KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN

GENOME EDITING

Position Paper of the Royal Netherlands Academy of Arts and Sciences

In recent decades, scientific advances in molecular biology have made important contributions to medicine, livestock breeding, agriculture and horticulture, the chemicals industry and the food sector. Some of these advances have raised ethical and societal dilemmas, for example regarding the use of recombinant DNA technologies or embryonic stem cells. The scientific community recognises the need to be vigilant and to address such dilemmas, so that such advances will benefit society while also taking ethical and societal aspects into account.

Basic research has recently led to the development of new techniques, for example CRISPR/Cas,[1] which can specifically modify individual nucleotides in the genome of living cells. These techniques are called 'genome-editing' and can be used in two different ways. First, they can be used to alter one or a few nucleotides. The genome of the resulting organism may be identical to existing variants or to variants that can be produced using natural mutations or traditional mutagenic techniques (e.g. radiation and chemical agents). But where mutagenic techniques often give rise to multiple, off-target mutations across the entire genome, genome editing results in one or a few targeted mutations. Second, genome editing makes it possible to insert new genetic material into the genome (from a few base pairs to multiple genes). While the result is comparable to that of older genetic-modification techniques, genome editing is cheaper, more precise and more efficient.

Genome editing is already popular in biological and biomedical research. The precision, simplicity, speed and low costs of these techniques also make a growing variety of different applications possible in medicine, plant breeding, animal breeding and biotechnology. Scores of scientific articles and reports have described the rapid development of genome editing and its uses. In this paper, the Academy expresses its views on important scientific, ethical and societal questions that such uses raise. The Academy believes that broad international discussion of this subject is vital, in part because biotechnological advances are regulated mainly within the European and international context. The Academy's conclusions and recommendations are given in brackets below.

Scientific research

Genome editing plays an important role in driving scientific research into the functions of specific genes, genetic variations and genetic interactions, leading to significant advances in our knowledge.

The Academy considers it vital that such scientific research can proceed subject to prevailing statutory rules and according to prevailing ethical criteria, assessments and supervision, so that:

- genome-editing techniques can be developed further
- our knowledge of the biology of organisms, including human and animal embryos, and germline cells increases

[1] In 2015, CRISPR was selected by *Science* as its 'Breakthrough of the Year'; see Travis J (2015), 'Making the cut. CRISPR genome-editing shows its power'. *Science* 350: 1456-1457

- we gain a better understanding of the advantages and disadvantages of potential new uses, specifically how safe they are for humans, animals and the environment.

Human somatic applications

Promising clinical applications based on this new technology focus on the modification of somatic (non-reproductive) cells. Examples include editing the blood stem cells of patients who have a congenital blood disease, metabolic disorder or immune deficiency, or improving the capacity of immune cells to attack cancer cells.

The Academy considers it important to conduct sound scientific research into the risks and possible advantages of every new clinical application of genome editing before it is incorporated into standard medical practice. Current and evolving regulatory frameworks for gene therapy, clinical trials and genetic modification are satisfactory for assessing the somatic-clinical use of genome editing. The relevant authorities can assess the advantages and disadvantages of clinical applications versus existing therapies within such frameworks.

In addition to the therapeutic use of genome editing to address disease, it could also be used to develop preventive strategies, for example to make cells infection-resistant.

The Academy believes that the introduction of genome editing as a preventive strategy must be preceded by discussion of the ethical aspects and, if necessary, by sound regulation. The focus there, however, should be on the treatments themselves, and not on the underlying technique of genome editing in general. Furthermore, such discussion should take into account alternative interventions, such as drugs that could be used in similar ways. The relevant authorities can then assess the advantages and disadvantages of such applications on that basis.

Taking things a step further would be to edit the genome of individuals who are basically healthy but, for example, want to improve their muscle cell function with a view to sports performance (genetic doping).

The Academy believes that any public discussion of such uses should be framed within a broader debate about other technologies that can ‘improve' human beings. If the outcome means that certain forms of genome editing leading to human improvement are permitted under specific conditions, then sound regulation is needed to guarantee their safety.

Human germline applications

Genome editing could also be used to introduce genetic mutations into human germline cells or embryos and so alter the genome of offspring. One requirement here is that the gene in which the mutation is to be introduced must have been identified. The resulting mutations will be expressed in all the cells of the offspring and will be passed on to future descendants. Possible applications range from the prevention of serious inheritable disorders to the introduction of certain desirable traits in descendants. Genome editing could thus prevent descendants from developing certain health problems and allow people more reproductive choice.

Current European and Dutch legislation does not permit deliberate alteration of the genetic material in the nucleus of human embryos or of the germline cells intended to establish pregnancy. This prohibition does not cover mitochondrial transplantation. Dutch law does allow pre-implantation diagnosis and embryo selection in in-vitro fertilisation to prevent serious genetic disorders in offspring. Embryo selection, however, only allows for choosing between the parents’ two different genes in the case of mono-genic diseases, whereas genome editing also allows more precise modification of multiple parental genes, with a minimal risk of off-target effects elsewhere in the genome with accompanying health risks. Genome editing could also be used to ‘cure’ embryos that are now destroyed in embryo selection, so that they can be implanted and result in pregnancy.

Genome editing in the germline or in embryos raises certain questions, however, concerning:

- the health risks associated with faulty or incomplete (mosaicism) editing
- the difficulty of predicting the effects of genetic alterations on individual functioning.

In addition, there are uncertainties about:

- the consequences for future generations that carry the genetic alterations
- the consequences for others, for example owing to rising social inequalities and declining genetic diversity.

It should be noted that the final two points are also concerns in embryo selection.

Given the great strides being made in genome editing, the Academy considers that we are approaching a time when such techniques can be used to alter human germline cells or embryos. The Academy believes it would be irresponsible to use genome editing to create offspring until:

- we have sufficient knowledge of the risks, potential advantages, and available alternatives to make an appropriate assessment
- society has reached consensus about the moral acceptability of the applications in question.

Before using genome editing in the germline to create offspring, we need more research and public debate as to how we can safeguard important ethical values and limit negative side effects. Public debate would give patients, care providers and society an opportunity to discuss controversial issues, to assess the risks, advantages and conditions of potential germline applications based on growing scientific insight, and to develop good practices and further regulation. Only after these steps have been successfully completed can the law be amended to permit genetic modification in the germline under specific circumstances and subject to specific conditions.

Animal applications

Genome editing in animals is a broad and varied field that raises many different societal and ethical questions. As in humans, genome editing in animals can be used to treat or prevent illness, for example infectious diseases or congenital defects. It can also be used to improve farm animal welfare (e.g. by obviating the need to dehorn cattle) or production traits. At the moment, most uses of genome editing do not appear to be economically profitable in large-scale stock breeding. Genome editing can also be used in animal modelling to generate more specific and more diverse models. In addition, genome editing might eventually prove useful in xenotransplantion (transplantation into a human recipient of organs or tissue from a non-human animal source). Finally, genome editing can be used to combat infectious diseases transmitted to humans by animals, for example by genetically modifying mosquitos so that they no longer carry malaria. This leads to questions about the impact on the ecosystem, specifically if CRISPR is used to develop a gene drive that eradicates a specific species (locally). Some of the uses cited above are subject to regulations governing genetically modified organisms ('GMO regulations') and additional legislation pertaining to animals. In practice, genetic engineering of animals is now only permitted in the Netherlands for biomedical purposes.

The Academy has noted confusion as to whether GMO regulations pertain to limited genetic mutations that could also arise in nature. The Academy would like more regulatory clarity on this point. The possibility that genome editing can improve animal and human welfare requires a re-evaluation of current practices permitting animal genome modification solely for biomedical purposes. Before genome editing can be used more broadly in animals, however, we must first

- have sufficient knowledge of each application to make sound decisions concerning the risks, potential benefits and available alternatives, and
- have reached broad consensus on the moral acceptability of the application in question.

When amending existing legislation, the focus should not be on the technique but rather on the result of using that technique and whether it is safe for animals, public health and the environment.

Applications in micro-organisms

Natural selection has provided us with very few micro-organisms optimised for industrial biotechnology. Scientists have therefore been genetically modifying micro-organisms for several decades now, with the aim of developing new raw materials and products, accelerating the production process, and improving yields. Their efforts have made it possible to study and produce drugs, chemicals, fuels and foods. Because CRISPR and similar techniques allow researchers to introduce multiple targeted mutations simultaneously, the time needed to introduce genetic mutations in micro-organisms has been cut from years to days. These modified micro-organisms pose very little risk to human life or the environment because they are produced in closed systems and have been optimised for a specific production environment. There is thus little chance of their surviving in nature, and the risk of their dispersal into the environment is virtually non-existent. Under current GMO regulations, modified organisms created by means of a small number of genetic modification techniques are exempt. These techniques are regarded as safe based on many years of experience.

The Academy has noted confusion about the extent to which GMO regulations apply to micro-organisms created by genome editing. The Academy would like to see more legislative and regulatory clarity on this point. It also believes that legislation should be simplified, in any event where it concerns modifications of the genome of micro-organisms similar to those that already occur spontaneously in nature or that can be created using traditional non-targeted mutagenesis. After all, they pose comparable risks to human beings and the environment. Safety is regulated in such cases by additional biosafety and biosecurity arrangements. The Academy believes that GMO regulations should not evaluate the technique used to create the organism, but rather the product itself and whether it is safe for public health and the environment.

Applications in plants

Genome editing is of great importance to plant breeding. The combination of improved knowledge of gene function and genetic variants and the speed with which traits can now be engineered based on that knowledge offers huge opportunities for agriculture and horticulture. Genome editing offers a faster way than conventional breeding techniques to create crops with desirable traits, for example better quality, higher yields, and disease- and pest-resistance. Because genome editing is a relatively simple technique, it can be used by smaller plant breeders, provided the regulations are clarified and simplified so that it remains affordable. Once again, it is unclear to what extent GMO regulations apply. This is specifically relevant in the case of small-scale genome modification and where it is impossible to distinguish between edited plant genomes and genetic variants in populations that occur spontaneously or after mutation.

The Academy notes the great importance of clarifying regulations both for research and for small plant breeding firms in particular. Once again, the Academy believes that it is not the technique used to create the organism that should be evaluated, but rather the product itself and whether it is safe for public health and the environment. A distinction should be made between genome-editing applications whose result does not differ from variations that could occur in nature and modifications in which genetic material is inserted that can be identified as originating from a different organism. In the former instance, the regulations can be simplified. After all, we cannot expect the dispersal of that kind of genetically modified plant into the environment to have a greater negative impact than the dispersal of plants whose genome has been altered using traditional plant-breeding techniques. Human and environmental safety is regulated in such cases by additional arrangements.

Regulations

It is unclear how existing GMO regulations apply to genome-editing techniques and the resulting products. While this is certainly a concern with regard to plants and micro-organisms, it may also be relevant when the technique is applied in animals. Where EU and/or Dutch regulations are less accommodating of advances in genome editing, there may be negative consequences both for research in the Netherlands and for commercial applications in agriculture and horticulture – sectors in which the Netherlands plays a prominent role internationally. To avoid unnecessarily blocking innovation and the use of genome-editing

techniques, the EU must clarify and, where required, amend legislation pertaining to 'genetically modified' organisms.[2]

The Academy advocates simplification of the regulations governing modifications of the genome of micro-organisms and plants that are comparable to variants that occur spontaneously or that could reasonably be obtained by natural mutation or traditional mutagenesis. Such regulations should not apply at all to genome editing of this kind, or current regulations should make it exempt. The rationale here is that such products do not pose more of a risk to humans and the environment than those obtained by traditional mutagenesis and considered safe based on many years of experience – in fact, these products are expected to be safer owing to the more targeted nature of the mutations. Another consideration is that the final products of these various techniques are indistinguishable, making it difficult to enforce GMO regulations. In a general sense, the Academy would like to see GMO regulations amended so that they no longer evaluate the technique used to create the organism, but rather the product itself and whether it is safe for public health, animals and the environment.

International discussion

Genome editing in animals and humans gives rise to critical ethical questions.

The Academy considers a broad international discussion of vital importance. After all, the regulatory framework goes beyond that of individual countries, with jurisdiction increasingly being transferred to international alliances such as the European Union. The discussion should involve not only researchers and ethicists but also physicians, patients, policymakers, politicians and the public. As far as the Academy is concerned, it should not focus on 'yes or no' but rather on 'how we can use genome editing in the future in a manner that safeguards critical moral values (e.g. equality, respect for diversity, alleviation of suffering) and limits the negative side effects as much as possible'. There are lessons to be learned from the introduction of earlier techniques and from other countries.

The Academy believes that the academic community has an important role to play in encouraging and initiating public discussion. Various international parties are aware of this responsibility and are organising conferences and discussion seminars or publishing their positions and strategic agendas. The Academy is contributing to the discussion by organising a symposium on genome editing on 7 September 2016, by publishing this position paper and by participating in the Genome Editing project run by the European Academies Science Advisory Council (EASAC).

About this publication

The Royal Netherlands Academy of Arts and Sciences publishes position papers dealing with current issues in science in order to contribute to public debate. Genome editing is such an issue.

This position paper was drawn up by a committee consisting of the Academy members Prof. Ton Bisseling, Prof. Hans Bos, Prof. Cock van Duijn, Prof. Paul Hooykaas, assisted by secretaries Hanneke van Doorn and Dr Jean Philippe de Jong. The paper builds on three previous documents published by other national academies (*On Human Gene Editing: International Summit Statement*, Organizing Committee for the International Forum on Human Gene Editing, 3 December 2015; *The Opportunities and Limits of Genome Editing*, Nationale Akademie der Wissenschaften Leopoldina, Deutsche Forschungsgemeinschaft, Acatech and Union der deutschen Akademien der Wissenschaften, 2015; *New Breeding Techniques*, EASAC, 2015), the symposium organised by the Royal Netherlands Academy of Arts and Sciences on 7 September 2016 (*Genome editing, Kansen en grenzen van moderne genetische-modificatietechnieken*), *Trendanalyse Biotechnologie 2016* drawn up by COGEM and the Health Council of the Netherlands, and the COGEM-authored document *Signalering en advies CRISPR-Cas; revolutie uit het lab* (CGM/141030-01), 2014.

[2] GMO legislation does not pertain to humans.

A draft version of this position paper was submitted for review to:

- Prof. Dirk Inzé, professor of Molecular Plant Biology and Physiology, Gent University, Belgium
- Prof. Jos van Putten, professor of Infection Biology, Utrecht University
- Prof. Sjoerd Repping, professor of Human Reproductive Biology, Academic Medical Centre, Amsterdam
- Prof. Inez de Beaufort, professor of Health Ethics, Erasmus Medical Centre, Rotterdam

The Academy owes the reviewers a debt of gratitude for their suggestions. The reviewers bear no responsibility for the substance of the report.

This position paper and more information about Academy activities related to the subject of genome editing may be found on the web page: knaw.nl/genome-editing.

This publication may be cited as follows: Royal Netherlands Academy of Arts and Sciences (November 2016). *Genome Editing, Position Paper of the Royal Netherlands Academy of Arts and Sciences.* Amsterdam, KNAW.