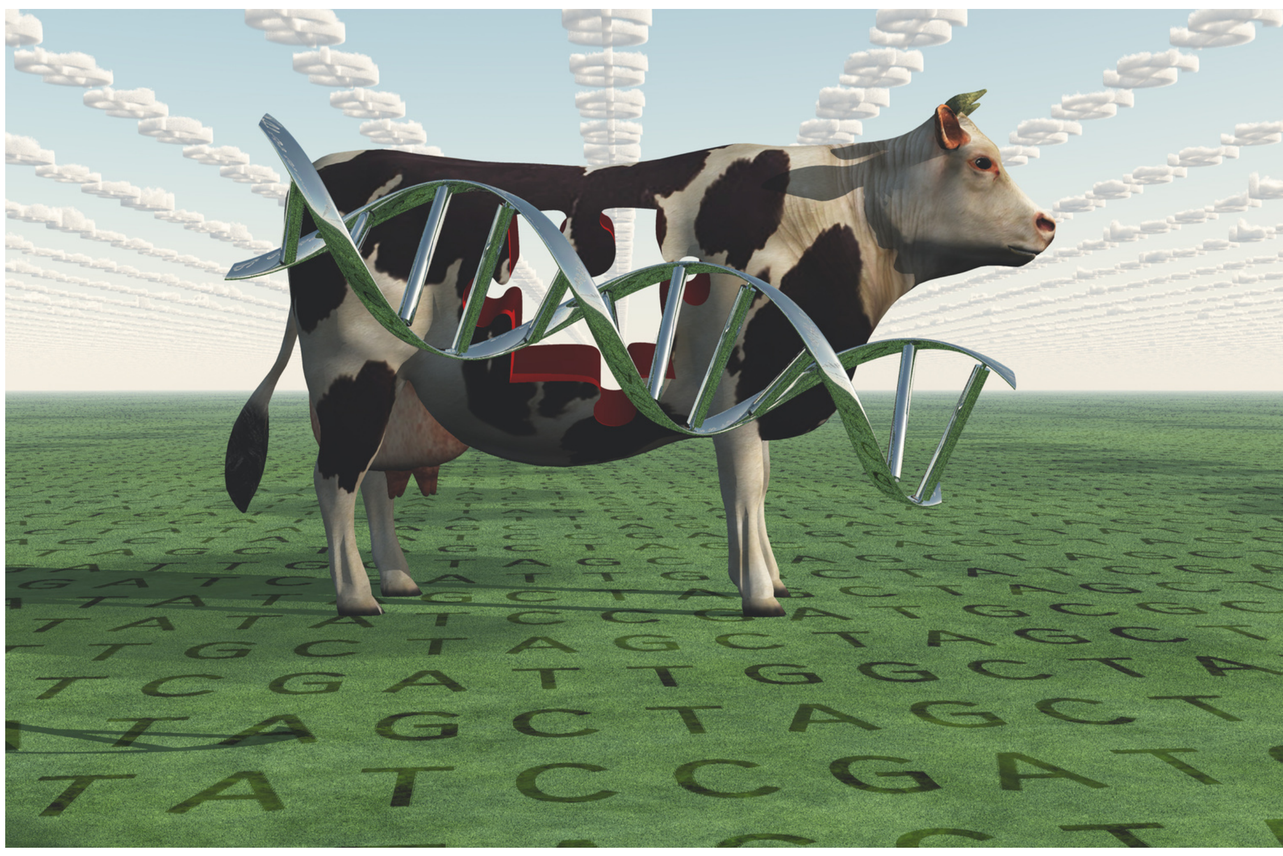
THE REGULATORY CHALLENGE

Following the decision of the European Court of Justice (CJEU) in 2018 (case C528/16, concerning oilseed rape), organisms including animals obtained using these genome editing tools are legally considered under the scope of the European GMO directive.
The study on NGTs (New Genomic Techniques) conducted by the European Commission and published in April 2021 concludes that NGTs have the potential to contribute to more sustainable food systems and that the EU GMO directive is not fit for purpose. The EC also concluded that there are different levels of availability of safety data for these techniques in plants, animals and microorganisms, adding that there is not enough safety data available to start a policy action on NGTs in animals.
Whilst the EC study recently published a legislative proposal for plants obtained by targeted mutagenesis and cisgenesis, precise moves to ensure future policy actions for farmed animals are needed. Moreover, in other countries, particularly in the UK, new legislation is under development. The absence of a clear political ambition and legal framework for New Animal Genomic techniques in the EU is already creating a disturbance in research and innovation activities in the EU.

DRAWBACKS INDUCED BY THE CURRENT REGULATION: SCIENTIFIC OPINION OF RUMIGEN EXPERTS

The current legal framework under the GMO directive for genome editing is influencing the perception of these techniques from society and policymakers. It leads to the virtual absence of support (financial, societal and, indeed, institutional) to explore further the potential of these tools and their implementation outside species commonly used in laboratories where costs are slightly lower and societal rejection is less exacerbated.
This lack of support is a significant obstacle to fundamental research into the function of the genetic information of animals (genomics) and slows down the development of better knowledge of genotype to phenotype relationships. Yet we believe this knowledge could generate numerous benefits, not just for humans, but for animal health and welfare of farmed animals. Benefits could also go beyond farming, particularly in medicine.



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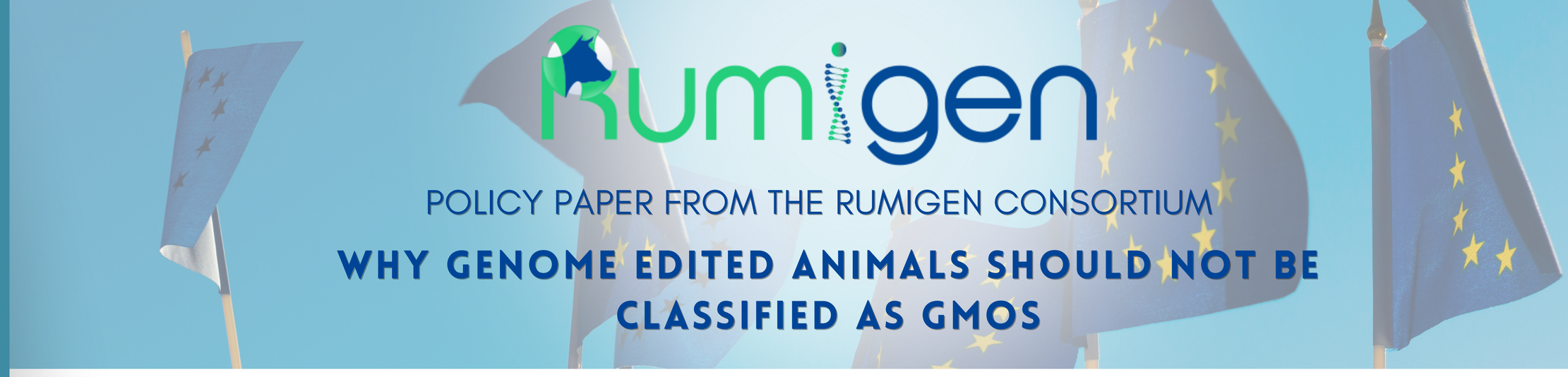

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Furthermore, research on improvements in the use of these genome editing tools in relation to new selection breeding strategies need to be further explored. Thus, the European Union is lagging considerably behind in these areas of research in comparison with other countries that have adopted less restrictive legislation that does not classify these animals as GMOs, potentially leading in the long term to a weakening of its livestock industry.

Another important consequence of this decision is that the European Union could be in an uncomfortable position to legislate on trade. The origin of products obtained using these tools in other countries that do not have the same legislation will not necessarily need to be traceable. Given it cannot be established a posteriori, will all agricultural products from these countries have to be banned from import into the European Union? Even if their origin is specified, what would be the classification of the offspring of such gene edited animals and of the animal products derived from them that are consumed in Europe?

Furthermore, local European breeds that highlight the specificity of the genetic diversity of animal populations reared in Europe will never benefit from these technologies, which could prove extremely useful in the event of a major health or environmental crisis that could jeopardize their future. These local breeds play an important social and environmental role, as they are often linked to a particular territory and culture. The use of these genome editing tools with which new targeted genetic variants can be efficiently and rapidly generated without affecting other genomic regions compared with current conventional selection methods, makes it possible to control the preservation of biodiversity at different levels, breeds, populations, and species. In this way, genome editing would not only help to preserve local breeds but also to use their genetic originality for the benefit of other breeds.

POLICY RECOMMENDATIONS

✓ **The European Commission needs to define a clear roadmap for revising the classification of animals** carrying new genetic variants generated by SDN1 and SDN2 methods and **make them exempt from GMO regulation**. Following the adoption of the legislative proposal for plants, research from projects like RUMIGEN, alongside other ongoing research in the EU, can provide sufficient and valuable expertise and safety data to the EC and EFSA. These tools should be recognized as vital for precisely aligning the aims of breeding with the future green deal objectives.

✓ **A proportionate and science-based pre-market risk assessment** can be developed to assess on a **case-by-case basis** the welfare of the animals and the safety of the edits, keeping in mind that one would expect the overall safety profiles of genome edited or precision bred and traditionally bred animals to be the same.

✓ **The ethical aspects and the evaluation of the sustainability of the edited traits** can also be taken into consideration in a **case-by-case approach**. As for other breeding approaches, eliminating unacceptable violation of animals (negative impacts on animal welfare / animal autonomy (including natural behavior) should be part of the acceptance regime of these techniques.

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