Rathenau Instituut

Genome editing in plants and crops

Towards a modern biotechnology policy focused on differences in risks and broader considerations

Report

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Syngenta, a seed breeding company where research is done on genetically modified crops. Copyright: Hollandse Hoogte

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Foreword

Genome editing allows for the deliberate altering of the DNA of organisms with unknown precision. Because it involves the building blocks of life, this technology raises fundamental ethical and societal questions. Experience has taught the Rathenau Instituut the importance of asking the right questions and examining them in multi-stakeholder approaches.

After the discovery of recombinant DNA technology in the 1970's, a small group of scientists initiated an ethical discussion that later expanded beyond science. In response to this debate, the Dutch government set up the Broad DNA Committee [Brede DNA Commissie] in the 1980s, which examined possible applications as well as societal and ethical aspects of recombinant DNA. In 2001, the government initiated a public debate, called Eating and Genes ('Eten en Genen') on the societal and ethical questions related to biotechnology and food. Besides risks to human health and the environment, the most important arguments were objections to tampering with nature and the concentration of power in global agrochemical and plant breeding companies. Differences of opinions exist on the usefulness and necessity of these innovations.

This longstanding debate was given new impetus by the emergence of CRISPR-Cas9, a breakthrough in genome editing that makes altering DNA in the lab less expensive, faster and more easy. In this report, we examine the use of these new genome-editing technologies in plant breeding. The debate mainly centres on the question whether the genome-edited plants are subject to the EU Directive on the deliberate release into the environment of genetically modified organisms. Civil society organisations, businesses and the Dutch government focus on two policy options: either genome-edited plants and crops are subjected to the GMO Directive, or they are exempted, provided no 'foreign DNA' is present in the plant. In this rapport, the Rathenau Instituut describes a third policy option, one that takes into account differences in risks as well as broader societal and ethical aspects.

The Rathenau Instituut has been studying the role of knowledge and evidence in political decision-making since the 1980s, and has experience with societal debate on contentious issues and innovative technologies. Here, we aim to contribute to the current debate on a modern biotechnology policy.

Dr Melanie Peters
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Summary

In 2015, the prestigious journal Science singled out CRISPR-Cas9 as the breakthrough of the year. Although it has been possible since the 1970s to alter the genetic material of organisms, it was not until the discovery of CRISPR-Cas9 that such technologies became, easier, faster, and less expensive. This caused a revolution in the laboratory, but also gave new impetus to the debate about the current regulation of biotechnology. The Rathenau Instituut studied the significance of genome-editing technologies for agriculture; specifically, its significance in the debate on the regulation of biotechnology in plant breeding in Europe. So far, the debate in Europe on genome editing in plant breeding has concentrated mainly on great expectations of this new technology, economic benefits and legislative issues.

With the new genome-editing technologies, it is possible to make small, targeted changes to the genome in the laboratory. In contrast to the older recombinant-DNA techniques, it is possible for gene-edited plants to not contain any foreign DNA. This has intensified the debate whether the European GMO Directive applies to this and other new breeding techniques. In accordance with the precautionary principle, this Directive was adopted to ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment, because genetic modification technologies introduce organisms with new characteristics in the environment. Currently, agrochemical and plant breeding companies, as well as many research institutes, argue that the risks of these new techniques are smaller than those of classic mutagenesis methods. And because these latter are exempt from the GMO Directive, the new genome-editing techniques should also be exempted. In contrast, NGOs and the organic sector claim that long-term safety for public health and the environment has not been demonstrated, as these techniques have only been in the lab for a couple of years. The European Court of Justice ruled in July 2018 that only conventional (in-vivo) mutagenesis methods that have been used for several decades without creating identified risks for the environment or health are exempt. Therefore, all products of genome-editing techniques (irrespective of the presence of foreign DNA) are subject to the GMO regulation. Although this has settled the discussion on the legal status of these new techniques, it has not settled the debate.

The ball is in the European Commission’s court. Two policy options for the EU dominate the debate on genome editing in plants and crops. One option is to uphold the GMO Directive, the other is to exempt genome-editing techniques from the GMO Directive if and only if there is no foreign DNA present in the endproduct. Here, we discuss the societal consequences and challenges of both policy options.

A third, less prominent policy option in the debate attempts to unify the benefits of both options. This third option requires new legislation. Applications will be assessed individually for safety at different assessment levels. Which level applies is based on, for example, the degree of genetic modification, the techniques used, the characteristics of the end product and their complexity. In addition, applications are assessed for their value for society.

Taking into account the differences of opinion of various stakeholders, as well as the ruling of the European Court of Justice, we offer a way forward to modernize the current biotechnology policy. In this report we present a level-based approval policy focused on differences in risks while simultaneously taking account of ethical and societal factors, based on a Norwegian proposal. The history of the GMO debate illustrates how important these cultural and ethical issues are. The space necessary for broader issues to be considered was created a number of years ago through a change to the European GMO Directive. This amendment gives individual member states the right to either ban or permit cultivation of genetically modified crops, based on societal, cultural and ethical issues. It is essential that these broader issues are taken into account when drawing up new regulation for biotechnology.

Introduction

The introduction of genetically modified (GM) crops into European agriculture in the nineties caused scientific controversy and public unease. Concerns included risks to human health and the environment and feelings of inevitability regarding the introduction of this technology into society. Doubts still exist about the societal goal of the technology and its value to society. In addition, there are objections to tampering with nature and the concentration of power in large, global agrochemical and plant breeding companies.[1] In addition, GM-crops are associated with the negative consequences the introduction of GMO's in agriculture had in the United States and Argentina, where introduction was accompanied by upscaling, a high use of pesticides and herbicides, and the increasing dependence of farmers on a small number of large breeding companies.[2] In contrast, advocates of these technologies highlight the possibilities the new techniques offer to develop better crops necessary to adapt to a changing climate, and ensure feeding a growing world population.

While worldwide there has been steady growth in the area covered by GM crops, there are only four EU countries where GM maize is grown.[3] In contrast, 19 EU member states have imposed a moratorium – either temporary or permanent – on the cultivation of genetically modified organisms (GMOs) in all or part of their territory.[4]

To protect public health and the environment, and to harmonise the legislation of member states, the European Union introduced a Directive for the deliberate release of GMOs into the environment in 1990, which was repealed by the current Directive 2001/18/EC in 2001.[5] Since then, a number of new plant breeding technologies have emerged to alter traits in plants and crops. Some of these new techniques present a challenge to existing legislation according to various stakeholders. This initiated a debate on whether the GMO Directive applies to these new techniques. The release of the advisory report by the Netherlands Commission on Genetic Modification (COGEM) *New techniques in plant biotechnology* in 2006, played a key role in initiating this discussion. The COGEM proposed that products

[1] Grove-White, R. et al. (1997). *Uncertain world. Genetically Modified Organisms, Food and Public Attitudes in Britain*. Center for the Study of Environmental Change, Lancaster.
[2] Munnichs, G., H. de Vriend, and D. Stemerding (2016). *Afwegingskader nationale teeltbevoegdheid gg-gewassen- Verslag van een stakeholderdialoog.* The Hague: Rathenau Instituut
[3] https://ec.europa.eu/food/plant/gmo/reports_studies/report_2016_mon_810_en
[4] https://gmo.geneticliteracyproject.org/FAQ/where-are-gmos-grown-and-banned/; http://europa.eu/rapid/press-release_MEMO-15-4778_en.htm.
[5]Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

of various new techniques should not be considered to be GMOs because “no changes are present in the genome and the products are the same as products obtained conventionally”.[6] At the initiative of the Dutch government, a working group was set up in 2017, tasked with investigating whether it is appropriate that the EU GMO Directive applies to some of these new plant breeding techniques.[7]

The emergence of CRISPR-Cas9

The emergence of a new genome-editing technology, CRISPR-Cas9 made modifying DNA in the laboratory faster, easier, less expensive, and more accurate. In recent years, this biotechnology has spread rapidly in the laboratory. The technology is expected to play a prominent role in innovations across the field of biotechnology: in industrial applications, plants, animals and humans.[8] This has given new urgency to the debate which techniques are subject to the GMO Directive. The European Court of Justice was asked to clarify the Directive, and ruled in July 2018 that the GMO Directive applies to the new genome-editing technologies, and that these technologies, unlike traditional mutagenesis techniques are not exempt from the Directive.

Many stakeholders in the agrochemical and seed breeding sector are seeking to amend this legislation. For this reason, the Dutch Ministry of Infrastructure and Water Management (I&W) initiated a stakeholder consultation in the Netherlands, focused on modernising biotechnology policy. At the same time, the Dutch Ministry of Agriculture, Nature and Food Quality (LNV) is engaged in creating an assessment framework as a result of the 2015 amendment of the GMO Directive. Europe decided in 2015 that individual member states could include broader considerations in their decisions on permitting GMOs in all or part of their territories. What considerations will be taken into account are scripted in an assessment framework, currently still under development in The Netherlands.

Because it is expected that genome editing will play an important role in the field of biotechnology as a whole, the Rathenau Instituut decided to study the influence of the new genome-editing technology on the political and societal debate on genetic modification in plants and crops. Currently, two policy options dominate this debate, although a third option is emerging. We will discuss and weigh the pros and cons of these three policy options presented by various players in the current discussion. Our objective is to clarify the discussion, and to document some of the challenges of each option.

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[6] COGEM (2006). *Nieuwe technieken in de plantenbiotechnologie.* Advisory and policy report. CGM/061024-02.
[7] COGEM (2009). *EU- Regelgeving updaten? Wetenschappelijke ontwikkelingen werpen nieuw licht op de proces-product benadering.* Policy reportCGM /090626-03.
[8] Ibid.

Central in this report is the question of how to develop a modernised biotechnology policy for plants and crops, considering the safety of the public and the environment, and the benefits for society. We assume that the government has a dual role: on the one hand promoting innovation and on the other hand giving direction to modernisation focussed on the interests of the public.[9]

Reader's guide

Chapter 1 describes the current regulation of traditional breeding methods, and GM-crops in agriculture and horticulture. We also briefly examine CRISPR technology and the history of the debate.

In the following three chapters, we discuss the above-mentioned three policy options. We present the arguments various stakeholders give for their preferred option. We consider how a particular policy option deals with safety for human health and the environment, and we will examine the challenges and possible consequences for society. In Chapter 2, we will discuss option 1, in which the GMO Directive is not amended. Option 2 is described in Chapter 3. In this option, the Directive is amended in order for the new genome-edited products containing no foreign DNA fragments to be exempted from the Directive, e.g. by amending Annex 1B. A third option attempts to combine the advantages of the first two options. We discuss this level-based regulation for GMOs in Chapter 4, using the current Norwegian proposal as an example.[10]

In the last chapter, we present the outlines of a modernised biotechnology policy for plants and crops, taking into account the ruling of the European Court of Justice, the arguments of both proponent and opponents of deregulation of genome editing, and the value and benefits for society.

[9] See, for example, Est, R. van et al. (2017). *Waardevol digitaliseren: Hoe lokale bestuurders vanuit publiek perspectief mee kunnen doen aan het 'technologiespel'.* The Hague: Rathenau Instituut

[10] We do not take a possible fourth option – banning GM crops – into consideration, because this option is not changed by the emergence of genome editing; a ban remains a ban.

1 The emergence of CRISPR-Cas9: a brief history

So far, the societal and political debate has centered on the economic benefits for European businesses, the enormous promises of the techniques, and the legal question whether the European GMO Directive applies to the new genome-editing techniques. This latter question was important, because the cultivation of GM crops is regulated differently from the cultivation of traditionally-bred crops. In this chapter, we describe the different ways traditional breeding methods and genetic modification techniqies are regulated. Next, we will examine the emergence of CRISPR technology and the technical improvements it created in the laboratory. The argument in favour of exempting these techniques from the GMO Directive is based on the technical differences between the possible products of genome-editing techniques and recombinant DNA techniques. We describe the arguments of various stakeholders and the ruling of the European Court of Justice, which clarified in July 2018 that the new genome editing techniques are not exempt from the European GMO Directive.

1.1 Current regulation of traditional breeding methods

If a plant breeding company wants to market a new plant variety produced with traditional breeding methods, the variety has to be registered in the National Variety Register. To enter the Register, Naktuinbouw[11], the Netherlands Inspection Service for Horticulture, carries out several tests to determine whether the new variety is distinguishable from existing varieties (*Distinct*), whether the variety is uniform (*Uniform*), and whether the variety remains stable during propagation (*Stable*)[12] (so-called DUS-testing). To enable varieties to be listed, the variety is required to have an accepted name. The Board for Plant Varieties then decides whether to accept the new variety. Agricultural varieties (in contrast to ornamentals and vegetables) are also subject to the Value for Cultivation and Use (VCU) test for admission to the national register.[13] A new variety requires a significant improvement to any variety already registered, according to Directive 2002/53/EG, 'whether for cultivation or for

[11] The Netherlands Inspection Service for Horticulture monitors and promotes the quality of products, processes and chains in horticulture. The focus is on propagating material (seeds and plant material). The Netherlands Inspection Service for Horticulture is an Independent Administrative Body and is under the supervision of the Ministry of Agriculture, Nature and Food Quality (LNV)

[12] https://www.raadvoorplantenrassen.nl/nl/kwekersrecht-en-toelating/sier-fruit-en-boomkwekerijgewassen/dus-onderzoek-sier-fruit-en-boomkwekerijgewassen/

[13] https://www.raadvoorplantenrassen.nl/nl/kwekersrecht-en-toelating/landbouwgewassen/cgo-onderzoek-landbouwgewassen

valorisation of the harvest or of the products obtained from it'. Once a crop is in the National Variety Register of at least one of the EU member states, it can be traded throughout the European Union.
In order to protect ownership of a plant variety, a breeder can also apply for plant breeders' rights. Plant breeders' rights give the holder the exclusive right to trade the seed and propagation material. Other breeders may, however, use this new variety for further selective breeding. This is significantly different from patent rights. A patent is an exclusive right. Others may only do further selective breeding if they purchase a – possibly expensive – licence.

1.2 Current regulation of GM crops

The European GMO Directive 2001/18/EC regulates the release of genetically modified (GM) crops into the environment. The aim of the scientifically based licensing procedure is to ensure a high level of protection of human life and health, and of the health and wellbeing of animals and the environment. Crops subjected to the GMO directive require an Environmental Risk Assessment (ERA). The ERA studies the direct, indirect and cumulative (immediate and long-term) effects of the GM crop on public health and the environment. Furthermore, these organisms have to be monitored. Under Directive (EC) no. 1830/2003, traceability and labelling is ensured, with the aim of informing consumers. Crops exempt from the Directive are thus also exempted from this risk assessment, traceability, monitoring and labelling. In addition, EU Directive (EC) no. 1829/2003 sets down rules with respect to licences, risk management and labelling for food and animal feed containing GMO ingredients.

Legislation of the cultivation, trade and import of GM products in the EU has concentrated on safety. However, as mentioned briefly in the introduction, a great many issues apart from safety play a role in the introduction of GM crops in society. These societal values or cultural considerations have mostly been ignored during the last decades. Besides, following a positive European risk assessment, member states did not have the possibility of banning GMOs from their own territories for cultural or societal reasons. They could, however, have recourse to safeguarding measures, which could only be based on new or supplementary evidence in connection with risks posed by GMOs. This led to a political impasse.

In 2015, an attempt was made to break through this impasse with an amendment to the GMO Directive.[14] The new legislation makes it possible for individual member states to restrict or ban cultivation of GMO crops based on, among other things,

[14] Directive (EU) 2015/412 of the European Parliament and the Council.

societal, cultural and ethical aspects, provided there is a sufficient legal basis in the member state's national legislation, after a licence has been granted to cultivate a GMO crop in Europe.[15]

Restriction of geographical scope

A large number of member states, including the Netherlands, has applied for a restriction of the geographical scope of application, banning cultivation of GMOs in these member states.[16] The Netherlands intends to develop an assessment framework for evaluating the cultivation of GMOs. Since 2015, the Ministry of Agriculture, Nature and Food Quality has been engaged in drawing up an assessment framework, which will help assessing the socioeconomic impact of individual EU-approved GM-crops.[17] Agricultural policy objectives, but also land use, town and country planning, or factors including those relating to cultural traditions, sustainability, and public disquiet are legimate reasons for member states to restrict or prohibit cultivation of GM plants and crops. As a result, broader aspects will play a role in legislation, which will enable various stakeholders and the general public to be more involved in decision-making. The government is still developing an assessment framework at a national scale.

1.3 The emergence of genome-editing techniques

New technologies have been developed in the last few decades to solve existing problems of the classic recombinant DNA technology. With this older form of genetic engineering, it was, for example, difficult to locate a desired change at an exact location in the DNA of the host organism. Genome editing technologies[18] offer a solution to this problem and in addition are more efficient in making genetic changes. For the first generation of genome-editing techniques, expertise was necessary because for every new genetic sequence a researcher wanted to cut in – in order to change the DNA – she had to create a new speficic molecule. This changed with a new genome-editing technique, the CRISPR-Cas9 complex.[19] To cut DNA in different places (sequences) using CRISPR-CAs9, is straightforward compared to the older techniques. The cell itself subsequently repairs the DNA. With the discovery of these 'molecular scissors', gene modification in the laboratory has become faster, easier, less expensive and more precise. CRISPR-Cas9 is

[15] Parliamentary papers II, 2014/2015, 27 428, no. 307.
[16] https://www.rvo.nl/onderwerpen/agrarisch-ondernemen/grond/genetisch-gemodificeerde-gewassen
[17] To this end, at the request of the Ministry of Economic Affairs, the Rathenau Instituut has consulted different stakeholders: Munnichs, G., H. de Vriend and D. Stemerding (2016). Munnichs, G., H. de Vriend, and D. Stemerding (2016). *Afwegingskader nationale teeltbevoegdheid gg-gewassen- Verslag van een stakeholderdialoog.* The Hague: Rathenau Instituut
[18] New technologies such as the meganucleases, zinc finger nucleases (ZFNs) and the transcription activator-like effector nucleases (TALENs).
[19] CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats.

currently the most promising genome-editing technique for applications, although researchers are seeking new, more specific and more refined genome-editing systems.

The new genome-editing techniques can alter DNA in many different ways. For example, they can add several genes, or very accurately change one single letter of DNA (a nucleotide), but they can also switch genes on and off, while the DNA code itself does not change. In some cases, only the intermediate products have foreign DNA, but not the end product itself.[20] Therefore, no foreign DNA (exogenous nucleic acid molecules) needs to be present in the end product of plants changed with CRISPR technology.

As previously discussed, the application of CRISPR-Cas9 arrived at a time when Europe was discussing whether some of the new techniques for modifying plants and crops should fall outside the scope of the European GMO legislation. The emergence of CRISPR gave renewed impetus to the debate about new breeding techniques. In July 2018, the European Court of Justice clarified that only mutagenesis techniques, which had a proven long-term safety record, are exempt from the GMO directive.

Here, we will discuss arguments of various stakeholders concerning safety issues. In the next three chapters, we will examine the broader societal aspects important for the discussion.

1.4 Legal framework

For the purposes of the current European GMO Directive a genetically modified organism (GMO) refers to an organism, with the exception of human beings, whose genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. This definition raises the question whether a crop modified with CRISPR-Cas9, which could also have occurred naturally, is a GMO.[21]

Disagreement exists. And even if it is a GMO, there is disagreement about whether it needs to be exempt from the Directive, similar to crops obtained by mutagenesis?

[20] High Level Group of Scientific Advisors (2017). *New techniques in Agricultural Biotechnology.* Explanatory note. European Commission, Brussels.

[21] The answer to the question depends in part on the interpretation of the phrase 'in a way that does not occur naturally'. If 'in a way' refers to the method, then the technique is relevant and all techniques that do not take place naturally fall within the scope of the GMO Directive. In nature, CRISPR-Cas9 does not cut genetic material in plants and therefore the CRISPR crops should be regulated as GMOs. However, if you assume that 'in a way' refers to the way the genetic material is rearranged, the technique used to rearrange the DNA is irrelevant, as long as the rearrangement could have taken place in nature. This reading of "in the way" excludes crops modified with CRISPR from the GMO legislation. However, the Court has clarified that all products of genome editing are subject to the GMO Directive.

Mutagenesis is the introduction of small genetic changes into DNA of cells. Before the GMO Directive was adopted in 2001, only conventional mutagenesis methods were available: radiation or chemical mutagenesis. Both exposure to radiation or mutagens can cause random mutations in DNA. These genetic changes can bring about phenotypic changes in the plant. Desired phenotypic changes can then be selected, and crossbred. Like mutagenesis, genome editing can introduce minor changes in the DNA of cells. In contrast to the older recombinant-DNA techniques, it is possible to have a genetically engineered plant without foreign DNA, because only small mutations were introduced. For this reason, genome editing is viewed by some stakeholders as a modern form of mutagenesis, but more accurate than traditional mutagenesis. Because mutagenesis in crops had been used for years without it resulting in negative risks to health and the environment, this technology was exempted when Directive 2001/18/EC was drafted. Various stakeholders therefore argue that products of genome editing should also be exempted from the Directive. The argument in favour of deregulation of genome editing thus rests mainly on the legal and scientific comparison of the genome-edited products with traditionally- bred crops or altered through mutagenesis. The main argument being that no difference exists at the nucleotide level. And because CRISPR is more accurate, some stakeholders maintain that genome-editing techniques are actually safer than mutagenetic techniques.[22] Here, 'more accurate' is translated as 'safer'.

Others argue, however, that genome editing in plants is relatively young, and still in development. The effects on public health and the environment are as of yet unknown. Therefore, the technology should be subject to the GMO Directive.[23] According to these groups, the fact that the genetic changes *could* have occurred without human intervention is based only on one outcome – the order of the DNA (the nucleotide sequence). It cannot (yet) be claimed that the method is irrelevant. Moreover, how do we know whether a mutation could have occurred in nature? And even if it would, is it relevant when it concerns the protection of public health and the environment? These advocates of regulation also argue that several of the new breeding techniques can be used simulataneously, creating a plant with lots of small changes, but also one that possibly differs substantially from the parent plant. New characteristics can also have unintended effects. For example, when the specificity or activity of an enzyme is altered, it can have consequences for a number of reactions in the plant. Finally, there are unintended effects and unforeseeable consequences of genome editing that are already known, such as

[22] Royal Netherlands Academy of Arts and Sciences (2016). *Genome Editing, Visiedocument KNAW.* Amsterdam, KNAW.
[23] *Open letter to the Commission on new genetic engineering methods.* (2015). http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/New_Breeding_Techniques___Open_Letter_27_Jan_2015.pdf; ENSSER (2017) *Statement on New Genetic Modification Techniques. Products of new genetic modification techniques should be strictly regulated as GMOs.*

'off-target effects', as they are called.[24] CRISPR-Cas9 can cut in unintended places, thus altering the DNA in various places.[25] Further crossing of the genetically modified plant can remove these off-target effects.

In addition to these scientific arguments, advocates of regulation also have a legal argument. The mutagenesis techniques were exempted because of their long-term safety record. This is not the case for genome editing, and as a consequence, genome editing cannot be eligible for exemption from the GMO Directive.

1.5 Ruling by the Court

The European Court of Justice was asked by the highest administrative court of France to clarify the scope of the GMO Directive and the scope of the exemption. The reason for this was a court case in France. Confédération paysanne, a French agricultural organisation representing the interests of small-scale farms, and eight environmental associations, tried to ensure that new plant-breeding techniques would be regulated as GMOs through a court decision. These new techniques can be used to produce herbicide-tolerant crops and the applicants wanted the cultivation and trade of these crops to be regulated. On the 25th of July 2018, the Court ruled that all organisms altered by mutagenesis methods or techniques, are genetically modified organisms according to the GMO Directive. It follows, therefore, that all products of genome editing are subject to the European GMO Directive. The Court also clarified that only organisms obtained through certain methods of genetic modification that had *conventionally been used in a number of applications and had a long safety record* are exempt (Annex 1B). Products of genome editing that no longer contain any foreign DNA are therefore not exempt. The Court also clarified that member states *may* regulate – in accordance with the GMO Directive or under national or other legal provisions – those mutagenesis methods that have been proven safe. As a result of the Court's ruling, the new genome-editing techniques can only be exempted from the GMO Directive through an amendment to EU Directive 2001/18/EC.

In response to the ruling, two opposing policy options dominate the current debate. Some stakeholders, such as NGOs and the organic sector, argue that the EU Directive should not be amended, because genome-editing techniques should be regulated as GMOs. Others, mainly agrochemical and plant-breeding companies,

[24] Ibid.; Econexus (2015). *Genetic Engineering in Plants and the 'New Breeding Techniques (NBTs).* Inherent risks and the need to regulate'. Briefing, Econexus http://www.econexus.info/publication/genetic-engineering-plants-and-new-breeding-techniques.

[25] Fu Y. et al. (2013). High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells. *Nature Biotechnology* 31, pp.822–826; Peng R., Lin G., Li J. (2015). Potential pitfalls of CRISPR/Cas9-mediated genome editing. *FEBS Journal* 283, pp.1218–1231.

some research institutes and the Dutch government, argue for the opposite: when no foreign DNA is present in the products of genome-editing techniques, the plants should be exempt from the GMO Directive. A third option, less prominent in the debate, advocates a level-based policy approach for all genetically modified organisms, including crops developed using genome editing. In this report, we will discuss the various arguments in favour and against these three policy options, focussing on safety issues as well as broader considerations such as economic, ethical, and societal aspects. Relevant issues range from trade issues, a level playing field for biotechnology companies and research institutes, the concentration of power of large multinational companies, co-existence with organic agriculture, the freedom of choice of the European citizen and possible public disquiet.

1.6 The use of concepts in the debate

One concern in the debate is the concepts used for the new technologies. When the term ‘genome editing’ emerged, it seemed to refer to the CRISPR technology and the previous, first-generation genome-editing technologies (engineered nucleases). As often happens when new technologies are introduced, the new concept emphasised the innovative nature of the technology, and distinguished it from the older recombinant-DNA technology. However, opponents often highlight the risks and uncertainties of the innovatieve technology. Consequently, supporters often react by downplaying the novelty of the new technique and highlight the similarities of the new techniques with the existing ones. A similar change can be seen in the discussion on genome editing. The genome-editing techniques are now often referred to as the new mutagenesis techniques to emphasize that there is nothing new under the sun.[26] By calling genome-editing techniques mutagenesis techniques, stakeholders tried to exempt the new technology from the GMO Directive.[27] They are also called new breeding techniques, to stress the comparison with traditional breeding techniques, and detach them from the negative connotated “genetic modification”. We also observe a change in the use of the concept “genome editing”. Some scientists now argue that the natural process of random mutations is actually also genome editing. This again is an attempt to highlight that there is nothing new under the sun.

According to Bunge and Dockser, companies prefer to talk about new breeding technologies rather than biotechnology when they discuss genome editing, as they

[26] Swierstra, T. and A. Rip (2007). Nano-ethics as NEST-ethics: Patterns of Moral Argumentation About New and Emerging Science and Technology. *Nanoethics* 1, pp. 3-20.

[27] Although plants modified by “traditional”mutagenesis techniques are GMOs according to the European Court of Justice, they existed before the term GMO came into being. The term GM-crops was a way to distinguish crops modified with recombinant-DNA techniques from the ones modified with these older methods.

want to distinguish between genetic modification and genome editing.[28] This can lead to confusion. Here, we will use the term new genome-editing techniques, to refer to all site-directed nucleases, although mainly it will concern CRISPR techniques (including CRISPR-Cas9), as these are thought to be most important in future. Moreover, this report will mainly discuss the use of CRISPR-Cas to replace or delete base pairs, without adding any foreign DNA, as the current Dutch debate is mainly concerned with this method of genome editing, although genome editing can be used to change DNA in many different ways.

[28] Bunge, J. and Dockser Marcus, A. (2018). 'Is this tomato engineered? Inside the coming battle over gene-edited food' *Wall Street Journal*, April 15, 2018.

2 Option 1: No revision of the European GMO Directive

If the European Commission does not amend the GMO Directive, the genome-edited crops will be subject to the GMO regulation. In this case, market approval will necessarily be preceded by a risk assessment in order to safeguard public health and protect the environment. However, this option does not address the arguments of those opposed to genome editing being regulated as GMO's. In this chapter, we will discuss these arguments and examine possible consequences of this policy option.

2.1 Safety

If the European Commission does not amend the Directive, a licence or notification is necessary for research activities involving GMOs within facilities such as laboratories and glasshouses ('contained use'). EU Directive 2001/18/EC regulates release into the environment (field trials and market authorisation). After products are launched on the market, it is compulsory to monitor these crops for possible effects submitted in the environmental impact assessments, and for unexpected effects on the environment.[29]

To NGOs such as Friends of the Earth, Greenpeace European Unit, GeneWatch and Testbiotech of Germany, it is essential that all products of genome editing be subject to the Directive because the genome editing techniques are still in their infancy. [30] Similarly, the European Network of Scientists for Social and Environmental Responsibility (ENSSER) argues that these techniques must be regulated due to scientific uncertainties.[31] Indeed, we have no scientific knowledge regarding the long-term safety of genome-editing techniques.

IFOAM Organics International opposes the argument that, because no major changes are generated at the nucleotide level, genome-edited products are safe. In

[29] https://ec.europa.eu/food/plant/gmo/post_authorisation/plans_reports_opinions_en; Even if these crops are not grown in the EU, but are imported from outside the EU, they have to be monitored with respect to environmental safety.
[30] Open letter to the Commission on new genetic engineering methods (2015). http://www.greenpeace.org/eu-unit/Global/eu-unit/reports-briefings/2015/20150127%20Open%20Letter%20on%20new%20GM%20technologies.pdf
[31] ENSSER (2017). Statement on New Genetic Modification Techniques. Products of new genetic modification techniques should be strictly regulated as GMOs. https://ensser.org/topics/increasing-public-information/ngmt-statement/

reality, there are several steps in the genome editing process – for example, culturing the cells, preparing the cells, the use of a method for DNA to enter the cell (the vector), and the use of methods to induce a particular stage in the cell cycle.[32] All these steps could carry risks, and at all these steps, changes at the cellular level are in principle possible. Furthermore, even small changes at the genetic level can lead to major changes at the level of an organism. For example, a point mutation (a change in one single letter in the DNA) in humans can lead to cystic fibrosis or sickle cell anaemia[33] – a small change thus, with enormous consequences.

Moreover, some drawbacks of the CRISPR-Cas9 method itself are already known. A first drawback is the off-target effects. Cas9 also cuts in locations other than the desired one.[34] The cell will repair these cuts, but frequently, small changes (mutations) in the genome occur in the DNA repair process. These genetic changes can change certain traits of the organism. However, through cross-breeding during development of new crops, these off-target changes can be eliminated. Moreover, mutagenesis also induces these small DNA changes. Second, recent research demonstrates an influence of the process itself (the technique) on the cell.[35] Reseachers discovered that human cells that allowed CRISPR to effectively and accurately replace DNA, have an increased risk of becoming cancerous cells. 'Healthy' cells exhibit a stress response in the event of a double-stranded DNA break, preventing CRISPR from accurately repairing the DNA in the way intended by the researcher.[36] Selection for cells with the intended change (where CRISPR has thus worked effectively) is therefore also selection for cells with an increased probability of proliferating uncontrollably. Another article in *Nature Biotechnology*[37] reports large deletions and rearrangements in DNA sequence, due to the use of CRISPR-Cas9. Because researchers often only check whether CRISPR has made the desired alteration in the gene, these large changes further away from the target site are sometimes missed. This first systematic study of unexpected DNA alterations when using CRISPR to modify DNA demonstrates that in the past, unintended genetic have been underestimated. Another study, using Arabidopsis plants, showed that the efficiency of CRISPR varied between the three varieties of the Arabidopsis plant tested. This could be due to their different genetic backgrounds or because of epigenetic differences. Epigenetic differences influence

[32] IFOAM Organics International (2017). *Compatibility of Breeding Techniques in Organic Systems.* Position paper.
[33] Steinbrecher, R.A. and Paul, H. (2017). New Genetic Engineering Techniques: Precaution, Risk, and the Need to Develop Prior Societal Technology Assessment. *Environment: Science and Policy for Sustainable Development* 59, pp. 38-47.
[34] Marx, V. (2014). Gene editing: how to stay on-target with CRISPR. *Nature Methods* 11, pp. 1021-1025.
[35] Haapaniemi, E. et al. (2018). CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response. *Nature Medicine* 24, pp. 927–930.; Kosicki, M., Tomberg, K. & A. Bradley. (2018) Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology* 36, pp. 765–771.
[36] Haapaniemi, E. et al. (2018). CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response. *Nature Medicine* 24, pp. 927–930.
[37] Kosicki, M., Tomberg, K. & A. Bradley. (2018). Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology* 36, pp. 765–771.

the activation of genes.[38] Possibly, the difference in efficiency of CRISPR is caused by the fact that DNA strands first have to separate before they can be cut – and that CRISPR cannot do its work properly if the DNA strands are firmly connected. These recent articles demonstrate limitations of CRISPR-Cas9, but more importantly, they remind us that the technology is new, and new evidence on the method is accumulating continuously.

A third drawback of the genome editing technologies is their potential risks to the environment. IFOAM, the umbrella organisation of organic agriculture warns against a reduction in genetic diversity, equal to the loss of diversity caused by the use of GMO's in agriculture.[39] IFOAM worries that patents on these genome-edited plants will drastically reduce genetic diversity and the availability of a wide diversity of seeds. In Europe genetic variation has declined over the last century while genetic variation is necessary for resilient agricultural systems in view of risk of infections. The UN's Food and Agriculture Organization (FAO) argues that the preservation of biodiversity is one of the most important ways of maintaining world food production, as plants have to be able to adapt to changing environments, caused by e.g. climate change.[40] Advocates of deregulating genome editing argue that it is in stead, the new techniques that will enable us to genetically alter plants to adapt to changing circumstances. However, this does not solve the problem of the vulnerability of monocultures. In addition, IFOAM advocates preserving our collective genetic heritage and biodiversity against the increase of new genetic modification techniques.[41] We have to preserve nature's integrity and diversity.

2.2 Societal considerations: transparency, freedom of choice and trade issues

In February 2017, the European Group on Ethics in Science and New Technologies (EGE) gave the advice to the president of the European Commission that the debate about genome editing should not only address safety, but also broader societal questions, such as justice, equality, proportionality and autonomy.[42] Below, we discuss a number of ethical and societal challenges frequently referred to in the debate: transparency, freedom of choice for consumers, and trade issues.

[38] Cho, S. et al. (2017). Accession-Dependent CBF Gene Deletion by CRISPR/Cas System in Arabidopsis. *Frontiers in Plant Science*, 8:1910.
[39] IFOAM Organics International (2016). *Genetic Engineering and Genetically Modified Organisms.* Position paper.
[40] The Food and Agriculture Organization of the United Nations and the Platform for Agrobiodiversity Research (2010). *Biodiversity for Food and Agriculture Contributing to food security and sustainability in a changing world.* Outcomes of an Expert Workshop held by FAO and the Platform on Agrobiodiversity Research from 14–16 April 2010 in Rome, Italy.
[41] IFOAM Organics International (2017). *Compatibility of Breeding Techniques in Organic Systems.* Position paper.
[42] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (2015). *Statement on Gene Editing.*

If the European Commission does not amend the GMO Directive, genome-edited crops will need to be labelled, which will maintain the freedom of choice of farmers and consumers. In particular for the organic agricultural sector this ability to trace genetically modified crops is important, as contamination could damage their image.[43] The economic importance of the European organic sector is increasing. Labelling is also important for the Dutch seed potato sector. The Netherlands controls 60% of the world trade in certified seed potatoes.[44] Some of the countries that import these potatoes require non-GMO declarations. Currently, these declarations are still straightforward to obtain, as no GM potatoes are grown in the Netherlands. Should the EC decide to amend the Directive, this could have economic consequences for the Dutch potato sector, and possibly the sector in other countries, as well as for European organic agriculture. Both the potato and the organic sector might have to take additional measures to ensure GM-free products. This raises the question of fairness: should non-GMO growers bear the burden of the costs and time involved in ensuring GM-free produce?[45]

The labelling requirement presents a challenge to the import of crops from regions outside the EU, where the techniques are not regulated.[46] To import these products into the European Union, they need to be labelled. Possibly, foreign companies will label their products in future in order to gain a share in the European market.[47] If not, certain products from certain regions may not be imported anymore. This could have at least two negative consequences. First, it could cause trade problems. A trade dispute could arise again between the EU and other countries, as happened previously with GMOs. The problems could be bigger this time, due to the increasing number of gene-edited crops currently in development.[48] Second, it could result in a limited range of products available in the EU.[49] In addition, there is some concern that gene edited food would be available on the European market without it being labelled, because it would be hard to detect or identify these foods. Whether this is a genuine concern, is a matter of debate. It should be recognised that plant breeders will want their genome-edited crops to be distinguishable from other crops. They will most likely provide the genetic modification in order to obtain intellectual property rights. And even at the genetic level the claim that gene edited

[43] IFOAM, EU Group (2015). *New Plant Breeding Techniques.* Position paper.
[44] https://www.agroberichtenbuitenland.nl/specials/aardappelen/nao
[45] IFOAM (2018). *Preliminary ruling of the European Court of Justice on the legal status of plant breeding and genetic engineering techniques C-528/16.* Press Briefing.
[46] Ministry of Infrastructure and Water Management. (2017). *Naar een toekomstbestendig biotechnologiebeleid.* Inspiration document. Ministry of Infrastructure and Water Management.
[47] Ibid.
[48] https://cspinet.org/news/european-union-issues-crucial-ruling-regulating-gene-edited-organisms-gmos-20180726
[49] COGEM (2010). *Geboeid door keuzevrijheid. Een verkenning van de ontwikkeling en rol van keuzevrijheid rondom ggo's in Europa.* Policy report. CGM/101230-02.

crops could not be identified as such is contested by Duesing and her colleagues.[50] Plant genes usually have several copies in the DNA. Whenever a crop is found with multiple copies of the same gene knockout (for example), it will almost be certain that genome editing was used. A natural mutation or one induced by radiation or chemicals is random and probably will only be found on one copy of the genome. Moreover, because of the precision of the technique, a modification can be found in a product, provided the seed breeder discloses the altered sequence. And even if there are no technical possibilities for identifying products, legislation can still be made for traceability, based on sworn statements. Again, agrochemical companies will themselves want their products to be recognisable, as it is necessary to uphold breeders' rights and patents. However, should crops be impossible to recognise, because identification is based solely on DNA analysis, it may be difficult to enforce the GMO Directive.

Precisely because it cannot always be recognised in the end product whether new genome-editing techniques have been used, traceability and labelling are important, according to the international umbrella organisation for organic agriculture, IFOAM.

2.3 Economic challenges

Large, medium and small biotechnology companies, and various knowledge institutions, united in the New Breeding Techniques (NBT) platform, argue that it is time-consuming and expensive to apply for a licence for GM crops in Europe. According to them, this hampers innovation. They also foresee that due to the restrictive policy only large multinationals in Europe will have the means to launch CRISPR-Cas-modified crops on the market, thus maintaining their monopoly positions (one of the arguments against GMOs), leading to an increased influence of large international companies on our food system.[51]

Testbiotech (Institute for Independent Impact Assessment in Biotechnology) objects to this latter argument.[52] A study on patents by Testbiotech in June 2018 shows that the large international agrochemical companies – DowDuPont, Bayer (plus Monsanto), Cellectis, Sygenta and BASF – have applied for the largest number of patents for genome-editing techniques. Very few traditional growers have applied for any patents.[53] The Dutch Arable Farming Union (Nederlandse Akkerbouw Vakbond) disclosed that only a handful of plant-breeding companies are left due to

[50] Duesing, N., et al. (2018). (2018). Novel Features and Considerations for ERA and Regulation of Crops Produced by Genome Editing. *Frontiers in Bioengineering and Biotechnology* 6, 79.
[51] https://www.eoswetenschap.eu/natuur-milieu/ggos-en-ecologische-landbouw-zijn-geen-tegenstelling
[52] https://www.testbiotech.org/en/press-release/more-and-more-patent-applications-crispr-plants-and-animals
[53] Ibid.

takeovers by these large multinationals.[54] Possibly, conventional farmers may thus also benefit from maintaining the EU Directive, if this avoids them becoming dependent on the large agrochemical (and seed) multinationals.

2.4 Commercial and research activities

The Dutch Arable Farming Union is disappointed with the clarification of the European Court of Justice and argues that genome-editing techniques should be deregulated in Europe in order to maintain a level playing field.[55] The European Seed Association and EuropaBio also warn against significant negative economic impact, should the GMO Directive not be amended.[56] They argue that legislation outside the EU is less complex, making it more difficult for companies based within the EU to compete. At the moment, the EU is still the world's second largest seed exporter. In addition, plant breeding companies and research institutes in Europe play a major role in international research and in developing new plant breeding techniques.[57] The COGEM and the Health Council of the Netherlands consider it a possibility that commercial and research activities will disappear from Europe if the EC does not amend the Directive.[58] For example, Dutch trader (and breeder) of seed potatoes HZPC announced it is considering moving part of its research work to the US.[59] Some stakeholders fear, that as a consequence, Dutch knowledge on this new techniques will lag. According to them, this could potentially result in an inability to evaluate international developments properly.[60]

2.5 Conclusion

The debate on genome editing in plants and crops centers around 'safety' and 'innovation'.

Because CRISPR-Cas9 has only been used in the laboratory for a number of years, and because recently research revealed risks associated with the technique not

[54] http://www.nav.nl/2014/01/tegenwicht-bieden-aan-zaad-chemiereuzen/
[55] http://www.nav.nl/2018/07/nav-zeer-teleurgesteld-over-uitspraak-crispr-cas/
[56] Michalopoulos. S. (2018). Industry shocked by EU Court decision to put gene editing technique under GM law. Euractiv. https://www.euractiv.com/section/agriculture-food/news/industry-shocked-by-eu-court-decision-to-put-gene-editing-technique-under-gm-law/
[57] https://www.trouw.nl/home/gaan-vs-aan-de-nederlandse-pieper-sleutelen-~a7f2ca93/ en https://www.nu.nl/economie/4517175/exporteur-pootaardappelen-hzpc-overweegt-onderzoek-vs-verplaatsen.html; Lusser, M. et al. (2011). *New Plant Breeding Techniques. State-of-the-art and prospects for commercial development.* Joint Research Center Scientific and Technical Reports. JRC
[58] COGEM, Health Council of the Netherlands. (2016). *Trendanalyse biotechnologie 2016, Regelgeving ontregeld.* Bilthoven.
[59] https://www.trouw.nl/home/gaan-vs-aan-de-nederlandse-pieper-sleutelen-~a7f2ca93/
[60] Munnichs, G., H. de Vriend, and D. Stemerding (2016). *Afwegingskader nationale teeltbevoegdheid gg-gewassen- Verslag van een stakeholderdialoog.* The Hague: Rathenau Instituut

previously known, advocates of preserving the EU Directive argue that caution is needed. In preserving the Directive, the European Commission would address the concerns that exist regarding the safety of the products of genome editing for human health and the environment.

Proponents of amending the EU Directive find the current situation unsatisfying. The existing regulation is a brake on innovation, and they forewarn that Europe will lose its commercial and research activities related to seed breeding. Moreover, according to them, genome editing can make important contributions to society, such as reducing the use of pesticides, reducing food waste and create crops adapted to new climates.

3 Option 2: an amendment to the European GMO Directive

If the European Commission amends the GMO Directive to exempt genome editing from the Directive – if no foreign DNA is present in the product – it creates room for agrochemical and plant breeding companies to develop and market new products in Europe. However, this option poses challenges, for example because no risk assessments or monitoring of these new products would occur. In this chapter, we describe how different organizations view the societal consequences of an amendment to the Directive. We elaborate on the discussion about the safety, benefits and necessity of using genome editing for crop breeding on the market position of large seed-breeding companies versus small and medium-sized companies, the patenting of genome-edited crops, and freedom of choice for consumers.

3.1 Amending the Directive

The long-awaited ruling by the European Court of Justice caused commotion.[61] Some organisations are disappointed, such as the Dutch Arable Farming Union[62], the European Academies Science Advisory Council (EASAC), the European Seed Association, EuropaBio,[63] the New Breeding Techniques Platform, and Plantum.[64] In general, agrochemical and plant-breeding companies react in two ways: first, they warn about the economic consequences for Europe. Second, they warn against ecological consequences. They argue that the Court's clarification will prevent Europe from meeting some of the major challenges we need to manage in the world today, such as climate change. For some researchers, the Court's ruling underlines the necessity to review the current GMO legislation in Europe.[65] It is expected that some companies and research institutes will lobby for an amendment

[61] https://nos.nl/artikel/2243150-europees-hof-remt-kwekers-vanwege-genetische-modificatie.html; https://www.nieuweoogst.nu/nieuws/2018/07/25/nav-zeer-teleurgesteld-over-uitspraak-crispr-cas; https://www.hollandbio.nl/nieuws/uitspraak-europees-hof-blokkeert-duurzaamheid-gezondheideninnovatie/; https://www.foodlog.nl/artikel/europees-hof-legt-het-spelen-met-dna-aan-banden/; https://www.wur.nl/nl/artikel/Uitspraak-Europese-Hof-van-Justitie-vraagt-om-herzien-regelgeving-nieuwe-veredelingstechnieken-in-Europa.htm

[62] http://www.nav.nl/2018/07/nav-zeer-teleurgesteld-over-uitspraak-crispr-cas/

[63] Michalopoulos. S. (2018). *Industry shocked by EU Court decision to put gene editing technique under GM law.* Euractiv. https://www.euractiv.com/section/agriculture-food/news/industry-shocked-by-eu-court-decision-to-put-gene-editing-technique-under-gm-law/

[64] http://www.nbtplatform.org/

[65] https://www.plantum.nl/hoofdnavigatie/actueel/nieuws-detail?newsitemid=2111733760

to the Directive.[66] HollandBIO calls on the Dutch government 'to commit itself with renewed energy to make new breeding methods available in the Netherlands and in Europe'.[67]

At the European administrative level, the Dutch Ministry of Infrastructure and the Environment (during the previous government) presented a proposal to amend the exemption of the European GMO Directive.[68] This initiative of the previous State Secretary was instigated by the grievances of plant breeders that market authorization processes were long and costly, and the ambiguity of the regulation of these new genome-editing techniques would lead to disharmonization in Europe. The proposal was to amend the exemption (Annex 1B) of the GMO Directive: the words 'they do not *involve* the use of recombinant nucleic acid molecules or genetically modified organisms' would be replaced by 'recombinant nucleic acid molecules or genetically modified organisms are *no longer present* in the product'. In this way, the exemption would no longer be based on the process, but on the product.

Genome-edited crops and plants without any foreign DNA present would be eligible for exemption. All other applications of genome-editing techniques would still be subject to the GMO Directive. In this Dutch proposal it is assumed that genome-edited plants are as safe as traditionally-bred plants if (i) plants have mutations that are comparable with mutations induced by mutagenesis; (ii) these mutations can also be obtained through traditional cultivation; and (iii) these plants are subsequently given the additional guarantees present for traditionally bred plants (a quality check and compulsory registration).[69] Accuracy at the level of nucleotide change is interpreted as safe.

3.2 Safety

If an amendment to the exemption would come into force, genome-edited plants and crops developed in the EU would be exempt from the GMO Directive, providing no foreign DNA is present in the end product. For these plants, no risk assessment would be required and a DUS test would be sufficient for market approval (see section 1.1). Other genome-edited, or genetically modified plants would remain subject to the GMO Directive.

[66] https://www.wur.nl/nl/artikel/Uitspraak-Europese-Hof-van-Justitie-vraagt-om-herzien-regelgeving-nieuwe-veredelingstechnieken-in-Europa.htm
[67] https://www.hollandbio.nl/nieuws/uitspraak-europees-hof-blokkeert-duurzaamheid-gezondheid-en-innovatie/
[68] Parliamentary papers II 2017/2018, 27 428, no. 346; Appendix to Parliamentary papers II 2017/2018, 27 428, no. 346.
[69] Ibid.

IFOAM and environmental organisations such as Friends of the Earth and Greenpeace, as well as the European corporate lobby watchdog, Corporate Europe Observatory, argue that risk analysis and monitoring of the new technologies should still occur, given that no safety data are available yet.[70] And even if short-term safety data would be available, according to NGOs and ENSSER the precautionary principle requires new and innovative techniques to be regulated, because of the absence of information on long-term safety. The precautionary principle is a fundamental principle of European legislation, but also of the Convention on Biological Diversity and the Cartagena Protocol on Biosafety, both signed by the European Union. The precautionary principle declares that a lack of full scientific certainty is no reason for postponing measures to avoid or minimize risks posed by a living modified orgamism resulting from biotechnology.

3.3 Benefits and the necessity to innovate

According to advocates of option 2 (amendment of the Directive), current legislation ignores the benefits of biotechnological innovations and the costs that accompany regulation. Legislation would benefit from a more balanced approach.[71] HollandBio believes companies need greater flexibility when developing new products in order for them to manage global challenges such as sustainability, health and securing the food supply.[72] The New Breeding Techniques (NBT) platform views the Court's ruling as depriving Europe from the capacity to address societal challenges such as climate change and food security.[73] Plantum, the Dutch association for the plant reproduction material sector, considers the ruling a missed opportunity to increase the speed to contribute to sustainability in agriculture and horticulture.[74] However, whether the new products of genome-editing techniques really are sustainable depends on one's interpretation of sustainability. For environmental NGOs, the social and economic consequences of the technology are part of sustainability. Therefore, if a technology reinforces the existing power imbalances and inequalities at the expense of vulnerable small-scale farmers, that technology is not

[70] Joint position paper (2016). http://www.greenpeace.org/eu-unit/Global/eu-unit/reports-briefings/2016/Joint%20position_New%20techniques%20of%20genetic%20engineering_March%202016-1.pdf; *Parliamentary papers II*, 2017/2018, 27 428, no. 346; https://corporateeurope.org/food-and-agriculture/2015/06/european-union-new-tech-products-gmos-or-not-european-commission-will

[71] Wiel, van de, C.C.M. et al. (2017). New traits in crops produced by genome editing techniques based on deletions. *Plant Biotechnology reports*, 11: 1-8.

[72] *Naar Toekomstbestendig Biotechnologiebeleid.* Ministry of Infrastructure and Water Management stakeholder meeting. 07 November 2017

[73] http://www.nbtplatform.org/

[74] https://www.plantum.nl/hoofdnavigatie/actueel/nieuws-detail?newsitemid=2111733760

sustainable.[75] And, as we saw earlier, it is mainly the large global agrochemical and seed-breeding companies that currently apply for patents. [76]

Benefits

Biotechnology can help achieve higher yields in agricultural crops to reduce the global food problem, as well as reduce the ecological footprint.[77] With genome editing, more nutritious crops can be developed that are resistant to diseases (e.g. viruses) and drought, or that remain fresh longer preventing food wastage. These crops are not banned in the EU, but they are currently regulated on a case-by-case basis to assess the risks to health and environment. Should these products be exempt from regulation, they can be marketed quicker and the societal benefits achieved earlier. Although for crops to be successful, not only their genetic composition is important, but also the weather conditions, soil conditions, the micro-organisms around the plant, the farmer, the supermarket and the consumer.

Various environmental organisations are sceptical about this way of reasoning. According to them, world food problems are often framed inaccurately and moreover, technology is not the solution to these problems.[78] They maintain that enough food is produced worldwide to feed the world population; instead, the unfair distribution is problematic. Furthermore, existing GM crops have not fulfilled the promise of solving these world problems in the last 30 years. Why would these new genome-edited crops be any different?[79] In contrast, industry and various research institutes maintain that this failure of GM-crops to contribute to societal problems is caused by the strict legislation and accompanying high costs. Those conditions ensure that commercial applications are limited to those that are relevant to large areas of land – the major crops such as grains (soya, maize and rice) and industrial crops such as cotton.

Although the GMO regulation influences the pace of market authorisation for GM crops, it does not consider the benefits or need of an innovation. The licensing procedure only considers risks. As of 2015, member states can refuse cultivation of GM-crops on all or part of their territory based on national concerns related to e.g. environmental or agricultural policy objectives, socioeconomic impacts, or public policy. In this case broader considerations are taken into account, however, only to opt out of cultivation, not to stimulate authorizing cultivation.

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[75] Asveld L. & D. Stemerding (2016). *Algae oil on trial. Conflicting views of technology and nature*, The Hague: Rathenau Instituut

[76] These global companies may be more inclined to listen to the wishes of their shareholders than solve major societal challenges.

[77] Ministry of Infrastructure and Water Management. (2017). *"Naar een toekomstbestendig biotechnologiebeleid".* Inspiration document.

[78] Helliwell, R. et al. (2017). Why are NGOs sceptical of genome editing? *EMBO reports* 18, pp. 2090-2093.

[79] Nuffield Council on Bioethics. (2012). (2012). *Emerging biotechnologies: technology, choice and the public good.* London, UK.

Advocates of both option 1 and 2 believe that the benefits of genome-edited plants should also be considered. Perhaps the benefits, need, and sustainability of innovations should be taken into account *during* the licensing procedure, and not only the risks.

3.4 Economic consequences

The export of European seed in 2017 is estimated at €7.8 billion. The Netherlands have a 34% share.[80] According to the multinational seed companies, an amendment to the Directive is essential if we want Europe to remain competitive in seed breeding and export because the current legislation is laborious, time-consuming and expensive. Companies are expected to move out of Europe to countries where the new techniques are less stringent regulated, for example to the United States. The US Department of Agriculture (USDA) announced in March 2018 that it is not planning to regulate genome-editing techniques.[81] It is therefore expected that products will quickly gain access to the US market. In the US, for example, a non-browning mushroom has been developed. With the use of CRISPR-Cas9, a number of base pairs were removed from the gene that encodes an enzyme that causes browning. Other crops that have been developed are e.g. a camelina (*Camelina sativa*) that produces more oil, a drought-resistant soya bean, and a sweeter strawberry. The gardening company Scotts Miracle Gro is developing genetically modified grass that would need less mowing.

The US decided as early as 1986 that no specific regulation was required for genetic modification techniques. Not the satefy of the technique, but the safety of the product needed careful examination. In the US, the general legislation for food safety and pesticides, for example, is considered sufficient for regulating the products of GM technology as well.[82]

As mentioned previously, some authors maintain that exempting the new techniques from the European GMO Directive can end the current monopoly position of seed multinationals.[83] Due to the duration and the costs of the licensing procedure, market authorization is confined to large companies. Exemption from

[80] Source of data: http://www.escaa.org

[81] https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation

[82] COGEM. (2008). *Should EU legislation be updated? Scientific developments throw new light on the process and product approaches.* Policy report. (090626-03).

[83] Mullins, E. (2014). Engineering for disease resistance: persistent obstacles clouding tangible opportunities. *Pest Management Science* 71, 645-51.; Jacobsen, E. and Schouten, H.J. (2009). Cisgenesis: an important sub-invention for traditional plant breeding companies. *Euphytica*, 170: 235.

this procedure would thus create a level playing field between large companies and small and medium-sized enterprises (SMEs).[84] The question is, whether start-ups and SMEs really can compete with large companies in practice, as we discussed in option 1. The answer partially depends on the possibility to patent crops obtained using new breeding techniques.

3.5 Societal considerations: identification, freedom of choice and a broader assessment framework

The current GMO Directive enforces GM crops to be labelled because farmers and consumers need to be able to identify them, in order for them to have freedom of choice to purchase them or not, based on their ethical and societal concerns or preferences.[85] If genome-edited crops will be exempt from the European GMO Directive, these crops will not require labelling, removing this freedom of choice.[86] Labelling is key to Europe's GMO legislation. In compliance with international trade agreements, safe GM products cannot be banned from the market, but they do require labelling. NGOs argue that citizens are concerned about safety of GM-crops, but also express worries based on societal, ethical and political grounds. Reasons for not buying GM products are, for example, the unnaturalness of GMOs or other convictions based on principles or beliefs. Avoiding GMOs can also be a form of solidarity with poor and/or organic farmers.[87] Abandoning the labelling requirement restricts the control that citizens have as consumers, and should therefore be avoided, according to NGOs. They would prefer farmers and consumers to instead have more power.[88] Others argue that the labelling requirement has reduced consumer choice, because of the limited range of GM products in the European supermarkets as a consequence of the labelling.[89] Another issue is that a large part of the population views a GMO label as a safety warning, even though these products have undergone a safety assessment.[90]

[84] However, these GMO-monopolies were established outside of Europe, as hardly any GM- crops are cultivated here, and thus independent of the EU licensing procedure, but depended on the less strict market in other countries.

[85] The threshold value for labelling is 0.9% per ingredient.

[86] Parliamentary papers II, 2018/2018, 27 428, no. 347.

[87] Meyer, R. (2012). *Grüne Gentechnik im Kontext landwirtschaftlicher Entwicklung -Reflexion gesellschaftlicher Kontroversen durch Technikfolgenabschätzung.* In: Grimm, H., Schleissing, S. (Ed.): Grüne Gentechnik: Zwischen Forschungsfreiheit und Anwendungsrisiko. Baden-Baden: Nomos, 369-386; COGEM (2010). *Geboeid door keuzevrijheid. Een verkenning van de ontwikkeling en rol van keuzevrijheid rondom ggo's in Europa.* Policy report CGM/101230-02.

[88] Helliwel, R. et al. (2017). *Why are NGOs sceptical of genome editing.* EMBO reports 18, pp. 2090-2093.

[89] COGEM (2010). *Geboeid door keuzevrijheid. Een verkenning van de ontwikkeling en rol van keuzevrijheid rondom ggo's in Europa.* Policy report. CGM/101230-02.

[90] Gaskell, G. et al. (2010). *Europeans and Biotechnology in 2010. Winds of Change?* Luxembourg: Publications Office of the European Union.

If Europe were to amend the GMO Directive and exempt some genome-editing techniques, individual member states would not have the right to exclude these crops on the basis of societal, cultural and ethical aspects. Indeed, if genome-editing techniques are exempted, they will also be exempted from the possibility to assess these broader societal issues at the national level, an option which has only recently been introduced in EU regulation. GM-crops that will have undergone an extensive risk assessment by the European Food Safety Authority (EFSA) can in contrast still be assessed nationally on the basis of broader considerations, such as protecting the diversity of agricultural crops, landscape values or ethical aspects.

The Dutch proposal to exempt genome-editing techniques from the Directive (if the end product contains no foreign DNA) would again reduce the debate and decision-making process to the safety question. This, while the last few decades have shown that societal acceptance is conditional on a broader assessment than one simply based on the safety for humans and the environment.

3.6 Conclusion

Options 1 and 2 reflect the contrasting positions of the old debate, created by the fact that the discussion about GMO cultivation principally revolves around safety and the economic importance of innovation. Option 2 ignores various arguments about long-term safety concerns of these new GMOs on public health and the environment. Additionally it ignores agricultural considerations, such as landscape quality or biodiversity and organic agriculture. Moreover, option 2 raises concerns about patents, labelling and freedom of choice.

4 Option 3: A level-based policy including broader considerations

In 2015, the EU tried to break the impasse with respect to GMOs by acknowledging that in society's assessment of GMO cultivation, many other, broader societal aspects play a role in addition to safety. A new policy should aim to include these societal aspects. Based on the current discussion in Norway, we examine two examples of a level-based approval system, which both aim to take into account broader societal considerations. Such a level-based policy approach takes into consideration the arguments of options 1 and 2.

4.1 Example of a current differentiated policy

Risk assessments are often differentiated, because of the many factors that need to be included such as the particular substance or organism, the method, and the level of containment. Such a differentiated policy already exists for working with GMOs in closed spaces, such as in a laboratory or in greenhouses. A risk assessment for contained use of GMOs examines two types of risk. First, the properties of the organism are considered, i.e. the host, the vector and the donor sequence.[91] Second, the use of the organism is assessed. Five different levels of containment exist (I, II-k, II-v, III and IV). Levels I and II require notification, while a licensing procedure applies for the higher levels. As well as determining the containment level, the physical space needs assessment. Together they determine the category of physical containment (CPC). For each CPC there are regulations governing the facility and safe working procedure.

A similar differentiation of risk assessment could be carried out for the release of (new) GMOs into the environment. Indeed, advocates of option 2 basically are arguing for a differentiated policy, although one based solely on the presence or absence of foreign DNA in the end product.

[91] https://www.ggo-vergunningverlening.nl/ingeperkt-gebruik/risicobeoordeling.

4.2 Norway's quest for a future regulatory framework

Due to the emergence of new technologies in agriculture, Norway is seeking a new regulatory framework for the assessment of GMOs. The Norwegian Biotechnology Advisory Board has examined how a new policy can be shaped and presented a statement to invite a constructive public debate. The Board's statement outlines and discusses two new level-based preliminary proposals for regulating the release of GMOs.[92] A public consultation took place in 2018, to test support for these two proposals, before one of them will be further elaborated.[93]

The Norwegian Gene Technology Act (GTA) of 1993 ensures that GMOs are developed and used not only in a safe way, but also in an ethically justifiable and societal beneficial way.[94] It ensures that only those GMOs are permitted that have been assessed in relation to ethical justifiability, benefit to society and sustainability. The societal benefits are assessed by looking at the short-term advantages and disadvantages of a new product for society at the national level, such as increased nutritional value or productivity. In contrast, the assessment of sustainability is based on long-term effects from a global point of view taking into account economic and social issues such as food security, animal welfare and the freedom of choice of the consumer, access to certain plants, and ownership of seed. Whether a GMO can be ethically justifiable is dependent for example, on the influence of the technology on vulnerable groups in society, the distribution of power, or particular core values of the general public.

The two proposals for a new regulatory framework offer different levels of intensity of regulation and various levels of risk assessment. The two proposed level-based models are based on different underlying principles. In the first proposal, the risk assessment level is based on genetic changes, while in the second model it is based on societal values.

4.3 Model 1: level of risk assessment is based on genetic changes

In the first proposal, the levels of risk assessment are distinguished based on the type and extend of the genetic change in an organism. In this manner, the risk assessment is adjusted to the expected risks. Simultaneous to a case-by-case

[92] Bioteknologirådet (2018). *The Gene Technology Act – Invitation to Public Debate* http://www.bioteknologiradet.no/filarkiv/2010/07/genteknologiloven-engelsk-hele-for-web-v-2.pdf
[93] The Norwegian Biotechnology Advisory Board expects to publish a report on the results of the public consultation in December 2018.
[94] Gene Technology Act. Act of 2 April 1993 No. 38 Relating to the Production and Use of Genetically Modified Organisms. https://www.regjeringen.no/en/dokumenter/gene-technology-act/id173031/

assessment of the risks for humans and the environment, an impact assessment is made based on ethical aspects, sustainability and benefits for society of the product, based in the Norwegian Gene Technology Act, and in accordance with EU Directive 2015/412.

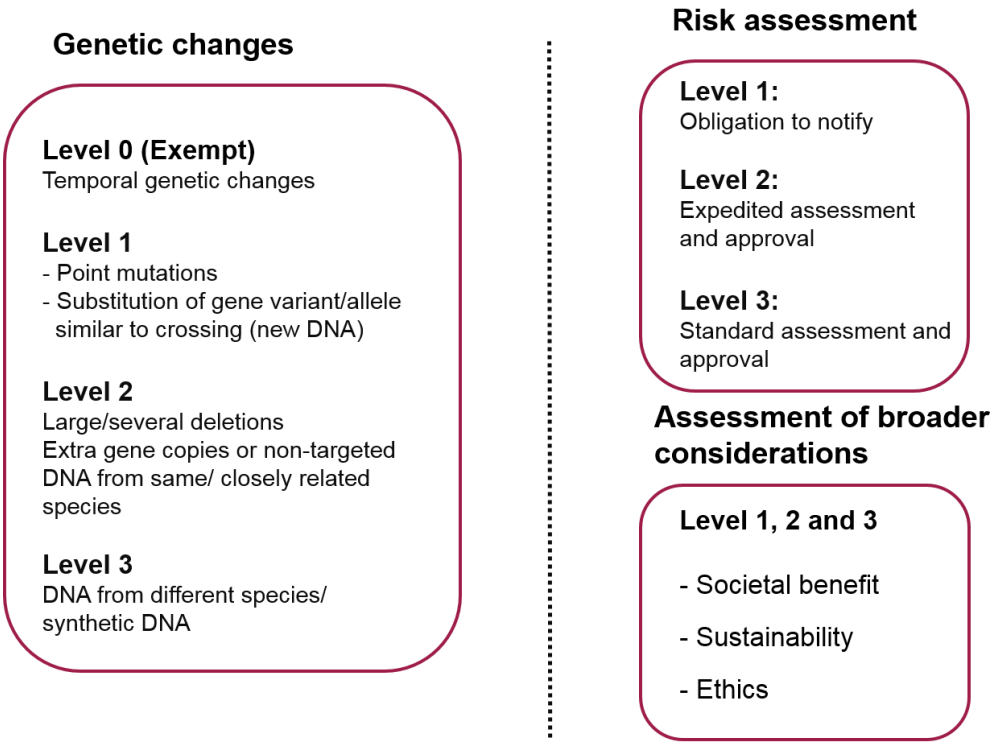

Figure 1 Model 1: level-based model based on type and extend of a genetic change.

If temporary, non-hereditary changes are made in an organism, there is an exemption from the Directive (level 0). For permanent genetic changes, there are three levels of risk assessment in this model. If genetic changes are created that can be achieved using conventional methods, a notification requirement (with compulsory waiting time for feedback from a 'competent authority') may be sufficient (level 1), although possibly additional documentation is required. When different types of changes in the DNA is made, a higher level of risk assessment may be necessary. A higher level can be a expedited risk assessment procedure. This would be adequate for organisms that contain new genes from the same species (level 2). If DNA from a different species has been introduced, the current standard risk assessment must be conducted (level 3). Which level is appropriate will always be assessed on a case-by-case basis. At levels 1, 2 and 3, the Norwegian Biotechnology Advisory Board assesses the criteria of sustainability, ethical justifiability and benefit to society in parallel with

the risk assessment. The information for the assessments has to be supplied by the applicant but can be supplemented with additional information if required.

A level-based system will provide a better match between expected risks of a GMO (including gene edited plants) and the strictness of the risk assessment and approval requirement, and it will uphold the case-by-case risk assessment for all GMOs. It can also help prioritize resources to where it is needed, and streamline the market authorization procedure. Smaller and well-known DNA-sequences changes may be easier to evaluate, as the consequences are easier to predict. However, when it is expected that a minor change can have major consequences it can be transferred to the next level of assessment. Because of the notification as a minimum requirement, the authorities will be able to maintain an overview of all products cultivated in Norway.

A challenge is this model would be the shifting of a product from one level to the next for it is not clear who will take this decision, and which criteria it will be based on. Another challenge is the fact that techniques with little to no experience can be subjected to an accelerated assessment (provided they provide benefits to society). The Norwegian Biotechnology Advisory Board questions whether this is in line with the precautionary principle and the GMO Directive, as their purpose is to strictly regulate techniques we have little experience with. The Norwegian Biotechnology Advisory Board also wonders whether we will retain public trust with such a level-based policy.

4.4 Model 2: Level of approval system is based on societal values

In the second proposal, the levels are initially distinguished not by the genetic change, but in stead by an evaluation of the policy objectives, socio-economic considerations and ethical justifiability (or public morals). This second model divides the market approval process into two phases. The first phase is an evaluation of public morals[95] and the second phase is an evaluation of risks. This streamlines the approval procedure by not wasting time and energy on products that are very likely to be rejected, as they do not meet the Norwegian criteria of sustainability, ethical justifiability and benefit to society. This evaluation of policy objectives, socio-economic and ethical considerations is also what the EU Directive 2015/412 permits its member states.

[95] The decision to refer to public morals in the first phase is strategic, in order to position this model in line with the language of the World Trade Organisation (WTO).

The first phase is divided into three steps. In the first step, the application for market approval has to proof the product is not in contradiction with policy aims and politically agreed standards. The exact requirements would need to be determined and adopted by politicians on the basis of expert advice and public consultation. Examples that could be included are genetic modifications using antibiotic resistant genes, which is not approved in Norway. A plant with this property would be rejected in this first phase.[96] If the plant does not violate any agricultural or environmental policy objective, the product is assessed for its ethical justifiability in a second step. This can involve the positive contribution to sustainability, the benefits for society, uncertainties associated with the technique, the availability and desirability of alternatives, and other relevant issues such as the degree of crossing species boundaries. This evaluation considers both product-related and process-related aspects, and determines the level of ethical justification (strong, medium or weak) in step three. In this third step the level of risk assessment is determined.

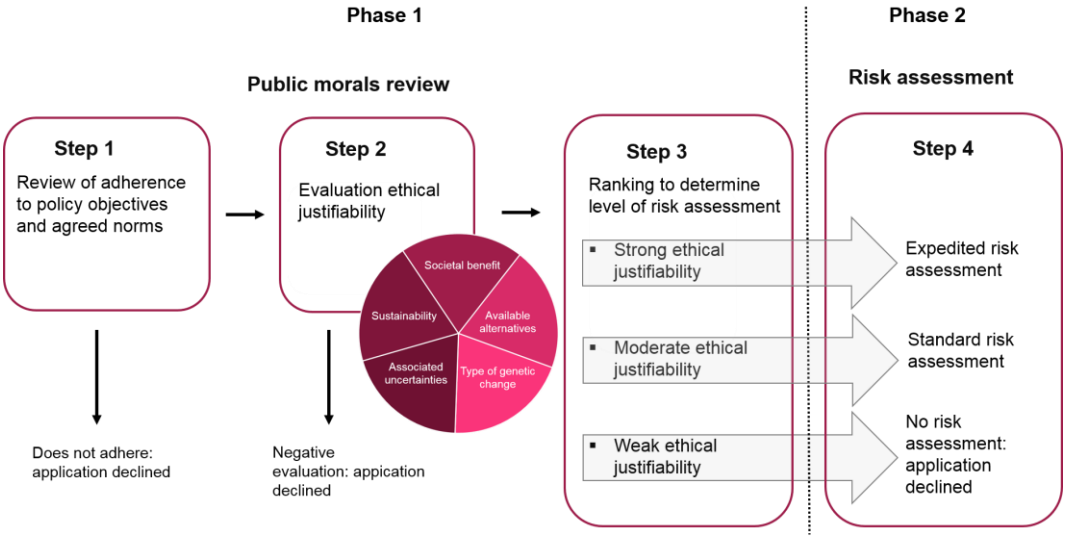

Figure 2 Model 2: level-based model based on broader considerations. These considerations determine the level of ethical justifiability, which in turn determines the level of risk assessment.[97]

During the second phase, the risks are assessed at one of the three different levels: 1) the current standard risk assessment, 2) an expedited risk assessment or 3) the application is declined because the ethical justification is too weak. The exact differences between the standard and an expedited risk assessment would need to be formulated. If appropriate, a product can be passed to another level. Despite a positive ethical assessment, it is possible that the use of a specific technique or the specific genetic modification will require a standard assessment. It is also possible

[96] Alhough it is not likely that a company would apply for market approval in this particular example.
[97] Bioteknologirådet, 2018. *The Gene Technology Act – Invitation to Public Debate*

that additional documents can be requested from the manufacturer, or breeder. At both levels, tracebility and labelling would be required.

Because the assessment of ethical justifiability is done before the risk assessment, a plant or crop will not undergo a costly and time-consuming risk assessment, only to be subsequently rejected on ethical grounds. At the same time, when the crop is thought to positively contribute to society, it can be rewarded by an expedited risk assessment.

One of the challenges of this second model is the difficulty in predicting the benefits of a plant to society.[98] What might be seen as very beneficial, could pose significant risks to the environment, and therefore not be beneficial at all. Indeed, benefits and risks cannot easily be separated from each other. Whether something promotes sustainability, also depends on the risks to health and the environment. Without evaluating risks first, it is therefore difficult to identity the benefits to society. Moreover, no clear framework has been developed to date to evaluate ethical justifiability.

4.5 Evaluation of the Norwegian proposals

Both Norwegian proposals ensure that all gene technologies continue to be regulated to ensure that authorities maintain control and overview, as well as the option to change the classification level if necessary.[99] Safety for human health and environment is therefore tested, but flexibility in strictness of the risks assessment and approval requirements is also ensured, thus taking the importance of innovation into account, based on predicted benefits to society. Moreover, the second model also takes into account the fact that depending on the product's contribution to society, the socially accepted risk level varies: we accept more risks if an application will greatly benefit society. As a result, the benefits of the technology have a more prominent place in the assessment procedure, which is what proponents of both policy options support. Both Norwegian proposals also ensure that sufficient attention is paid to public interests such as sustainability and socio-economic effects, which are embedded in Norway's Gene Technology Act, but are also recognized as important criteria in the EU Directive 2015/412. It is possible that this will reduce the likelihood of public disquiet. Tracebility and labelling will remain required giving consumers freedom of choice. Such a policy approach is in line with the wishes of Dutch citizens, as expressed in a public

[98] Ibid.
[99] Bioteknologirådet (2018). The Gene Technology Act – Invitation to Public Debate. http://www.bioteknologiradet.no/filarkiv/2010/07/genteknologiloven-engelsk-hele-for-web-v-2.pdf

survey recently carried out for the Ministry of Infrastructure and Water Management.[100] This survey showed that respondents expect that short and long-term effects of biotechnological applications are examined before they can be used or tested. Respondents also required technologies to be of value for society and useful.[101] The history of the GMO debate also teaches us that societal concerns about GMOs go beyond risks and safety. Actively involving citizens and acknowledging their concerns and interests are essential for a responble integration of innovative technologies in society. Factors such as the goal of a specific innovation, the contribution to challenges to society, and the desirability of GMOs as a solution to these challenges need to be given sufficient attention in the discussion. This is also in line with the intentions of the previous Dutch government: 'Being mindful of the Trend analysis and the results of the stakeholder consultation, we will explore the possibilities to improve involving public values when weighing the benefits and risks of specific biotechnological applications, as is more often the case in medical biotechnology.'[102]

4.6 Conclusion

Norway is anticipating the fast-paced development in gene technology, and has presented two new regulatory models to invite a constructive public debate. Both models take into account the new genetic engineering techniques with their varying anticipated risks, public health and the environment, and promote sustainability, societal benefit and ethics. The Norwegian proposals show that a nuanced regulation based on process and product, taking account of risks to public health and the environment, as well as broader societal and ethical questions, is possible. The second model provides space to consider the value of the product during the licensing procedure, and the possibility to reward the value by means of an expedited risk assessment. For some stakeholders, the lack of integrating the value of gene edited plants and crops in the EU legislation is a reason to call for deregulation: policy option 2, which was discussed in Chapter 3. Deregulation would facilitate market approval for gene edited crops that would contribute towards a sustainable agriculture, or help achieving climate goals. The Norwegian proposals show that this can also be achieved within a regulatory system. A key benefit of a regulatory system is moreover that these anticipated benefits can be evaluated by an independent committee, and not merely asserted by a company seeking

[100] Insitesconsulting (2017). De burger aan het woord: publieksopvattingen over moderne biotechnologie. Survey report.
[101] Ibid. p.2
[102] Parliamentary papers II, 2016/2017, 27 428, no. 335. Conclusion

economic gain. In all probability, this will also increase public trust in approved products.

The models proposed by the Norwegian Biotechnology Advisory Board fulfil the wishes and address the concerns of advocates of both policy option 1 and 2.

5 Focus on differences in risks and broader considerations

This study examined how a modernised biotechnology policy for plants and crops can be developed that takes into account the ruling of the European Court of Justice and that benefits society. The European Court of Justice ruled in July 2018 that all mutagenesis techniques are subject to the GMO Directive, and only those mutagenesis techniques with a proven long-term safety record are exempt. This has provided legal clarity about the issue whether genome-editing techniques are subject to the GMO Directive. In Europe, genome-editing techniques are regulated as genetic modification techniques, irrespective of the presence of foreign DNA in the end product. However, this has not ended the discussion on the modernization of biotechnology policy for plants.

This study shows that different stakeholders have different views on the possible risks of genome editing in plants and crops and on ways to deal with those risks. Besides risks, broader considerations, such as economic, societal and ethical factors are important when assessing new genetic engineering techniques. This study maps the arguments of various stakeholders concerning three policy options for the EU. The current discussion is dominated by two options: 1) the EC does not change the GMO Directive, and 2) Directive 2001/18/EC is amended in order for products of genome-editing techniques without foreign DNA to be exempt from the Directive (Annex 1B).

In this study, we also examined a third option. In this third option genome editing and genetic modification techniques are regulated based on a level-based model. Norway is currently developing such a level-based policy within their current GMO legislation, thus taking into account risks as well as broader aspects in the authorisation process for GM crops. In Norway, GMOs are assessed for ethical justifiability, benefits to society and sustainability. The option studied by Norway meets the wishes and concerns of both supporters and opponents of policy options 1 and 2. Norway shows that it is possible to change biotechnology policy taking into account a diversity in risks as well as broader societal and ethical considerations. The Rathenau Instituut advocates a similar policy approach for the Netherlands and Europe. This approach should address the difference in risks associated with different ways genetic engineering techniques can be used, and also address benefits to society and ethical considerations.

5.1 Level-based approval system

In 1990, Europe choose to develop a risk framework which distinguished between different plant-breeding techniques. GM techniques with a proven safety record, such as mutagenesis, were exempted from regulation. Other GM techniques are subjected to a risk assessment. Indeed, when the GMO Directive was drawn up, the short and long-term effects on human health and the environment of GMOs were unknown. Regulation of genetic modification techniques is therefore more strict than the regulation of traditionally cultivated crops. Some agrochemical and plant breeding companies promote the exemption from the GMO Directive of genome-edited crops that do not contain any foreign DNA, in order to facilitate innovation and market authorisation.

However, in July 2018, the European Court of Justice ruled that genome-editing techniques were not exempt from the GMO Directive. Only those techniques that have demonstrated short and long-term safety in the open field are exempt.[103] This is not yet the case for genome-editing techniques. The technique is new, it offers many different possibilities and long-term effects are not known. In addition, a number of studies published last year showed unknown effects of applying this technique (at the cell level).[104] We should therefore question whether an exemption from the GMO Directive, and the resulting absence of assessing and monitoring of safety is a responsible move at this stage.

A lack of monitoring techniques not yet proven to be safe can be a source of public disquiet, for example regarding the question of responsibility should anything go wrong. Moreover, an exemption of genome-editing techniques from the GMO Directive entails that individual member states would no longer have the right to exclude these crops on the basis of societal, cultural and ethical factors. If these broader societal considerations are excluded from the decision-making process, it can lead to discontent among citizens as well as among stakeholders that may suffer damage. For example, an important consideration is the landscape value in some areas.

The Rathenau Instituut believes it is desirable to develop a level-based approval system.
Such a level-based approach is in line with the importance of safety, as well as the need to encourage socially responsible innovation. Thus, this approach can serve to satisfy both the arguments in favour of options 1 and 2. The assumed risks

[103] Consideration 17 of Directive 2001/18/EC
[104] Haapaniemi, E. et al. (2018). CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response. *Nature Medicine* 24, pp. 927–930.; Kosicki, M., Tomberg, K. & A. Bradley. (2018). Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology* 36, pp. 765–771.

dictate the strictness and speed of the risk assessment procedure. Estimating these risks is based on the technique used and the safe use of that technique in practice. Genome editing is a technique that offers many different possibilities for altering DNA. Possibly, but not necessarily, foreign DNA is present in the DNA of the end product. The various applications of the genome editing techniques do not necessarily have similar risks. A differentiated risk assessment also allows for a differentiation in labelling, giving freedom of choice to consumers to express their preferences through their purchasing behaviour, and simultaneously maintain markets, such as the growing market for organic products.

5.2 The importance of broader considerations

Over the last few decades, the focus on safety in GMO market approval in the EU left no space for political and policy-related discussions on relevant societal aspects of good agricultural practices. Member states were only permitted to exclude GMOs by referring to risks and/or uncertainties with respect to health and the environment. An amendment to the GMO Directive in 2015 gave individual member states the right to exclude GM crops on the basis of, among other things, societal, cultural and ethical aspects, such as, sustainability or landscape value. This gave legal status to broader societal aspects that play a role in the debate on GMOs in agriculture. The Ministry of Agriculture, Nature and Food Quality is currently developing an assessment framework for the authorisation of GM cultivation in the Netherlands.

Including broader societal aspects in the authorisation process creates support and takes public values into consideration. Companies appreciate the benefits this entails. Before 2015, the EU approved the cultivation of GMOs in all member states. As a result, countries opposed to cultivating GM crops on their territories sometimes blocked market authorisation in the EU, even if the crop had already been assessed to be safe. A greater flexibility in dealing with GM crops within the EU was therefore desired. Through the amendment of the Directive in 2015, member States have the possibility to adopt legally binding acts restricting or prohibiting the cultivation of GMOs in their territory after such GMOs have been authorised to be placed on the Union market. A clear assessment framework increases the predictability of decision-making and thus provides clarity for companies.[105]

[105] Munnichs, G., H. de Vriend and D. Stemerding (2016). *Afwegingskader nationale teeltbevoegdheid gg-gewassen- Verslag van een stakeholderdialoog.* The Hague: Rathenau Instituut

The Rathenau Instituut thinks it is desirable to examine how a broader assessment framework for authorising GM cultivation can be in line with a level-based risk assessment process.

Factors such as the goal of a specific innovation, the contribution to societal challenges, and the desirability of GMOs as a solution to these challenges should be assessed by an independent committee, as is already the case in Norway. These factors should not only be assessed in order to exclude cultivation of GM crops from all or some of the individual EU member states, but also to positively contribute to the market authorization process.

5.3 Desired development

A level-based risk assessment is in line with both the precautionary principle and the need to encourage socially responsible innovation. The pace of the process of market authorization depends on the level of risk-assesment based on the presumed risks. If ethical and societal factors are included, these risks can be weighted against the benefits for society. Estimating the risks is based on the genetic changes, the method used, and the safe use of the used technique in practice. Genome editing is a technique that offers many different possibilities (methods) for altering DNA, not all with the same risks. A differentiation in risk assessment is therefore desirable. In addition, it offers the possibility of differentiation in labelling, thus giving freedom to choice to consumers and express their preferences through their purchasing behaviour, while maintaining non-GM markets, such as the organic market.

An approach that focuses solely on risks and safety aspects is insufficient. Recognising broader societal aspects and giving these a proper place in the decision-making process for new genome-editing techniques is of crucial importance for incorporating such techniques in society in a responsible manner. The Netherlands could take a lead in Europe, initiating the development of such a framework, and examining the possibility of a level-based risk assessment.

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