2018

The Gene Technology Act – Invitation to Public Debate

Bioteknologirådet
The Norwegian Biotechnology Advisory Board

CONTENT

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Publisher: The Norwegian Biotechnology Advisory Board

Published: 09.01.2018

Photos and graphics: The Norwegian Biotechnology Advisory Board

Photo: iStock, Wikimedia

Only available in electronic format at www.bioteknologiradet.no

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The Norwegian Biotechnology Advisory Board is an independent body appointed by the government, first established in 1991. The board is regulated by the Biotechnology Act and the Gene Technology Acts. In addition to providing advice on matters concerning the use of biotechnology and gene technology in humans, animals, plants and microorganisms, the board also facilitates dissemination of knowledge and public debate.

The board shall place particular emphasis on ethical and societal aspects of the use of modern biotechnology in their evaluations.

The Norwegian Biotechnology Advisory Board has 15 members, 5 deputy members and observers from 7 government ministries.

The Norwegian Biotechnology Advisory Board has a budget of 9,5 million NOK for 2018.

Bioteknologirådet
The Norwegian Biotechnology Advisory Board

PREFACE

The Norwegian Biotechnology Advisory Board has a special mandate for public dissemination of information and debate about all aspects of biotechnology. In light of the fast-paced development in the field of gene technology, especially with gene editing/CRISPR, and the global debates that follow, the Board presents this statement to invite a constructive and knowledge-based public debate and dialogue about these topics. The aim is to develop appropriate and robust regulatory frameworks that facilitate the harnessing of the potential of gene technology, while also avoiding harm to health and the environment, and promoting sustainability, societal benefit and ethics. These proposals are preliminary, and can be subject to change before the statement is finalised. We welcome views, comments and suggestions from all stakeholders, and will facilitate dialogue at several forums.

In this statement, the Board specifically addresses regulation of deliberate release of GMOs, focusing on a few select principal aspects:

- What should be regulated by the Gene Technology Act? Should all organisms developed using gene technology be regulated by the act or should some be exempted? Should organisms developed using certain conventional breeding methods be regulated differently that today?
- How should these organisms be regulated? Should the same criteria apply to all organisms, or can the criteria be divided according to different levels?
- What are appropriate requirements for labelling and traceability?
- How should contribution to societal benefit, sustainability and ethics be weighted?

The Norwegian Biotechnology Advisory Board has discussed these questions on a principal level, without going into detail, since the proposals will have to be thoroughly reviewed and specified by other authorities. The Board has not considered which legislative changes to Norwegian or other international regulations are necessary for the adoption of the proposals.

In this particular case, the Board has deviated from normal practice, allowing all 20 members and deputy members to vote. The issues have been discussed over many meetings, and all members know them well. Furthermore, the Board wants all viewpoints to be sufficiently represented in this principally important case.

Summary of the Norwegian Biotechnology Avisory Board recommendations:

As is the often the case on issues discussed by the Board, the members are divided in their opinion. Nevertheless, some prevailing directions has emerged.

A majority of 18 out of 20 members believe the requirements for risk assessment and approval of genetically modified organisms should be differentiated into different levels based on the genetic change that has been made, ethics and/or other relevant criteria. At the lowest level, 17 of these members argue that a notification to the authorities (receipt required before the organism can be released) may be sufficient, while higher levels can have different approval requirements. Two of the board members argue that all organisms regulated by the Gene Technology Act should be subjected to the same level of risk assessment and approval, according to the current system. However, differentiation through custom guidance documents should be more actively utilised.

There is more disagreement on the scope of the Act. None of the board members think that any organism made using gene technology should be exempted, except those with temporary, non-heritable changes such as DNA vaccines. On the contrary, a majority of 13 members argue that organisms made with certain conventional breeding methods (e.g. mutagenesis, triploidisation and cell fusion), which are currently not regulated specially, should be regulated in the same way as corresponding GMOs. These members justify their position with the principle of equality. A level based system would however be a prerequisite. A minority of 7 board members argue that for pragmatic reasons, we should keep the current distinction, where organisms produced using conventional breeding techniques (including

mutagenesis, triploidisation and cell fusion) are kept outside the scope of the Gene Technology Act. On the question of labelling and traceability, the board members are divided into two main groups. A majority of 17 members argue that labelling should be differentiated into different levels, so that consumers will have an even better basis for making informed choices than today. Five of these 17 members argue that organisms at the lowest level (with genetic changes that can also arise naturally or be made using conventional breeding techniques) should be exempted from the labelling requirements, while the others argue that all organisms covered by the Gene Technology Act should be labelled. This majority of 17 members also argue that requirements for traceability should be further reviewed, and they may be differentiated based on feasibility. A minority of 3 members think that current requirements for labelling and traceability for all GMOs should be kept unchanged. This, they argue, will ensure free consumer choice, while also being in accordance with international requirements.
Regardless of the scope of the Gene Technology Act and how the organisms it covers are regulated, the board members unanimously argue that societal benefit, sustainability and ethics should be assessed as part of the approval process. However, there is disagreement about how these requirements should be weighted. A majority of 13 members argue that all organisms under the Gene Technology Act should be required to contribute positively to societal benefit, sustainability and ethics. A minority of 7 members argue that the requirements should be differentiated according to the level-based system, where the absence of negative impact on society, sustainability and ethics should be sufficient for approval of organisms with genetic changes that do not cross species boundaries or involve the use of synthetic (unnatural) DNA sequences.

When it comes to research, the board members are in agreement – they believe it is important to facilitate the gathering of knowledge about technical and safety aspects of gene technologies, and to build competence in Norwegian research environments.

Public dialogue

Genetic engineering of plants and animals is a complex topic, and there are many different opinions about which regulatory frameworks are most appropriate. The recommendations presented here also raise many questions. The Norwegian Biotechnology Advisory Board therefore invites public debate and dialogue to get comments and thoughts from all relevant stakeholders, as further basis for discussion before the statement is finalised.
To facilitate this, we plan to host open meetings and talks in all of the largest Norwegian cities over the next months. More information will follow online at www.bioteknologiradet.no/genteknologiloven. Views and comments can be emailed to post@bioteknologiradet.no.

Deadline for comments: 15th May 2018.

The Board hopes this statement will contribute to knowledge building and fruitful discussions about this important topic. Our ambition is that the statement will also be a constructive contribution to the international debate about how organisms produced with gene technology should be regulated.

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1. Why are we discussing this?

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The purpose of the Norwegian Gene Technology Act is to ensure that the production and use of genetically modified organisms (GMOs) is ethically sound, beneficial to society, consistent with the principle of sustainable development, and does not pose a threat to health and the environment. This includes aspects such as protecting animals and humans from health risks, preventing or limiting harm to nature, and respecting moral and political limits in terms of interfering with natural processes and respecting nature's intrinsic value. Such considerations are important in the current, fast-paced development of gene editing and the political debates that follow.

The technologies for genetically modifying plants, animals and microorganisms have existed for over thirty years. The global GMO market is currently dominated by plants which are resistant to different types of herbicides and/or produce insecticides. Such GMOs have been developed for large, commercial markets. Over recent years, novel genetic engineering techniques that are both cheaper and easier to use, and which allow for more ways to alter the genetic material of any organism, have been developed. The use of gene editing/CRISPR has seen an exponential growth within both academia and the industry. This has resulted in increased research and development of organisms with a range of new traits, which is expected to lead to an increase the number of applications for approval of such products within a five-to-ten year perspective.[1] This could potentially contribute to the development of products that are beneficial to society, sustainable and ethically sound.

However, such powerful technology may also bring several challenges, as it may be used to make organisms that are very different from those that currently exist. Examples include microorganisms with fully synthetic genes that may behave very differently from existing organisms when introduced into the environment, or gene drives that are designed to spread genetic changes to entire populations of wild plants or animals. The increasing accessibility of the technology, for example as a tool to use at home or at community labs outside government control (DIY-biology), makes it difficult to enforce regulations (see statement from 14.02.2017[2]).

The laws which define and regulate GMOs in Norway, the EU and other parts of the world, were developed when gene technology was still in its infancy. Given the recent development of new methods for genetic modifications, new and global

debates on how gene technology should be regulated, including whether current laws and regulations are suited to ensure effective and responsible research and development of the products of tomorrow, are ongoing.[3,4,5,6,7,8,9,10,11]
The basic principle of the regulatory framework is to ensure safe, societally beneficial, sustainable and ethically justifiable use of technology. Legislation must be manageable, comprehendible, and set a predictable precedent. Consequently, the Norwegian Biotechnology Advisory Board wishes to take part in this debate.

The debate is twofold: 1) how are organisms developed using gene technology regulated according to today's framework, and 2) how organisms should be regulated in the future. The Norwegian Biotechnology Advisory Board will not address the former question at present time, beyond assuming that all organisms developed using gene technology today would be regulated under the Gene Technology Act according to its current definitions and scope, unless specific exemptions are made. In this statement, the Norwegian Biotechnology Advisory Board will express principal viewpoints on what the Gene Technology Act should include, and what rules and requirements should apply to the development and use of the organisms it covers. The Gene Technology Act will define the framework for the use of gene technology in the future bioeconomy, and positive and negative consequences of the different alternative forms of regulations should be weighted against each other. Through the EEA Agreement, the EU Directive on Deliberate Release of GMO (Directive 2001/18) is implemented in Norwegian law. As with the Norwegian Gene Technology Act, the directive applies to living GMOs - for example animals, plants that are cultivated and sprouting seeds - or products containing living GMOs. Through a permanent exemption from the EEA Agreement, Norway has the right to emphasise sustainability, societal benefit and ethics when considering whether a GMO should be approved.

Processed foods and feed from genetically modified organisms are included in Norway by the Food Act and in the EU by the Regulation on Genetically Modified Food and Feed (Regulation 1829/2003).[12] The regulations set by the Gene Technology Act should be seen in conjunction with the regulations dictated by the Food Act.

In this statement, the Board has considered only the Norwegian Gene Technology Act, but are aware that we have commitments to the EU through the EEA Agreement that can be decisive for the regulatory framework. Consequently, any alterations made to the EU's regulatory framework, or the interpretation thereof, may impact Norwegian regulations and decision making. The same applies to the regulations set by the UN's Convention on Biological Diversity and the Cartagena protocol. Additionally, the WTO's trade agreements may affect how the provisions are handled in practice. On the other hand, Norway can also contribute to the harmonisation and development of international rules and guidelines if required.

The Norwegian Biotechnology Advisory Board has reviewed the Gene Technology Act, focusing mainly on the scope, definitions and requirements for approval and labelling. The Board has taken into account the technological developments that have taken place. At the same time, the Norwegian Biotechnology Advisory Board wishes to protect and retain the main principles regarding assessment of health and environmental risk, sustainability, societal benefit and ethics, and that living GMOs should be regulated under the Gene Technology Act.

2. Background

The Gene Technology Act makes a clear distinction between organisms produced by genetic engineering on the one hand and all other so-called conventional breeding methods (as defined in footnote[13]) on the other, but no distinctions are made between the various types of GMOs that currently exist. In the legal preparations for the Act, this was justified by a wish to distinguish between biological processes that occur naturally and those that do not, but the history of safe use of traditional methods was also emphasised. [14]

Table 1 shows the division between methods according to today's definitions:

The provisions set by the EU contain a similar distinction as a premise for the definition of a genetically modified organism: "organisms in which the genetic material has been altered in a way that does not occur naturally during reproduction and/or natural recombination." However, the Norwegian Ministry of Climate and Environment did not want to employ this definition in the Norwegian law because it was perceived as too wide: the EU definition would also include mutagenesis (the use of chemicals or radiation to create mutations), and it would therefore be necessary to specify an exemption for these methods, since it was desirable to exclude these for pragmatic reasons (mutagenesis had been used as a breeding method since the 1920s).[14] Moreover, the definition could be misunderstood and interpreted as also applying to traditional breeding.

Conventional breeding methods that are not regulated by the Gene Technology Act
Crossbreeding
Mutagenesis (using radiation or chemicals to induce mutations)
Triploidisation (applying thermal or pressure shocks to fertilised fish eggs to produce an extra set of chromosomes in order to make the fish sterile)
Cell fusion within the same species (fusion of cells results in extra copies of the genetic material - used within plant breeding)

Genetic engineering techniques that are regulated by the Gene Technology Act
Inserting novel genes from the same or a different species ("classical genetic modification")
Gene editing which is used to make targeted changes to the genetic material of an organism, with or without inserting new DNA
Temporary transfer of nucleic acids (e.g. RNA/DNA-vaccines)
Regulating gene expression (e.g. using RNAi or epigenetic changes, where nucleic acids are used to change gene expression, but not the actual DNA sequence)
Cell fusion between different species

CONVENTIONAL METHODS NOT INCLUDED IN TODAY'S GENE TECHNOLOGY ACT:

Crossbreeding: The genetic makeup of an offspring resulting from sexual reproduction consists of a mixture of the genetic material of the parental organisms. This way, beneficial traits from different individuals can be combined. A genetic trait will therefore be inherited alongside other undesirable traits. During the production of gametes (sperm and egg cells), a number of genetic changes occur through so-called homologous recombination, where segments of the genome exchange places within a chromosome pair (where the cell's own molecular machinery cuts, replaces and glues the DNA back together) to create more genetic variation in the subsequent generation. In addition, genetic variation is created through spontaneous mutations. The rate of mutation varies, but is quite similar within groups of organisms. For higher-ranking organisms such as animals and plants, about 0.1-100 mutations occur from one generation to the next, depending on the size of the genome.[15] For example, the ratio for rice is about 20 mutations per generation.[16] Some mutations lead to functional changes, which may be either beneficial or detrimental to the organism, while most have little or no effect.

Mutagenesis: From the 1920s, radiation and chemicals have been used to create a higher frequency of mutations to achieve more and new genetic variation in domesticated plants. This usually occurs by a so-called double-stranded break, a cut, in the DNA, which is subsequently repaired by the cell's own repair mechanisms. Errors during this repair process lead to mutations. With the use of radiation and chemicals, many - often hundreds or thousands - of mutations occur randomly in the genome.[17,18] Most mutations are either harmful or have no effect, but sometimes mutations arise that result in desirable traits suitable for breeding purposes. According to the FAO (United Nations Food and Agriculture Organization) and the International Atomic Energy Agency (IAEA), over 3,000 plant varieties from over 200 different species in more than 60 countries have been bred this way and released into the wild. Over 1,000 varieties constitute important food crops such as rapeseed, rice and barley, and many are commercially available.[19] The method is still used to a relatively large extent, with over 600 new varieties registered with the IAEA since the beginning of this millennium.[20]

Triploidisation: Within aquaculture, triploidisation is used to create sterile fish.[21] By exposing fertilised eggs to high pressure and high temperature, the cells get an additional copy of the entire set of chromosomes; they become triploid. In addition to sterility, this leads to unintended effects.[22] These include for instance a higher occurrence of diseases like osteoporosis and cataracts. This is a technology without a long history of safe use.

Cell fusion within the same species: Cell fusion is a method of plant breeding used to create new plant varieties by combining cells from different plants.[23] The plant cells are first treated with enzymes to break down the cell wall and then bathed in a chemical solution that allows the cells to fuse. The method causes the cells to get additional copies of the genome (polyploidisation), and can, for example, be used to make sterile plants. The method has been used to create varieties of cabbage and broccoli. Polyploidisation may occur naturally and will usually cause significant genomic changes in relatively few generations.[24] Such changes are not predictable and can be difficult to reveal even with genome sequencing. Like triploidisation, this is a technology without a long history of safe use, although natural polyploidisation is an old and well-known phenomenon.

GENETIC ENGINEERING TECHNIQUES:

Insertion of genes using classical gene modification technology: The first methods of gene modification, which were developed in the 1970s and 80s, are based on isolation and insertion of genes into the genome of a cell. Various methods for transferring the genes exist. In plants, bacteria are often used as carriers of the genetic material, or it is transferred by chemicals, electricity or with a so-called gene gun. Chemicals or electricity, in addition to microinjection of the gene or viral transmission, can also be used to transform animal cells. Such methods have in common that genes are fairly randomly inserted into the genome and that unintended additional copies and rearrangements are not uncommon.

Gene editing: Gene editing enables changes to the genetic material to be made in a more targeted way. This occurs by enzymes recognising and cutting a specific DNA sequence, resulting in a double-stranded break equal to those that are induced for example, by UV radiation or chemicals. During the subsequent repair process initiated by the cell, segments of DNA can either be removed, replaced or inserted into the site of the cut, thus achieving a specific change. New gene editing methods also allow for modification of individual bases by altering the chemical structure, without cutting the DNA at all. That way, one can alter the sequence of a gene so that it, for example, becomes identical to a variant of the gene already present in other individuals of the same species, without getting other unwanted genetic traits along, as is often the case with traditional crossing.

Temporary transfer of RNA/DNA (vaccines): By transferring short pieces of RNA or DNA from viruses or bacteria into an animal, an immune response can be stimulated. The method therefore works as a vaccine, and gives the same result as regular vaccination using living vaccines. The RNA/DNA is made in a way which prevents its integration into the organism's genetic material, is not heritable, and disappears over time.

Change of gene expression: Various methods may affect how genes are expressed without changing the DNA sequence itself. One example is RNA interference (RNAi), whereby short RNA molecules bind to and degrade specific mRNA molecules that occur as intermediates in the production of proteins and other gene products. Another example is RNA-dependent DNA methylation (RdDM) where RNA is delivered to cells that changes DNA methylation (chemical tags on the genome), which in turn affect the activity of the gene (how much it is expressed).

Cell fusion (between species): In principle, the method corresponds to that used for species-specific cell fusion, but is done using cells from different species.

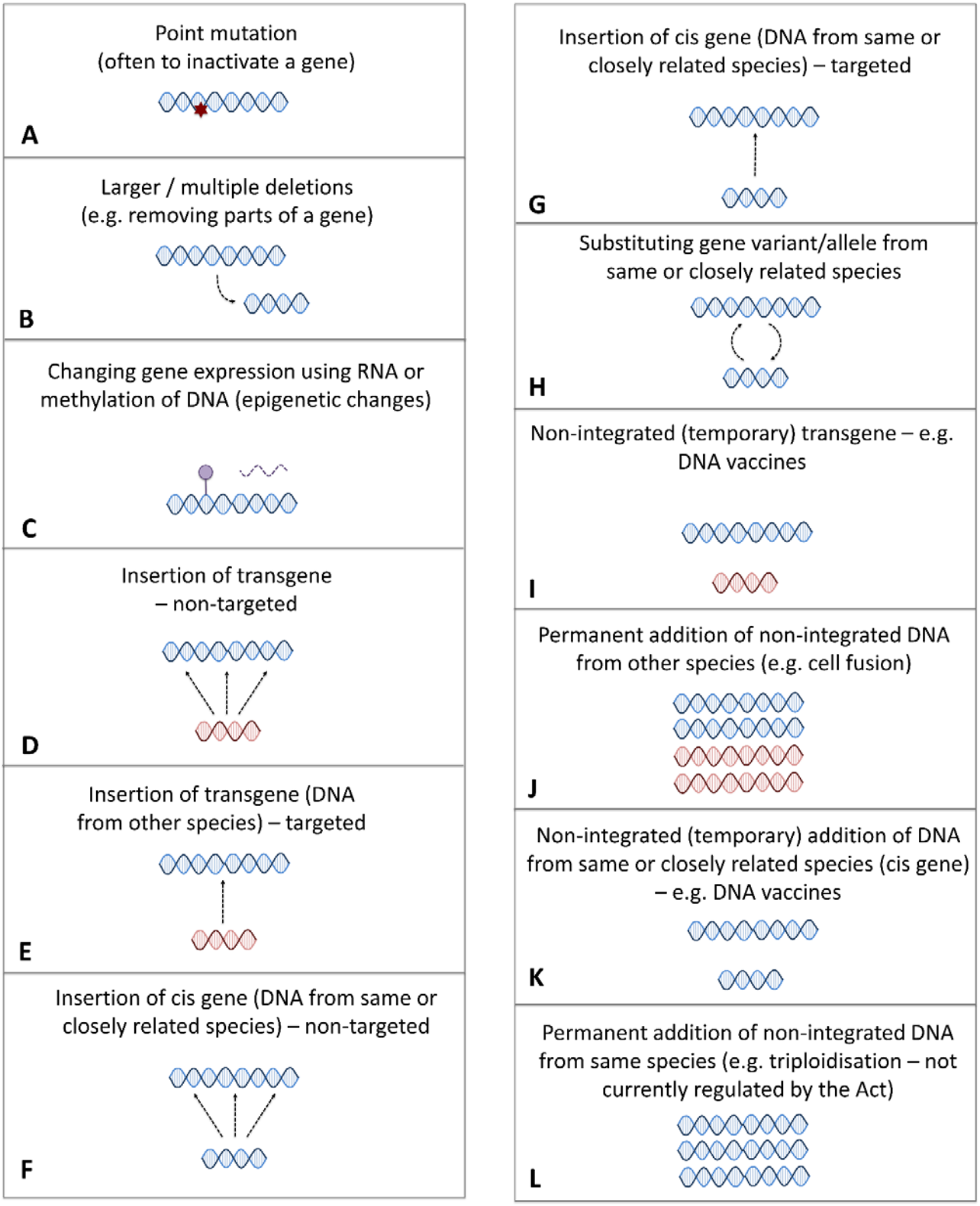


Figure 1: Various methods for genetic engineering can result in a wide range of genetic changes.

3. A need for new dividing lines?

3.1 Similarities between conventional and genetic engineering methods?

Current legislation is, in addition to history of safe use, based on the distinction between what can and cannot occur naturally.[25] Gene technology now makes it possible to create a variety of changes, spanning from those that may occur naturally, to those that absolutely cannot arise in nature or be made with conventional breeding methods (See BOX 1 for description of both conventional and genetic engineering methods, as well as BOX 2 for comparisons of the methods conducted by an expert committee under the EU Commission). Studies show that unintentional changes can occur using both novel genetic engineering methods and conventional breeding methods, and that this also depends on the type of organism.[26] However, the precision of the new genetic engineering techniques is continually being improved.[26,27,28,29,30,31,32,33] Genome sequencing technology now makes it possible to examine whether unintended genetic changes have occurred, in addition to the intended changes. [34,35,36]

From a biological perspective, methods that are currently not regulated by the Gene Technology Act can also give rise to different genetic changes, both small and large, intentional and unintentional. Crossbreeding may produce species-specific genetic combinations that have never existed before. Mutagenesis by means of radiation or chemicals will generate hundreds of random mutations. Triploidisation, a method of making sterile salmon, and cell fusion, one method used in plant breeding, both causes the organism to get additional copies of the entire genome. This can have major consequences for the plant's or animal's traits. On this basis, one might argue that all or some conventional breeding methods should also be regulated. On the other hand, experience using such methods, pragmatic considerations, and the fact that they have yet to be defined as gene technology, could indicate that they should still be exempted from the Gene Technology Act.

Experience using conventional breeding methods is informative when considering the risk of using genetic engineering methods when the end result is equivalent, which may be of regulatory significance.

The Gene Technology Act is both process and product-based; it is the technology that triggers regulation and GMO-labelling, but it is the product and its properties that are examined and assessed. Although there may be significant similarities between organisms produced by conventional methods and genetic engineering, they are currently regulated differently on the basis of the technology used. For example, mutations made by gene editing will be regulated by the current Gene Technology Act, while mutations made by mutagenesis will not. Another example is RNA/DNA-vaccinated organisms, which are defined as genetically modified as opposed to organisms that have been vaccinated by recombinant viruses, although the result is in principle the same. The Norwegian Biotechnology Advisory Board has previously stated that non-integrating DNA vaccines (Figure 1 I and K) should be exempted from the Gene Technology Act.[37] In accordance with the recommendation of the Board, the Norwegian Ministry of Climate and Environment concluded during the summer of 2017 that fish vaccinated using the DNA vaccine Clynav should not be classified as GMO.[38]

Since methods other than genetic engineering can give unexpected and unpredictable effects, one might ask whether both the method and trait should trigger regulation, both from a risk and societal perspective. For example, the major changes that may occur through conventional methods such as mutagenesis, or the degree of "naturalness", can be used as arguments that such methods should be regulated more strictly than they currently are, and possibly similar to GMOs.

3.2 The concept of "naturalness"

The technological development and knowledge we have acquired since the Gene Technology Act was adopted in 1993 may indicate that the original distinction between genetic engineering on the one hand and conventional methods on the other, no longer provides the best basis for regulation. If we assume that the reason for regulating genetic engineering in particular is that it is unnatural, an objection would be that both natural and man-made changes could potentially involve health and environmental risks.

The concept of naturalness is problematic both scientifically and philosophically, but is a term that most people have an immediate understanding of and is useful in many contexts. It denotes what is not created or ruled by humans, and is meaningful, for example, as a backdrop or contrast to what is man-made. "Natural" can also be used to describe what is considered normal or can occur under normal circumstances. Both of these interpretations can be used in the layperson's scepticism towards technology in general, and genetic engineering in particular. The term is also used normative, in a positive sense. Arguments for something being good because it is natural are classified as fallacies, but are considered valid when a reason for that something being better because it is natural is provided. When someone says that you should not enlarge your lips using Botox because it is unnatural, it can be understood as an expression of an aesthetic or moral ideal rather than a fallacy. Thus, statements that GMOs are unnatural can be interpreted as an expression of what is considered a good way to develop new varieties of plants and animals.

The use of the term "natural" in the discussion about gene modification is ambiguous. Mutations occur naturally and, as a consequence, all gene modification involves methods that occur naturally. However, those that are sceptical with reference to the natural, may also consider what occurs normally in nature, and as a result include reproduction by crossing - and cloning for some species - in their definition of what is natural. Crossing of species boundaries, on the other hand, cannot occur naturally.

There is reason to believe that most people do not operate with an absolute distinction between natural and artificial, but rather are concerned with the degree of dissimilarity39 and the type of 'unnaturality'.[40] In such a perspective, one could argue that different types of plant and animal breeding are more or less natural, depending on how much humans intervene and control the development. The greater the degree of human intervention, the more stringent the requirements should be for approval of the product. Such a ranking of methods for plant development can be justified on different grounds, for example on the basis of religion, respect for nature or scepticism to human - including scientific - arrogance. On the basis of a hierarchy of naturalness, one can still defend regulating genetic engineering differently than breeding, because the one is less natural than the other. However, it can also provide a basis for a level based regulation in line with the suggestions that follow later in this document.

3.3 Experiences with safe use

Generally, few organisms have been systematically tested for health and environmental risks. Nevertheless, traditional breeding methods are considered safe because they have a long history of safe use. The EU also refers to history of safe use as an argument for exempting organisms produced by mutagenesis using radiation/chemicals from GMO regulation.

However, no organisms or methods can be considered absolutely safe. For example, a traditional food can cause allergy in some individuals, or may be toxic if not cooked in certain ways. The term "history of safe use" is also not clearly defined. It is not determined how long, to what extent and under what conditions an organism or method must have been used to be considered safe.[41] Depending on how the term is interpreted, one might argue that some GMOs have been in use long enough to fulfil the criteria.

Photo: iStock

A consequence of today's GMO regulation is that organisms produced using methods not defined as gene technology are automatically excluded, although we do not have a long history of using such methods. One example is triploid, sterile fish. The production method was developed in the 1980s, but has only recently been used in experiments in the aquaculture industry. Research shows that there are challenges associated with the health of triploid salmon, especially when growth conditions are not optimal. However, sterile salmon obtained using gene editing (point mutation) appear to be equally healthy as other farmed salmon.[43] However, different regulatory requirements could favour triploidisation to achieve sterility, which is an attractive trait for the aquaculture industry, even though this method could have more severe consequences.

A relevant question is therefore whether the current distinction between organisms produced by gene technology and other methods is appropriate, if history of safe use should be a guiding principle for regulation.

3.4 Current debate in EU

There is a lot of discussion globally about how organisms made using new breeding techniques should be regulated, also within the EU.[3,4,5,6,7,26,61] The discussion has been ongoing for some time, but has become more pressing in light of recent technological developments. It is difficult to predict the outcome in the EU, which has discussed the issue since 2007, and when a final decision will be made. The authorities in Sweden, Finland, the United Kingdom and Germany have concluded that point mutations in plants made using gene editing (Figure 1A), which corresponds to mutagenesis, are exempted from the EU directive.[45,46] In 2015, upon a request from the EU Commission to conduct a technical analysis, EFSA also concluded that mutations made using gene editing correspond to mutagenesis (as defined in the EU Directive).[47]

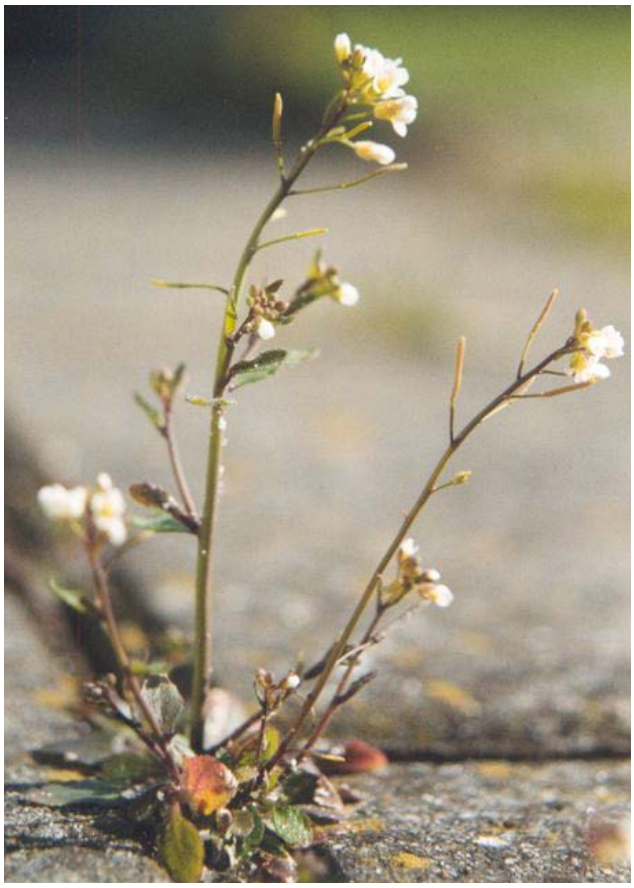


Photo: Wikimedia

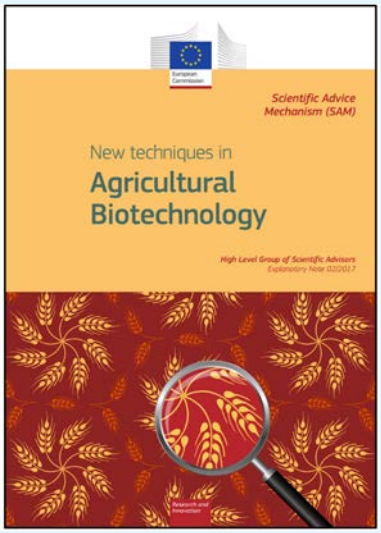
EFSA also concluded that changes in gene expression (epigenetic changes) do not alter the gene sequence itself (Figure 1C), which is required to fulfil definition of GMO in the EU Directive. In 2017, the EU Commission published a report comparing gene editing and other new breeding techniques to both established techniques of genetic modification and conventional breeding techniques (see BOX 2). However, neither the EU Commission nor the majority of EU member states have considered the legal issues, and the Commission has asked member states to await their decision. The discussions are still ongoing. For instance, the authorities in Denmark have announced that they will initiate a process to clarify their position,[48] and the Dutch Parliament has recently asked the government to assess whether some types of gene edited organisms should be exempted from the GMO legislation.10 Similar discussions are also taking place within the Norwegian ministries.

In October of 2016, the French Council of State (Conseil d'État) asked the European Court of Justice to clarify the question concerning regulation of organisms with mutations made using gene editing.[49] The European Court of Justice will decide whether such organisms fall under the regulatory framework governing GMOs. In addition, the court will decide whether these will be classified as GMOs on EU's list of plant varieties, and if individual countries can ban products made using the new technologies if they are exempted from the GMO regulation. The court has also been asked whether exempting such organisms from a precautionary approach, risk assessment and traceability as required by GMO legislation would pose a threat to the precautionary principle set in Article 191 No. 250 on EU's environmental policy under the Treaty on the Functioning of the European Union (Treaty of Lisbon).

However, the discussion is not only about how current legislation should be interpreted (the issue that the European Court of Justice has to decide on), but also about which future regulatory frameworks are the most appropriate, given that the technological possibilities have changed significantly since the regulations were first drafted. European Commission itself has emphasised the importance of a broad debate on the use and regulation of new gene technologies.[51,52]

Summary of the EU commission report on new breeding techniques from may 2017.

In May 2017[26], the European Commission published a report that compares gene editing and other new breeding techniques to both the established techniques for genetic modification and conventional breeding techniques, based on published scientific studies, review articles and official statements. The purpose of the report was to provide an up-to-date scientific knowledge base for the Commission. However, the aim is not to provide legal advice. The work was carried out by an expert committee consisting of internationally leading experts in life sciences, sociology and political science.



The main conclusions of the report were:

- All living organisms are subject to alterations in their genetic information due to molecular processes (e.g. errors in genome replication, or mutations), which can occur spontaneously or by exposure to environmental stressors. This leads to genetic variation.
- All breeding techniques (conventional methods, established techniques for genetic modification and new techniques) make use of genetic diversity and change, both man-made and naturally occurring, to develop organisms with desired traits.
- There are differences between the various new techniques; some are more similar to established techniques for genetic modification, while others are more like conventional breeding methods. This is reflected in the wide range of end products that can be obtained.
- Gene editing technologies can generate targeted and precise changes in the DNA sequence, ranging from point mutations (changes in one or a few bases) to the insertion of genes. Other techniques may affect gene expression without altering the DNA sequence.
- The variety and versatility of new techniques means that grouping them together may not be optimal for scientific or other reasons.
- Differences between groups of techniques of relevance to unintended effects and efficiency depend on the extent to which changes can be targeted and how precisely they can be made. Unlike conventional breeding methods and established techniques for genetic modification, unintentional changes associated with new techniques such as gene editing are rare. In general, the frequency of unintended effects in organisms made with new techniques is much lower than in those produced by conventional methods and established techniques for genetic modification. This is currently subject to much research, as evident from the rapidly growing number of publications in the field.
- The precision and efficiency of the new techniques means that some products can only realistically be obtained using such methods, and not using conventional methods or established techniques for genetic modification.
- Conclusions cannot be drawn about the absolute or comparative safety of techniques. A risk assessment can only realistically be made on a case-by-case basis, depending on the characteristics of the end product. Genetically and phenotypically similar products made with different methods are not expected to give significantly different risks. However, the report does not address the question of risk further.

3.5 Regulation based on technology and/or product?

The main purpose of the regulatory framework is to regulate where necessary, both in terms of health, the environment and societal aspects. In Norway and the EU, GMO regulation is triggered by methods defined as gene technologies. Nevertheless, it is the organism and its traits that are assessed according to certain requirements.

Whether it is most appropriate to regulate on the basis of the technology used and/or product traits depends on whether the production process itself poses a risk to health and the environment, or involve challenges related to sustainability, societal benefit and ethics. Which regulatory framework best captures relevant cases also matters.

From a risk perspective, an argument for keeping a process-based regulation is that we can control the use of technologies that do not have a history of safe use. For instance, a technology may allow for larger changes to the organism in a shorter amount of time than other breeding methods, which may increase the risk of potential adverse effects in the short and long term.

On the other hand, one can argue that it is the properties of the organisms, and not the production methods themselves, that determine health and environmental risks. Using such an approach, the specific genetic change/trait should decide how organisms should be handled and what requirements should apply during risk assessment.[53,54,55]

This is, for example, the main principle for regulation in Canada, which regulates products made using biotechnology as part of the regulatory framework governing ”new products”. Here, a risk assessment of new plants for cultivation, and as new food or feed products, is required regardless of the method of production.[56] A novel plant is defined as a plant expressing a trait that has previously not been present in this particular crop in Canada, or expressing a trait that is applied or utilised differently than in the variety already present. Novel food is defined as food made using a process that has not previously been applied to food, products that have no history of safe use, and food made using genetic modification or biotechnology.[57] Both the product’s traits and the production process can therefore trigger regulation. Whether the plant or food is considered novel is determined on a case-by-case basis.

The risk assessment in Canada is guided by the same principles as in the EU and with the same general requirements for information and what should be assessed. In terms of plants, the requirement differ from case to case. The type of plant, its intended uses, and the environment the plant will be released into, will be decisive factors. Until now, most ”new products” have been GMOs, but plants made with conventional breeding methods have also been assessed and approved under this system. Gene edited organisms where DNA has been removed is also regulated, and a gene edited rapeseed has been approved in Canada.

A more product-based approach has also gained support in reports and discussion papers published by several organisations, such as the European Academies Science Advisory Council (EASAC),[58,59] the European Plant Science Organization (EPSO),[60] the European Seed Association (ESA),[61] the Royal [15]

Forest and Agricultural Academy (KSLA)[62] in Sweden and the National Academy of Sciences (NAS) in the United States.[63] Others, including environmental organisations, organisations for organic farming and other non-governmental organisations have expressed a preference for keeping technologybased regulation.[64,65,66,67,68]

> The Committee believes more research should be conducted on the new, gene edited GMOs, such as the CRISPR technology. It is absolutely necessary to acquire more knowledge before gene edited GMOs can be approved for use outside closed systems. As with the traditional types of GMOs, there is a risk that new, genetically modified organisms may spread in nature and have unintended consequences. The Committee therefore believes that one should continue to enforce a restrictive policy on GMOs. Genetically modified organisms must be regulated by the Norwegian Gene Technology Act and they cannot be approved until warranties are given that they are traceable and thus can be monitored.

However, the current discussion is about more than just risk. The regulation will also affect social aspects such as sustainability, societal benefit and ethics, and will be discussed separately in the next chapter.

4. Sustainability, societal benefit and ethics - important considerations

The purpose of the Norwegian Gene Technology Act is to ensure that GMOs are developed and used in an ethically defensible and societally beneficial way, in accordance with the principle of sustainable development. Norway was the first country to consider such criteria when assessing GMOs. Other countries have since adopted similar approaches, and the EU legislation has become more similar to the Norwegian. The EU directives do to a certain extent allow considerations of ethical aspects, and many other countries' regulations do the same. By 2015, the EU agreed that each member state may prohibit the cultivation of an EU-approved GMO due to, for example, socioeconomic reasons, environmental policy, urban and regional planning, land use, avoidance of GMOs in other products, agricultural policy or other policies.[70] The Cartagena Protocol (Article 26 on imports of GMOs) declares that member states can emphasise socio-economic considerations when deciding whether to approve a GMO.

4.1 Societal consequences of different regulatory systems

There is a growing interest among various stakeholders within agriculture and food production to utilise new genetic engineering methods, and a variety of applications are under development (see BOX 3). In Norway, this would most significantly affect the agriculture and aquaculture industries. If regulation is disproportionately strict, it would naturally follow that such methods would not be widely employed to create novel plants and animals, since it would become, for example, too unpredictable, time consuming and expensive to develop products for the commercial market. The Gene Technology Act also regulates field trials, which cannot be carried out without a permit. The regulation will also affect the stakeholders' competitiveness on the international market. Today, only a few large multinational companies offer GMO plants on a large scale. It has been argued that the current strict regulation has contributed to increased monopoly because it favours large-scale products and large multinational companies. One may argue that a less rigorous regulatory framework can facilitate the development of more niche and societally useful products, and that the product traits rather than the production process determine whether they are beneficial, sustainable and ethically sound.

However, if the regulation is too relaxed, the technology could be used to make products that are not sustainable, beneficial or ethically defensible. This may favour process-based regulation. For example, there may be challenges associated with the use of a specific technology, or to products that can only be produced using a specific technology. If the production process of a genetically modified farm animal has negative impacts on the animal's welfare, and conventional breeding methods for producing a similar animal do not, there may be reasons to regulate them differently. Another example is the use of a given technology that leads to changes in agricultural practices that do not contribute to sustainable development, regardless of the characteristics of the products. Another variable, related to technology, is the socio-economic framework.

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In principle, it is possible to think of genetic engineering as an unacceptable intervention in the genetic integrity of an organism and a lack of respect for nature, and thus as overstepping biological, moral or political boundaries. The ultimate consequence of such a viewpoint may be to ban any use of GMOs. A widespread view is that extensive use of GMOs can reinforce the development of agriculture and food production based on large-scale and industrial farming, monocultures and high levels of pesticide use, which can lead to an undesirable distribution of power and unfortunate consequences for health and the environment. This can affect other forms of agriculture and food production, such as organic farming.

EXAMPLES OF TRAITS DEVELOPED USING NEW GENE TECHNOLOGIES.

Listed below are examples of products that are currently being researched and developed using new techniques. Some of them have traits that have already been attempted or developed previously using other breeding methods and genetic modification. Others are only made possible using new techniques (for example the removal of traits).

Disease-resistant animals and plants:

- Pigs resistant to Porcine Reproductive and Respiratory Syndrome Virus (PRRS)[71,72] or African Swine fever[73]
- Rice[74], wheat[75] and tomatoes[76] that are resistant to fungal infection
- Cucumber resistant to virus infection[77]
- Citrus fruit resistant to bacterial infection[78]

Plants with modified nutritional content:

- Maize with reduced phytate content (when consumed by livestock, it increases the absorption of phosphorus and thus reduces the levels of phosphate in the environment)[79]
- Potatoes with reduced amount of carcinogenic acrylamide created when exposed to heat[80]
- Rapeseed that produce oil with less saturated fat[81]
- Wheat with reduced gluten content[82]
- Rice with increased amlyose content (can reduce the risk of a variety of diseases such as diabetes and cardiovascular disease)[83]

Plants with increased productivity:

- Tomatoes that flower more often (and therefore produce more) per season[84]
- Corn with improved growth during drought[85] and rice that produces more grains per plant[86]
- Rice with increased shelf life during storage[87]

Animals with other traits:

- Livestock without horns (to avoid dehorning of calves)[88]
- Sterile farmed salmon (to avoid gene introgression in wild salmon stocks)[89]
- Cashmere goats with thicker fur[90]
- Laboratory animals as models of human disease to study mutations that cause disease, and to develop new medical treatments[91]

Pesticide-resistant plants:

- Rapeseed resistant to pesticides containing the active ingredient sulfonylurea[92]

The Gene Technology Act does not regulate intellectual property rights (abbreviated IPR, i.e. patents, trademark protection, etc.), which provide specific rights to those who develop new products or methods. However, IPRs will affect which methods and products that are employed in research and development, and ultimately what products that end up on market, and the associated societal and ethical consequences of using the products. An increased number of genetically modified organisms on the market may result in more patented products, which could lead to unfortunate hurdles to future breeding efforts, the farmer's rights to save and re-plant patented seeds, and access to patented GMOs for carrying out independent risk research. On the other hand, patents and other forms of intellectual property rights can stimulate desirable development and innovation. Another issue is that it may be ethically problematic to allow patents on living organisms, regardless of whether they are genetically modified or not. For organisms produced using the new gene editing methods, the patenting situation is currently unclear and may differ between organisms depending on the genetic change that has been made. The outcome of patent issues related to gene editing may have different societal consequences.

4.2 Ethical considerations

Modern biotechnology should be used in a manner that is ethically defensible, and the regulation that governs its use must reflect relevant ethical considerations. There will always be an ethical reasoning behind a certain standpoint on how technology should be used and how the legislation should be worded and framed. However, these aspects are not always clearly expressed. Perceptions on what constitutes appropriate use and acceptable legislation will differ, and it is therefore important to clarify ethical aspects.

Which considerations to include during an ethical assessment may be based on various ethicalphilosophical positions.

1. Consequentialism: That one alternative can be expected to have a better outcome than another, can speak in favour of the former. Such a view rests first of all on (a) a premise that something is intrinsically good, and (b) that we have an obligation to act in a manner that is generally expected to lead to a good outcome. There are several interpretations of what is good. Well-being (pleasure and decreased suffering) and autonomy are two common variants. Maximising a good outcome also requires certain assumptions about the expected outcome of an action. When the consequences of actions are uncertain, the assessment will have to include considerations about what are rational/wise ways to act under uncertainty (see section 4.1).

2. Deontology: Actions should not (only) be assessed based on their consequences, but also based on the action itself. Punishing a person who has not done anything wrong is wrong, even if it does not lead to harm, or even has a good outcome. We have certain obligations that are (partly) independent of the consequences of the actions. One way to justify such obligations is to demonstrate that all people have self-worth (human dignity) and that we have an obligation to act in a way that respects this.

3. Relational / care ethics: The norms of our actions are shaped by our relationship to humankind or other organisms. This gives reason to treat such individuals with care and respect. The relationship may be a result of someone entering into a role - for example, as a health care provider or guardian - and thus undertakes a certain commitment. Some believe that commitments are stronger towards humans and other organisms belonging to the same society or environment as oneself. This can be called relational ethics. A variation on this is care ethics. It underlines the importance of emphasising the nature and quality of the relationship, as well as the important role that power, dependency and vulnerability may play during the complex assessment of what is right and wrong.

4. Virtue ethics: To act in a good way is judged not only based on consequences, obligations or relationships, but character traits. To be able to act in a good way you must strive to be good. Good actions follow from good traits, such as courage and mercy. There may be different opinions about what represents good characteristics and, like with the previous ethical perspectives, this can be defined in several ways.

In principle, all the above-mentioned considerations can be part of an ethical assessment of a GMO. A reasoning that encompasses the different aspects requires good judgment. It is also possible to include, to a smaller or lager degree, other considerations than those already mentioned, such as the core values of society, bioethics and eco-philosophy. Regardless of one's political view, it is necessary to clarify which ethical principles a political standpoint is built on.

Ethical assessments, and the operationalisation of these, may differ under different regulatory models. Regardless of regulatory model, it may be desirable to develop an appropriate framework for how such assessments should be carried out, which is currently lacking.

It is essential that products approved according to the Gene Technology Act, regardless of type, are trusted by society. The consumer must be able to rely on legislation to ensure safe, sustainable, beneficial and ethically defensible use of genetic engineering, while at the same time not creating unreasonable obstacles to the development of desired products. There must be an openness about how the technology is used, and the consumer must be able to make knowledge-based decisions. The objective must be to adopt a system that facilitates the development and use of technology for the benefit of society, in accordance with the intention of the Gene Technology Act. To succeed in this aim, different regulatory models must be compared.

One might ask whether the scope and definitions set by the Gene Technology Act should be kept, or whether changes should be made to exempt certain organisms made using genetic engineering, or to include those that are currently excluded from the regulatory framework. Another consideration is whether different types of organisms should be subject to different requirements. Regardless of which regulatory frameworks apply, appropriate distinctions must be made. Such distinctions may be based on the type of genetic change, the extent of the change(s), the trait that has been altered, the potential risk to health or the environment, and/or other considerations such as sustainability, societal benefit and ethics. This may depend on which rules or requirements for approval that apply.

The following chapters first describe the current system for approval of GMOs, before possible alternatives are presented and discussed.

5. Current system for approval of GMOs

Before a GMO can be approved, the potential risks to health and the environment must be assessed. This is mandatory in both Norway and the EU. In Norway, assessments of sustainability, societal benefit and ethics are also required. Requirements for labelling and traceability come in addition to the approval scheme.

5.1 Risk assessment and management

With the current legislation, there is a clear division of labour between the bodies that perform scientific risk assessments (i.e. risk assessors), such as EFSA and VKM[93], and those that advise and make the political decisions about the course of action in the case of presence of risk (i.e. risk managers), such as the Norwegian Food Safety Authority, the Norwegian Environment Agency and the Ministry of Climate and Environment.

During quantified risk analysis, risk is assessed by combining the probability and the severity of the potential injury. Risk assessors shall also take uncertainty and lack of knowledge into account.

However, beyond decision theory, there is a lot of ambiguity associated with the terms ”uncertainty” and ”risk”. Both refer to a situation where you are uncertain about the outcome of an action. There are at least three types of uncertainty.

1. It is unclear what an action will lead to, but the probability distribution of possible outcomes is known. This is called (in decision theory) risk.
2. The possible outcomes are known, but not their probability distribution. This is called uncertainty.
3. Neither the outcomes nor the probability of the different outcomes are known. This is called ignorance.

When it comes to decision-making during risk, maximising the expected value is considered rational. The expected value of the various options is calculated based on the estimated probability and value of the outcome. This procedure is not applicable under uncertainty and ignorance.

An important principle for rational decision making under uncertainty is the maximin principle. It only requires estimates of the outcome value, not their probability. Here, the option with the best minimum outcome - that is, the option that has the least severe consequences in a worst case scenario.

Such an approach is sensible if there is little to gain and much to lose by choosing the riskier option. If the potential benefits are significant, however, it seems unwise not to take them into account when comparing different courses of action.

In hybrid situations where the probabilities of the different outcomes are partly known, one can choose the option that has the lowest probability of the worst case scenario.

Based on an overall assessment, risk managers will decide the acceptable level of risk, what to do in the case of risk and how to take into account inadequate knowledge or scientific disagreements. Here, the precautionary principle is an important basis for different legal frameworks.

5.1.1 The precautionary principle

The precautionary principle is an important prerequisite of the legislation that govern gene technology both in Norway and in the EU. The precautionary principle regulates actions under doubt or uncertainty. References to this principle are found in the preparatory works for the Gene Technology Act. It is argued that the wording of the regulation, i.e. that the production and use of a GMO must be ”without health and environmental harm”, is used to emphasise the aim of assessing health and environmental risks in advance and to avoid possible harmful effects, and that the precautionary principle should guide decisions. The proposition of the regulation outlines how to interpret the principle:

> The ministry emphasises that the precautionary principle does not imply that all use of genetic engineering is regarded as inherently risky. If however, following a specific assessment, there is any reasonable doubt concerning risk, this would be an argument against its use.[94]

However, what is meant by ”reasonable doubt” remains unclear. In the comments made to the article stating the objective of the regulation, it is stated that the precautionary principle should be used as basis for the assessment of adverse effects on public and animal health and the environment, and that ethical considerations will have to be emphasised when deciding whether or not to approve a GMO application.

The precautionary principle is considered one of several principles that define the term sustainable development. Paragraph §9 of the Nature Diversity Act describes the use of the precautionary principle as follows:

> When a decision is made without sufficient knowledge of the effects it may have on the environment, one should aim to avoid significant harm to biological diversity. If there is a risk of serious or irreversible harm to biological diversity, lack of knowledge shall not be used as justification for postponing or avoiding the implementation of protective measures.

The risk assessment must be based on both quantitative and qualitative criteria in order to, for instance, assess whether harm can be irreversible and whether an adverse effect can have a catastrophic outcome even if there is no short-term damage. If the precautionary principle is used, various measures can be employed to address uncertainty. These can include a permanent ban, a moratorium (a temporary ban to allow for more time to acquire the necessary knowledge), a stepby-step strategy (with well-defined milestones that must be achieved for each step), a slow-paced strategy (where an activity is followed up through dedicated programs, e.g. in research) or a monitoring strategy (an extensive activity is followed up by monitoring programs and reporting systems, but also taking into account the principle of reversibility). After an action has been initiated, the goal should be to reduce uncertainty, for example by conducting research or ask for more data on aspects where there is uncertainty.

However, the precautionary principle can be interpreted in different ways. It may therefore be appropriate to define the criteria to identify the level of knowledge required for rejecting a precautionary approach, to avoid it becoming a strategy for preventing the approval of GMOs in general.

5.1.2 The EUs guidelines for health and environmental risk assessment

The EU has developed guidance documents for the assessment of environmental and health-related risks of genetically modified plants, microorganisms and several types of animals.[95] The documents contain guidelines for how applicants can assess the impact that a GMO may have on the environment or on health, and explain why certain data or methods are recommended for risk assessment. An important principle in assessing GMOs is evaluation on a case-by-case basis, because potential risks can be different. Therefore, the information required may vary depending on the type of GMO and trait, the intended use, the environment into which the organism is to be released and whether there are other GMOs already present in the environment. Another principle is that GM plants should be assessed step by step. This implies that initial experiments are carried out in laboratories, followed by several and increasingly larger field trials. Because ecosystems are so complex, it is hard to predict all possible outcomes in advance.

The guidance documents further contain recommendations on methodology and what to measure. GMOs have been approved even if they do not fulfil all the requirements described in the documents. There have been several discussions in the EU whether the methods are adequate to provide the intended information, but also if any of the recommendations have been unnecessary. Changes have been proposed and the documents have been updated at irregular intervals.

GMOs should be compared to non-GMOs according to certain guidelines. The approach is based on the history of safe use of non-GM plants for humans and animals, and that the biology of the nonGM plants is already known. For example, during an environmental risk assessment, a GM plant should be compared to the nearest non-GM relative under the same ecosystem conditions.

For an environmental risk assessment, information can be obtained from field trials, molecular description of the composition of the plant, description of the nutritional content of the plant, ecotoxicological testing, modelling and/or literature review studies. A monitoring plan should also be provided that can be put into effect if a GMO is approved, to collect information about the effects of the deliberate release. In addition, the guidance documents provide information about the choice of comparators, the environment in which the GMO is to be released, and long-term effects.

The risk assessment of GMOs is performed in six steps:[96] 1) Problem formulation, including identification of hazards, 2) Description of hazards, 3) Description of the exposure,

4) Risk description, 5) Risk management strategies, and 6) Comprehensive evaluation of the risk.

5.2 Risk assessment of new DNA techniques under current regulations

A few international institutions have suggested ways to assess health and environmental risks for GMOs made with new gene technologies such as gene editing, without recommending how the techniques themselves are to be regulated. As described above, the steps involved in risk assessment include identifying differences and evaluating whether such differences constitute a potential hazard, and finally to determine the risk, i.e. the likelihood that an undesirable event will occur, multiplied by the consequences.

In 2014, the Environment Agency Austria, EAA (Umweltbundesamt), presented relevant questions based on the EU's principles for risk assessment. EAA argued that similar principles for risk assessment of GMOs can be used as a starting point to identify possible risks associated with the new DNA techniques. According to the EAA, the following should be part of the assessment of organisms made with the new techniques:

- Changes in the plant genome (both intended and unintended)
- Knowledge of and experience with the traits altered
- The presence of DNA sequences other than those of the plant's own
- Change in gene expression (e.g. change in the expression of certain proteins or RNAs)

EFSA has produced a report on risk assessments of plants where new DNA has been inserted using site-specific mutagenesis (CRISPR etc.) and recommends that the same aspects should apply to such plants.[97] However, this does not apply to plants where no new DNA has been inserted.

Researchers at GenØk - The Center for Biosafety - also concluded in a report from 2015 that the same aspects should be included in the risk assessment of genetically modified organisms containing mutations made with gene technology, so-called site-specific mutagenesis (CRISPR etc.) and oligo directed mutagenesis (ODM).[98] In addition they pointed out that the novelty of the techniques, in addition to incomplete knowledge about all the molecular mechanisms involved, gave rise to uncertainty associated with the assessment of unintended effects. They recommended performing a case-by-case assessment of each organism and mapping all the genes, proteins, etc. (so-called omics methods; genomics, proteomics) to detect unintended/off-target changes.

The researchers also pointed out that, although a change in the DNA is small, the effect may be significant if a biochemical pathway is eliminated or rendered more or less effective due to altered ability of the enzymes to bind to other proteins.[99] In contrast, a major genetic change might have a minor effect, depending on the type of change. For example, duplication or inversion of segments of the genome - events that can happen naturally, using conventional methods or using gene technology - can occur without obvious phenotypic effects.[100] When the technology for detecting genetic changes improve, it will also become possible to detect differences that were previously not detectable.

Others argue that products made with genetic engineering do not pose any greater risk than equivalent products produced by other methods.[8,9,26] If the EU decides that, for example, mutations made with gene editing are to be considered as mutagenesis, and thus exempted from the GMO regulation, there will be no requirement for a separate risk assessment.

5.3 Assessment of sustainability, societal benefit and ethics

The Norwegian Gene Technology Act emphasises that the products or the release of the products have "societal benefit", are "ethically defensible" and promote "sustainable development" to achieve a more comprehensive approach to evaluate the use of biotechnology beyond focusing only on risk.

Thus, an important question is what kind of beneficial products the new technologies can provide and whether these are as good as or better than those produced using other methods. This may impact both public acceptance and demand for the products. If a product provides clear benefits to society or the individual consumer, people are usually willing to accept greater risk and uncertainty. According to the current GMO regulation, the products must be better than existing alternatives. Assessment of sustainability, societal benefit and ethics are carried out by the Norwegian Biotechnology Advisory Board.

Societal benefit is assessed with respect to impact nationally and in the short term. Both societal advantages and disadvantages must be considered. Increased productivity,

improved nutritional content, reduction of harmful substances or increased shelf life may potentially be traits that are more relevant than those approved for GMOs to date. Benefits for third parties are also considered, not only benefits for the applicant, the individual producer or the consumer.

Assessments of sustainability expands the perspective in time and space compared to a normal health and environmental risk assessment, and also take into account social and economic conditions. The perspective is long-term and global. As a consequence, conditions in the country of production must also be considered, and particular emphasis can be placed on issues that are important in a North/South perspective. Issues of interest can be food security, animal health and welfare, living conditions and profits for farmers, living conditions and profits in the production area, access and rights to further breeding of plants and animals, ownership of seeds, plant varieties and animals, coexistence and consumer choice.

The requirement that the production and use of GMOs should be conducted in an ethically defensible manner may apply to genetic changes affecting the welfare or integrity of individual animals, the integrity of the species or environmental conditions that affect the ecological balance or the relationship between humans and nature. It may also take into account whether new technology/new products are in line with the core values of the general public, or how it affects vulnerable groups in society and the distribution of power. This may apply to the characteristics, production and/or use of products.

Assessments of sustainability, societal benefit and ethics are based on a series of questions concerning aspects that are considered relevant to the product in the particular context, which the applicants are asked to clarify. If available, documentation from similar products and other types of knowledge can also be used. However, the operationalisation of these assessments is not unambiguously defined and is subject to discussion (see chapter 12).

5.4 Requirements for labelling and traceability

The King of Norway may provide regulations on the labelling of products consisting of, or containing genetically modified organisms or products from cloned animals.

The Gene Technology Act regulates labelling, transport, import and export of GMOs (regulation 2 September 2005 No. 1009).[101] It specifies that an approved GMO product must be labelled as containing GMOs. The label must be placed on the packaging unit or in the accompanying document or notice. Products made by genetic engineering that do not contain genetically modified organisms are not required to be labelled. This could for instance be proteins or other substances produced using genetically modified bacteria. Processed food and feed made from GMOs where DNA is not present in the final product is regulated by the Food Act and must be labeled.[102]

The preparatory works for the Gene Technology Act emphasises that, from a consumer point of view, health and environmental aspects of living genetically modified organisms are important, but that the production process is not decisive for the traits of the end product.[14] The current discussion on labelling often revolves around consumers' and farmers' choice, i.e. that consumers should have a right to choose what food they want to buy or what types of farming they want to support. However, it is unclear whether consumers perceive labelling as a warning about potential health and/or environmental risks, even though the approval of the product implies that there is no significant risk.[103,104]

In order to enforce labelling requirements for a GMO, the EU also has requirements for traceability, as stated in Article 4 of the Directive on Deliberate Release, which also applies in Norway, as well as Regulation 1830/2003 which has yet to be incorporated into Norwegian law. The provisions require countries to ensure document-based traceability, methods of detection and labelling of approved GMOs. Additionally, the regulations on impact assessment in the Norwegian Gene Technology Act stipulates requirements for information on plans for surveillance, including methods for tracing the genetically modified organisms, monitoring the effects, as well as techniques for detecting the transfer of the introduced genetic material to other organisms. Such requirements are implemented to effectively manage any potential negative consequences that might arise due to the GMO.

However, analytical traceability/detection requirements may be difficult to enforce for many of the organisms produced using new DNA techniques such as gene editing (see discussion in Chapter 12).

6. Alternative ways forward

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With the extensive discussions about which regulatory frameworks should apply to GMOs currently ongoing, considering different regulatory options is timely. Issues that need to be addressed include what organisms should be regulated, how to regulate them, what ethical considerations should be taken into account under different regulatory alternatives, and what impact these regimes might have on society and the environment.

Regarding the question of what should be regulated under the Gene Technology Act, there are three main alternatives:

1. Keep today's distinction between organisms produced by conventional methods and genetic engineering
2. Incorporate organisms/methods currently exempted from the Gene Technology Act
3. Exempt certain organisms produced by gene technology from the Gene Technology Act

Of equal importance is how organisms should be regulated. A key question is whether the same overall requirements for approval/risk assessment should apply to all organisms regulated by the Gene Technology Act, or if differentiating these requirements is appropriate. To evaluate this, one must determine what the aim of a level based system should be, important considerations that need to be included, and what the consequences of different options might be. Although the consequences may be small for risk assessments, they may be greater for assessments of sustainability, societal benefit and ethics, or vice versa.

The level of flexibility available to adapt the requirements for approval under current legislation should also be clarified. If parts of the Gene Technology Act are changed, it is also necessary to clarify whether it is necessary to amend the scope and definitions of the Act (what should be considered as genetically modified organisms or what the regulation should include if extending beyond genetic engineering) or rather the individual provisions set by the Act.

The following chapters describe various possibilities for differentiating the approval scheme for different GMOs. First, the possibilities for differentiation under the current regulations are described. Next, two alternative proposals for level-based regulation are outlined, which would require a change of current practice.

7. Differentiation between different types of genetically modified organisms under the current regulatory framework

7.1 Differentiation of deliberate release approval through guidance documents

In principle, the current regulation opens up for differentiation between different types of GMOs, for example in terms of approval, requirements for risk assessments and labelling. The law does not state explicitly how to divide the uses of GMOs into various levels, except between deliberate release and contained use. In practice, there is a differentiation through different provisions and guidance documents for risk assessment of microorganisms and plants.

The regulations on impact assessment in the Gene Technology Act[105] allows for differentiation between different types of GMOs, and further states that not all GMOs necessarily require the same or equal amounts of information, and that there may be significant differences in terms of the details required.

§§13 and 15 of the Article refer to Appendix 1 which elaborates on the content of the impact assessment, where it is stated:

> All of the points listed will not apply in each particular case. Therefore, for each application, only those points considered relevant in a given case shall be taken into account. The accuracy of the information necessary for each point may vary depending on the type and extent of the deliberate release.
>
> Future developments within genetic modification may make it necessary to adapt this appendix to align with the technical progress or to develop guidance notes that will complement this appendix. A further differentiation with regards to the information required for different types of genetically modified organisms, e.g. single-celled organisms, fish or insects, or for certain uses of genetically modified organisms, e.g. development of vaccines, may become possible when sufficient experience with applications for deliberate release of certain genetically modified organisms is obtained in the EEA.

The EU also has its own guidance documents for plants and microorganisms and for risk assessment of genetically modified animals, insects and fish, where Norway has had the opportunity to contribute. Norway can use these as a guide during the assessment of applications.

The risk assessment should provide information about whether the GMO is harmful to human and animal health or the environment. The attached documentation, and the experiments that have been conducted, must be sufficiently comprehensive to be able to answer these questions. Not all of the recommendations for required experiments and data outlined in the guidance documents will be relevant in all cases. The applicant must first consider what is required based on the guidance document, while those who assess and manage risk determine whether the submitted documentation is sufficient in each case.

For instance, the requirements for risk assessment of certain genetically modified organisms where no foreign DNA has been inserted into the genome may be less extensive than for other GMOs under the current regime, because there are no inserted genes to examine. There is also a possibility to urge Norwegian authorities or EFSA to clarify the guidelines or prepare separate guidance documents for certain types of GMOs where novel techniques are being employed. Research and documentation on how the techniques work, in addition to gradually increasing experience with them, may result in future amendments to the requirements for risk assessment.

7.2 A level-based approval system for contained use of genetically modified organisms

One example of a level-based system is the regulation of contained use of genetically modified organisms. Here, specific regulations exist for plants, animals and microorganisms. All three are divided into levels, but according to different criteria. The differentiation is based on the measures required to prevent the organisms from spreading outside laboratories/greenhouses/animal facilities. A distinction is also made according to whether an approval is required or a notification to the authorities is sufficient.

In the regulations on contained use of genetically modified plants, there are three levels of containment based on the ability of the plants to establish in the environment, the

ability to spread and the ability to release pollen.[106] The applicant must submit a preliminary evaluation of the risk of disease or injury to humans, animals, plants or the environment in the case of establishment and spread in the environment, and in an agricultural context. This preliminary evaluation determines the requirements for containment and containment levels. The societal and ethical aspects of the activity should also be considered, with particular emphasis on the objectives of the activity.

In the regulations on contained use of genetically modified microorganisms, there are four levels or classes of levels for contained use based on risk:[107] 1) no or insignificant risk, 2) low risk, 3) moderate risk and 4) high risk. Classes 1 and 2 require, with certain exceptions, only a notification, while classes 3 and 4 require approval. The applicant should make a preliminary evaluation of the risk of disease or injury to humans, animals, plants or the environment and classify the activity. For the purpose of classification, the EU Directive 90/679/EEC and international or national classification schemes (WHO, NIH, etc.) may be used. The preliminary evaluation determines which requirements and containment levels are appropriate to protect human and animal health and the environment. In some cases, ethical and societal aspects and animal welfare should be considered. All classes have requirements for contingency plans, supervision, safety measures for waste management, etc.

In the regulations on contained use of genetically modified animals, there are three classifications with regards to containment measures: a) vertebrates, b) invertebrates and c) aquatic animals.[108] The applicant must submit a preliminary evaluation of the risk of disease/injury to humans, animals, plants or the environment. The preliminary evaluation determines the requirements for containment measures. The applicant must, in particular, assess societal and ethical aspects of, for example, the genetic modification of vertebrate animals and the production and use of GM animals for sale or use in industry, and in some cases animal welfare. Objectives and ethical aspects beyond protection of animals should be assessed separately. Experiments on GM animals that are conducted solely for scientific research purposes, which are approved in accordance with §13 of the Animal Welfare Act, require only a notification to the authorities under the Gene Technology Act. All other types of use require approval.

8. A level-based approval system also for deliberate release of GMOs?

There is currently an extensive international debate about whether certain genetically modified organisms should be exempted from the GMO legislation. In particular, this concerns organisms where no new DNA has been inserted into the genome, such as point mutations generated by gene editing and temporary, non-hereditary changes. Those in favour of such exemptions argue that, from a scientific perspective, such organisms are unlikely to pose greater risk than organisms developed using traditional methods, nor do they impose greater challenges in terms of sustainability, societal benefit and ethics. They further argue that the current system for approval of GMOs is timeconsuming and costly for the producer. A review of all GMOs that had undergone risk assessment in the EU between 1998 and 2015 showed that the actual approval process took an average of almost five years,[109] and two US studies show that the approval process alone cost the producers from 10 to more than 30 million dollars, depending on the product and where the approval was sought.[110,111]

Others do not want to exempt such organisms from the GMO regulations because they believe we do not have adequate knowledge and experience with the new techniques to ascertain the risks, the societal benefit or disadvantages, or the consequences for sustainable development and ethical aspects.

An alternative solution is to differentiate requirements for impact assessment and approval for deliberate release of GMOs according to a level-based model, to a greater extent than is currently possible under the Gene Technology Act. This way, the time and cost of development and approval could be reduced while still providing the authorities with sufficient overview of the products and the option to intervene if necessary.

A similar argument was used when amendments to the regulation of the deliberate release of alien organisms were adopted in the Nature Diversity Act in 2014. The amendments opened up for a levelbased regulation. According to the regulation on alien organisms (regulation 19 June 2015 No. 716), certain forms of use of specific alien organisms are either permitted without further notice, require notification to the authorities, or require permission. A notification is sufficient for some freshwater organisms, marine plants and fish for confined use in aquariums and for large earth bumblebees for pollination in greenhouses. In the remarks made to the regulation, it is argued that such notifications provide the authorities with an overview of the import or deliberate release of the organisms in question, and that it will provide the opportunity to perform general environmental risk assessments and, alternatively, adjust the level of regulation if necessary.

In a similar manner, it may be possible to outline a differentiated approval system for the deliberate release of GMOs. However, it may be advantageous not to make the system too detailed, to avoid its operationalisation becoming unmanageable or difficult to understand, but at the same time sufficiently differentiated to provide different levels of control.

Some relevant questions/considerations that should be discussed:

1. Should the approval process be level-based?
2. How should sustainability, societal benefit and ethics be taken into account?
3. Should the organism be labelled?
4. Should there be different level-based systems for e.g. plants, animals and microorganisms?

A level-based system requires appropriate divisions between the levels, either based on the type of genetic change, the extent of the change(s), the altered trait, the intended use of the organism, the risk to health or the environment, sustainability, societal benefit and ethics and/or other criteria. If the circumstances in a particular case indicate that a more thorough assessment is necessary, it should be possible to transfer an organism to a higher level. There is also a need to clarify the necessary requirements for transferring an organism between levels and to appoint a competent authority for making such decisions.

The following chapters outline and discuss, at a general and principal level, two different proposals for a level-

based system. The members of the Norwegian Biotechnology Advisory Board have different views of the models and the accuracy of the descriptive and normative elements that are included. The views of the individual members are specified in the voting.

In the first model, the levels are distinguished based on the type and extent of a genetic change that has been done in an organism. The purpose is to adjust the risk assessment requirements to better reflect the expected level of risk, thus simplifying and facilitating the approval process. There are requirements for sustainability, societal benefit and ethics at all levels. The model safeguards the principle of a case-by-case assessment by allowing for more extensive impact assessment if needed. Assessments of health and environmental risks, sustainability, societal benefit and ethics are performed in parallel to ensure an efficient approval process while also ensuring that decisions are made on a comprehensive basis. This is in line with the Government's new routines for GMO approval with the intention of facilitating a more streamlined, simplified and predictable process, as stipulated in July 2017.

In the second model, the levels are distinguished based on a moral and ethical assessment, including an assessment of sustainability and societal benefit, which will define the extent of the subsequent risk assessment. The purpose is to actively evaluate the benefits of GMOs, and to simplify and streamline the approval process by avoiding wasting resources on risk assessments of products that are likely to be rejected because they do not adhere to the ethical, societal and sustainability requirements. The model safeguards the principle of a case-by-case assessment, and the requirements for impact assessment can be increased if needed. This is in line with the approval process described in the EU Directive 2015/412 which states that an evaluation of management goals, socio-economic effects and ethical assessments can be performed before a risk assessment and be used as a basis for determining whether a member state wishes to consider the GMO for cultivation or not.

8.1 LEVELS ALTERNATIVE 1: Based on the genetic change

There are several possible ways of dividing regulation of genetically modified organisms into levels. One possibility is a three level hierarchy based on the assumed extent of impact assessment needed.

For example, such a system can be based on certain general principles concerning the genetic change that has been made, as outlined in Figure 2:

This model is based on principles of risk, ethical considerations, pragmatism, and the intent to facilitate wider use of genetic engineering in sustainable, beneficial and ethically defensible ways. Particular weight has been placed on whether the genetic change can also be achieved by other methods that are not regulated by the Gene Technology Act and hence the likelihood that the changes represent risks

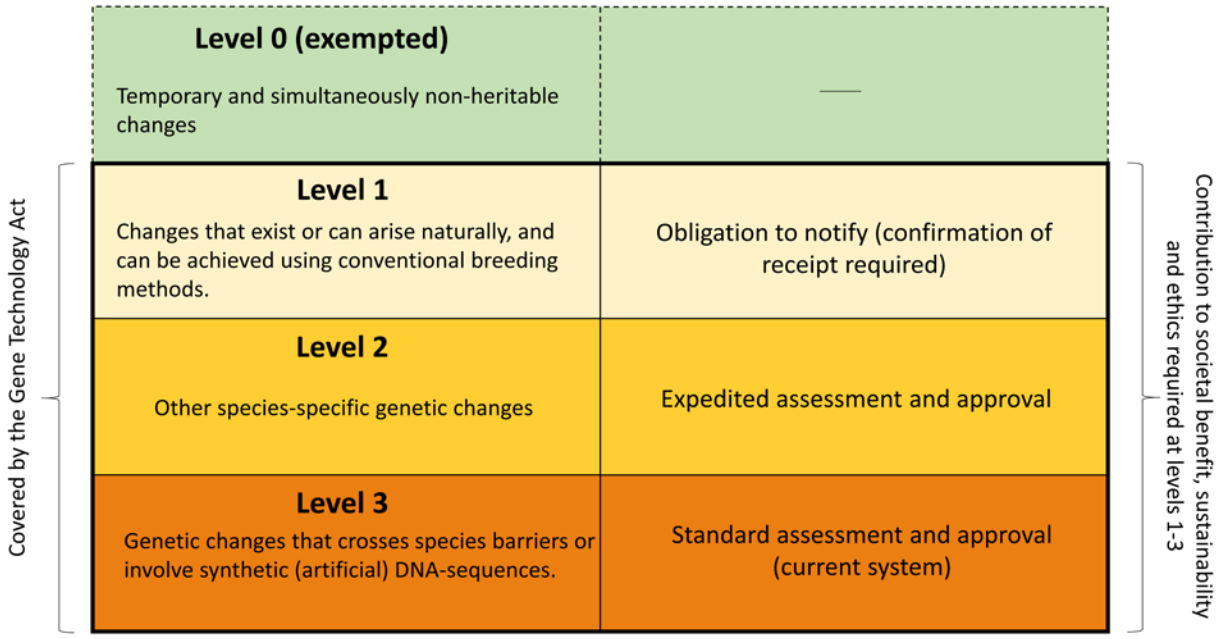

Figure 2: Example of principles for levels based on genetic change.

specific to genetic engineering, whether the changes can occur naturally, and whether they contribute to sustainability, societal benefit and ethics as a requirement for all organisms included in the model. Important criteria for the levels in the model are:

5. Whether there is new DNA present in the end product or not (conferring a novel trait or not).
6. Whether or not genetic material has been introduced from other species (transgenic).
7. Whether the change is made only to some of the organism's cells (somatic) or systemically (including germ cells, i.e. a hereditary change).
8. Whether the change is permanent or temporary.

Level 0 - organisms with temporary, non-hereditary changes.
If certain organisms currently regulated by the Gene Technology Act are to be exempted, the main criteria for this category can be the absence of integrated genetic material in the final product (regardless of whether nucleic acids have been used at an earlier stage during the production process), and that the alterations are temporary and non-hereditary.

For certain types of organisms, genetic material has been used during parts of the production process without causing permanent changes in the final product, and thus could be exempted from the Gene Technology Act based on the proposed criteria. One example is fruit from plants that have been grafted onto a genetically modified rootstock. It is very unlikely that the genetic material has been transferred from the root to the grafted plant and subsequently to the fruit.[112,113] However, the rootstock itself will be defined as a GMO. Another example is where new DNA has been integrated into the product temporarily but subsequently removed. This could for instance include transgenes that are present during certain stages of the plant's development, but are not inherited in the germ cells (spores).[114] Another example is a selection marker (e.g. an antibiotic resistance gene) that has been inserted during the development of a plant, but later been removed.[115]

Based on similar criteria, the Norwegian Biotechnology Advisory Board has previously recommended that RNA- and DNA-vaccinated organisms should not be regulated by the Gene Technology Act (Figure 1/2 I and K). This is in line with the previously mentioned decision by the Norwegian Environment Agency not to classify fish vaccinated with the DNA vaccine Clynav as GMO. Using the same argument, other methods of gene modification could also fulfil these criteria (for example, some forms of RNAi and epigenetic changes that are not hereditary (Figure 1/2 C))

Level 1 - organisms with changes that correspond to those achieved by conventional methods.
Novel gene technologies provide a range of possibilities for creating genetic changes that can also be achieved by other methods that are not regulated particularly, such as crossbreeding or mutagenesis. If the absence of unintentional changes in an organism produced using gene technology can be documented, and the modified variant is also found naturally or could be produced using conventional methods, approval of the organism without extensive impact assessment may be appropriate. This can be justified by the fact that the potential risks associated with two identical end products will largely be independent of the production method. If, in some cases, specific challenges related to risk, sustainability or ethics can be expected, the system allows the authorities to transfer the organism to a higher level.

An example is organisms with point mutations that have occurred naturally or that are made using mutagenesis or gene editing (Figure 1/2 A). For instance, small mutations created using gene editing has produced pigs resistant to Porcine Respiratory and Reproductive Syndrome (PRRS),[118] rapeseed resistant to pesticides belonging to the sulfonylureas group,[119] and sterile salmon.[120] Another example is where a gene variant has been replaced with another by gene editing, yielding the same result as by crossbreeding (Figure 1/2 H). Dairy cows with a gene encoding 'hornlessness' have been obtained using gene editing, as well as with conventional breeding.[121]

However, it may be reasonable to require that documentation on the intended and unintended genetic changes that have taken place are provided to the authorities. This is now reasonably achievable through genome sequencing. In addition, the applicant should be required to provide their own evaluation of potential health and environmental risks. Applicants should also account for relevant aspects related to sustainability, societal benefit and ethics. All documentation should be evaluated by the authorities to ensure that the criteria are fulfilled. The authorities may also use other types of available documentation as references during their evaluation. For level 1 organisms, it may for example be sufficient to provide a notification to the

authorities (with feedback required before the release can take place), but without the need for specific approval.

Level 2 - Other genetic changes within the same species

Genetic engineering techniques can be used to make different types of changes in the genetic material of an organism. Examples include removing large DNA segments (Figure 1/2 B), as demonstrated in rice where a piece of a chromosome containing ten different genes that influence disease resistance has been removed,[122] or to insert elements (genes, parts of genes or regulatory elements) that confer species-specific traits (Figure 1/2 F, G and L) like potato with genes from wild potato conferring resistance to late blight.[123] In such cases, a health and environmental risk assessment may be warranted. However, the requirements could arguably be reduced when DNA is removed or the inserted genetic material (both temporary and permanent, targeted and nontargeted) originates from the same or closely related species (which has a different variant of the same gene), since the integrity of the species is preserved and the traits are already established. A simplified impact assessment can reasonably be expected to reveal whether such organisms can cause significant health and environmental risks. Such genetic modifications may also be less ethically challenging than crossing species barriers. However, an assessment of sustainability, societal benefit and ethics should be conducted. Organisms at level 2 can be subject to simplified requirements for approval and impact assessment.

Level 3 - organisms with permanently added genetic material from different species or synthetic (not naturally occurring) DNA sequences (transgenes)

In cases where new DNA is permanently added to an organism, either from other species or synthetic DNA sequences (which do not naturally exist), there may be reasons to keep the current regulation and requirements for approval and impact assessment. This applies irrespective of whether the insertion of DNA has been targeted or not (Figure 1/2 D, E and J). For example, it is now mandatory to perform field trials and to keep track of how the organism behaves and interacts with the environment it is exposed to over time. It is also necessary to document that the changes remain stable over several generations. Justification for placement on level 3 is based on a possible increased health and the environmental risk associated with the addition of genes that do not occur naturally in the species, and that it can be ethically problematic to cross natural species boundaries. This will include both transgenic organisms, such as plants that contain bacterial genes to make them more tolerant to pesticides, and organisms produced by cell fusion between different species. Gene drives will also be placed on this level. Increased risk may justify increased requirements for sustainability, societal benefit and ethics compared to level 1 and 2. Organisms placed on level 3 can be subject to the current requirements for approval and impact assessment.

An example of how such a model may look in practice is shown in Figure 3. There may also be other criteria relevant for differentiation.

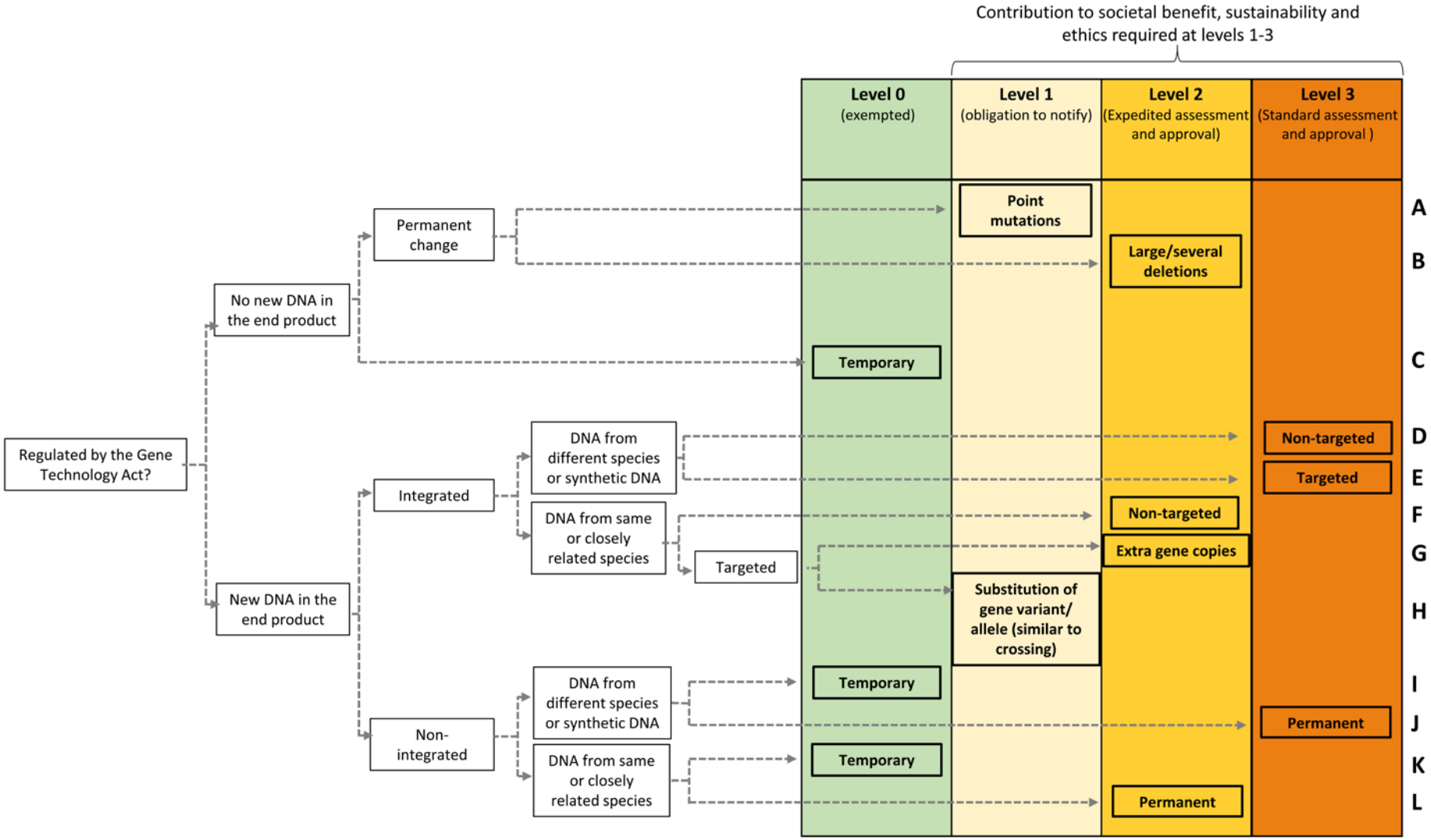

Figure 3: Example of a levelbased model based on genetic change. The letters to the right refer to Figure 1.

8.1.1 Advantages and disadvantages of the model

There are both advantages and disadvantages of such a level-based model. One of the advantages of differentiation, as for the contained use of GMOs or the deliberate release of alien species, is that the extent of the impact assessment and approval requirements will better match the expected risk and other relevant criteria. For example, in most cases, the risk associated with few and targeted changes is assumed to be lower and more predictable than for random and extensive changes that may affect major biological systems with several unknown, unintended changes. In exceptional cases where minor changes can reasonably be suspected or expected to have major consequences, it would be appropriate to transfer the organism to a higher level. The smaller and more targeted the genetic change, the easier it is to evaluate and predict the consequences. When the change itself or the impact assessment becomes less predictable, the need for more extensive documentation and assessment also increases. Therefore, it may be appropriate that only minor changes are subjected to a notification requirement. If a trait already exists in a species, and thus is already known and integrated into the ecosystems, can also be correlated with reduced risk.

A large number of products are expected to be developed and sought approval for in in the near future. This makes it important to facilitate the appropriate handling of applications.1 A level-based system can help prioritise governmental resources where most needed. A similar argument was used when introducing a level-based regulatory system for deliberate release of alien species under the Nature Diversity Act. Differentiated requirements can also provide a higher level of predictability for producers. Differentiation could lower the threshold for using the technology, which can facilitate more beneficial and sustainable products. Sustainability, societal benefit and ethics criteria will apply to all levels of the model (level 1-3), and will be evaluated by the authorities that handle the application. A model where all GMOs are subject to an obligation to notify the authorities as a minimum requirement will ensure that the authorities have an overview of products, and safeguards the principle of a case-by-case assessment. Concurrently, it will be possible to apply measures to limit damage if adverse effects of an organism or product arise, as stipulated in §§ 20 and 21 of the Gene Technology Act, as applicable for alien species regulated by Nature Diversity Act, and as applicable to all food according to §11 of the Food Act. This can maintain a higher level of public trust compared to a situation where certain organisms are exempted from the regulations, which, in the case of gene editing, is Sweden's interpretation of the EU directive at present.

The main reason for developing and adopting a new procedure for assessing GMOs in Norway recently was to facilitate a more simplified and efficient approval process. In short, this implies that a GMO is only considered once by the Norwegian authorities and in parallel with the EU assessment. Consequently, Norway can make a decision immediately following the decision in the EU. It is emphasised that this will significantly reduce the use of resources and the processing time. A levelbased impact assessment could be performed within the proposed deadlines, and could potentially simplify and streamline the process even further.

Compared to the current situation, a level-based system will reduce the requirements for products regulated at the lower levels. The EU and Norwegian regulations are based on the intent to regulate organisms developed with new technologies that we do not have experience with, and state that the precautionary principle should be employed. It should therefore be considered whether carrying out a simplified risk assessment of plants and animals made using methods that we do not have long experience with, conforms with the regulatory framework and the precautionary principle. Additionally, whether a notification to the authorities or simplified impact assessment is sufficient to maintain public trust is an additional consideration.

Thus, another challenge with a level-based system is that the number of potential factors relevant for assessing whether to transfer an organism to a different level could be so numerous that it becomes more like a standard case-by-case assessment. This could render the process less predictable. For a level-based model to be appropriate, it will be necessary to clearly define the criteria for placing GMOs at different levels, and establish clear requirements for the impact and risk assessments. In particular, determining the cut-off point between level 2 and 3 may be challenging. From a risk perspective, it can be difficult to make distinctions based on the type of genetic change. Several considerations make it challenging to establish predefined levels of requirements; health and environmental risk depends on both intended and unintended changes, the genetic background of the organism, whether the organism is a plant, animal or microorganism, and the environment the organism is released into. These are factors that can form the basis for an alternative level-based system. In addition, the ethical challenges do not always correspond to the suggested levels. Experiences with different types of genetic

changes, technologies and products can contribute to the gradual adjustment of level-based practices over time.

The question is whether or not the advantages of adopting a level-based system outweighs the disadvantages, and whether the considerations for health, environment, societal benefit, sustainability and ethics is adequately safeguarded. In this respect, it will be important to make a thorough assessment where the advantages and disadvantages of a level-based system are carefully weighted.

8.1.2 Approval or notification

If a notification to the authorities and self-declaration (level 1) system is established, some producers might argue in favour of placement at a lower level than what should apply to the specific product. The aim may be to avoid having to perform experiments that demonstrate how the GMO behaves in the environment in which it is to be released, or experiments that show adverse effects of consumption of the GMO on human or animal health. By documenting that the entire DNA sequence has been mapped, the producer can argue that the trait is known and tested, or that the gene variant is known in similar organisms (such as close genetic relatives) and as a result has already been tested and has a history of safe use. The producer must also account for aspects relating to sustainability, societal benefit and ethics (see Chapter 11), which will be decisive for whether the requirements for notification only are fulfilled. The regulations must clearly state the type of documentation to be included and which organisms that are subject to notification only. Subsequently, it will be the competent authorities, according to defined areas of responsibility that determine whether the notification is complete (the Norwegian Food Safety Authority or the Norwegian Environment Agency, after advice from the VKM and the Norwegian Biotechnology Advisory Board). This will be in line with the new procedures for processing applications under the Gene Technology Act, as stipulated by the Ministry of Climate and Environment in the summer of 2017.[125] The notification will become public in accordance to the Freedom of Information Act/Environmental Information Act, but a public hearing will probably be unfeasible.

There are different types of notifications: (i) notification without any requirements for feedback before the release can be carried out; (ii) notification with required feedback from the authorities before the release can be carried out (where the receipt is a confirmation that the requirements for the notification have been met), or (iii) notification with the possibility of ad hoc approval requirements if the authorities consider it necessary.

For contained use of genetically modified animals, the notifying party can initiate the intended activities immediately after the notification has been submitted, on the condition that an approval has been issued according to §13 of the Animal Welfare Act on the use of animals for experimental purposes. However, the authorities may request further information if considered necessary.[126]

Provisions for notification of contained use of microorganisms in class 1 and 2 are specified in the regulation on genetically modified microorganisms:[127]

Once the competent authority has received a notification or application, it shall evaluate

1) whether the notifications/applications are in accordance with the regulatory requirements
2) whether the information provided is accurate and complete,
3) whether the preliminary assessment and classification of contained use are correct,
4) whether containment measures, other protective measures and waste and emergency measures are sufficient.

If necessary, the competent authority may ask the applicant for additional information or to change the circumstances of the planned contained use or the classification of the contained use. In that case, the competent authority may require that the contained use does not commence if planned, or is suspended or terminated if in progress, until the competent authority has given its consent on the basis of the additional information received or changes in the conditions of the contained use.

Once the competent authority has received the required information needed to approve the information and assessments as complete and correct, the competent authority shall inform the notifying party or applicant that a complete notification or application has been received.

If the competent authority later receives information that could significantly impact the risks associated with the contained use, the competent authority may require the user to change the terms of the contained use, or temporarily suspend or terminate it.

The handling of notifications for the deliberate release of

alien species under the Nature Diversity Act is based on the same principles as for contained use of genetically modified organisms.

Certain activities regulated by the Nature Diversity Act requires explicit feedback from the competent authorities before the activity can be implemented, and the authorities are allowed to change the terms if necessary. Examples are agricultural activities:

> § 55. (Obligation to notify agricultural activities)
> An agricultural activity that affects areas of selected habitat types and that does not require approval must be notified to the municipal authorities before the activity is implemented. A response must have been received from the municipal authorities before the activity is carried out. The municipal authorities shall consider the activity under the provisions of § 53, second and third paragraphs. If the municipal authorities find that the activity may result in reduction of the range of the habitat type or deterioration of its ecological status, the authorities may refuse to permit the activity or impose additional requirements for how the activity shall be implemented in accordance with the regulations made under § 11, first paragraph, of provisions for the Act of 12 May 1995 No. 23 relating to land (the Land Act).

Similarly, one of the reasons for proposing a notification system for the deliberate release of genetically modified organisms, as opposed to exempting them from the Gene Technology Act, is to ensure that the authorities maintain control and overview and the option to change the classification level if necessary. One requirement could be that feedback from the authorities must be received before the deliberate release can take place, as with certain activities regulated by the Nature Diversity Act. If all organisms placed on a specific level are automatically allowed to be released unless concluded otherwise, and that no individual feedback is required as a result, it may be advisable to introduce a deadline (e.g. 30 days) before the deliberate release can be initiated. This can ensure that the authorities have sufficient time to evaluate whether the GMO is appropriately classified and potentially to notify the applicant of their decision to transfer the organism to a higher level. For example, transfer of an organism to a higher level will be relevant if the authorities discover that the organism does not meet the requirements for notification after all, or other factors which suggest that a more thorough assessment is needed (see example in BOX 4).

EXAMPLES OF TRANSFER OF GENETICALLY MODIFIED ORGANISMS TO A HIGHER LEVEL:

One possible reason for increasing the requirements for approval may be the presence a potential health risk. For example, gene editing can be used to make small genetic changes in potatoes, such as point mutations, which can affect how much acrylamide is formed during heat treatment. Acrylamide can be carcinogenic in large doses. If a mutation which inactivates the gene is made, one would expect the level of acrylamide to decrease, which could result in a health benefit. Mutations that are expected to increase gene activity could, on the other hand, pose a health risk. According to the proposed model, both potato variants would be placed at Level 1 based on the nature of the genetic change. It would, however, be appropriate to perform a more thorough assessment and have requirements for approval for the latter, therefore warranting transfer to a higher level.
Other examples of factors that may trigger the transfer to a higher level can be a high risk of genetic introgression in the wild - either because a genetic change is expected to affect the ability to spread or that the plant is of a variety that spreads very easily. Another example may be a genetic change that increases the tolerance to pesticides, in which case it may be desirable to perform a more thorough assessment and impose additional requirements for approval.

Particular ethical considerations must be taken into account when using higher animals for research and/or production. The Animal Welfare Act §25 prohibits breeding, including genetic engineering methods, that (i) changes the genetic material in a way that adversely affects or impair the physical or mental functions of animals, or that passes on genetic material of this kind, (ii) reduces the ability of animals to perform natural behaviour; or (iii) provokes public ethical reactions. Furthermore, §13 of the Animal Welfare Act stipulates requirements for all research, including applied research, that involves higher animals. For example, animals can only be used for applied research to (i) avoid, prevent, diagnose or treat disease, poor health or other abnormal conditions, or their effects, in humans, animals or plants, (ii) assess, detect, adjust or change physiological conditions in humans, animals or plants or (iii) improve the welfare of animals, hereunder the conditions of animal production. Such research will include animals made with genetic engineering. A notification system has already been introduced for the contained use of genetically modified animals in research, on the condition that an approval under the Animal Welfare Act has been issued.

A requirement that approval under the Animal Welfare Act should accompany the notification under the Gene Technology Act for the release of genetically modified animals at Level 1 may be appropriate.

8.2 LEVELS ALTERNATIVE 2: Based on a preliminary assessment of ethics

This model places weight on the fact that according to current legal definitions, genome editing techniques are biotechnologies and therefore the products generated through their use should be regulated under the Gene Technology Act. It also builds on recent political statements concerning GMOs, such as the recommendation by the Parliament Committee on Business and Industry that genome editing should be regulated under the Gene Technology Act (in a statement about the white paper on agriculture "Jordbruksmeldingen" Innst. 251S 2016-2017) and decisions in which it has become clear that there is both a willingness and legal ability to analyse and refuse a GMO application on the basis of its ethical justifiability (ban on maize 1507). Furthermore, it follows the intention set by EU Directive 2015/412, in which the assessment of GMOs against policy objectives, socio-economic impacts and ethical issues are performed before a risk assessment is carried out, and can be used as the basis to determine whether a member state wishes to open for cultivation and therefore proceed with further safety assessment or not. The alternative model presented here has also been devised to address the regular calls to more actively consider benefits in the decisionmaking process. Since ethics is concerned not only with articulating and avoiding what is bad, but also understanding and promoting what is good, using ethics as a basis to determine different demands and levels of scrutiny for GMOs opens for a more active consideration of the benefits during the regulatory process. In this model this includes consideration of the benefit to society and contribution to sustainable development, but also other aspects relevant for ethical justifiability such as those relating to the type of genetic change, the process used to achieve it, the associated uncertainties, and the available alternatives.

The alternative framework presented in this model (see Figure 3) proposes a two-stage/four-step process. The two stages are i) public morals review and ii) risk assessment. The first stage of public morals assessment (i) involves 3 steps. These are: 1. Review of foundational ethical requirements in the form of policy objectives and politically agreed norms, 2. Evaluation of ethical justifiability, including not only the type of genetic change but also other relevant factors such as benefit to society and sustainable development, and 3. Determination of an ethical justifiability ranking (i.e. as strong, moderate or weak) to determine the level of risk assessment. In stage ii), which represents step 4 in the model, risk assessment is conducted according to the decided level (i.e. expedited, standard or declined). A summary overview of the connection between the evaluation of ethical justifiability and the levels of risk assessment is given in figure 4. Each of the steps in the process of this model is outlined in more detail below and illustrated in figure 5.

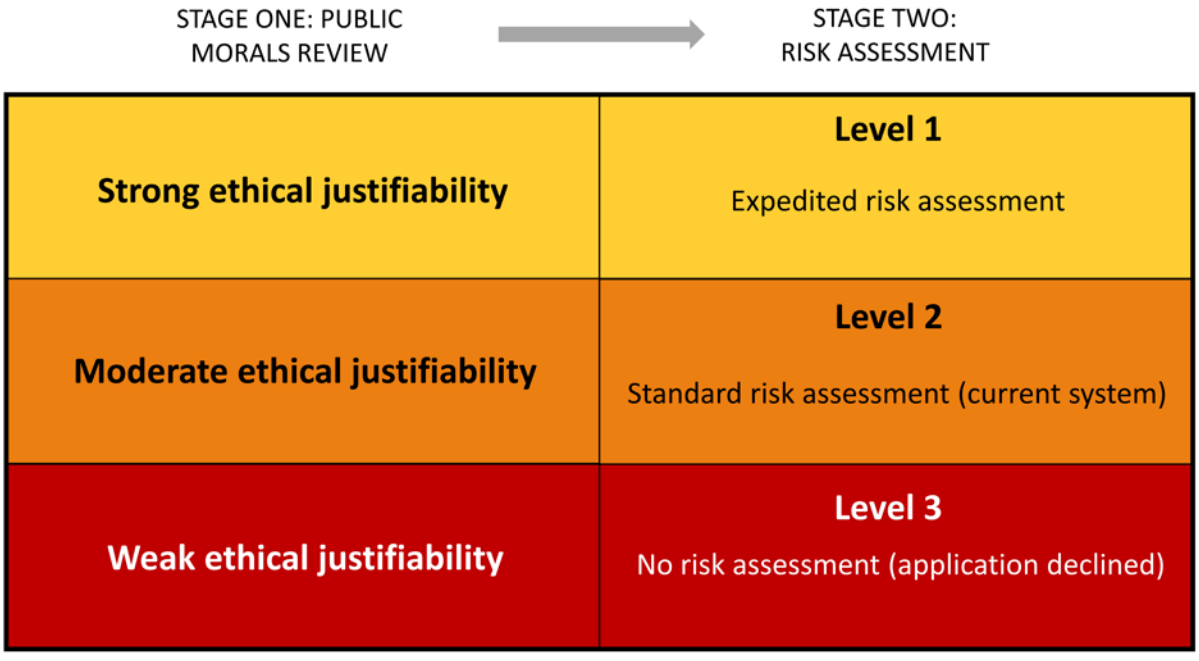

Figure 4: Example of how to divide into different levels on the basis of ethical evaluation

8.2.1 Why refer to the first stage as a review of 'public morals'?

As already stated, the process of performing evaluations based on policy objectives, socio-economic considerations and ethical considerations prior to risk assessment (as presented in this model) mirrors what became permissible under EU Directive 2015/412. However, using the term 'public morals' to describe what is being reviewed and assessed at stage one is a strategic choice to help make clear the position of the framework and what it is proposing according to the rules and language used by the World Trade Organisation (WTO). Critically, the WTO has stated that 'public morals', in addition to health and environmental concerns, are a legitimate basis upon which to establish what would otherwise be seen as 'barriers to trade'. Therefore, positioning stage one and the assessment of the 'other' criteria of the Gene Technology Act under an overarching umbrella of public morals review marks this as a socio-cultural layer of assessment that is broader than risk and safety concerns, while at the same time strengthening the legitimacy of this form of assessment in the eyes of organisations such as the WTO.

8.2.2 The Two Stage/Four Stage Assessment Process

Stage 1: Public Morals Review

Step One – Review of adherence to policy objectives and agreed norms

In the first step of stage one, and before it is permitted to move further forward, the product application would have to prove that it is aligned with agricultural and environmental policy objectives and not in violation of any foundational ethical values and norms of Norwegian culture (i.e. that it does not offend Norwegian public morals). The content of the requirements found in this step would need to be politically decided and established, ideally through extensive processes of expert consultation combined with public deliberation and engagement. There are, however, already examples of the type of policy objectives and politically agreed norms that may be included in such a step. This includes the current political position that is no acceptance of: the use of antibiotic resistance genes, engineered resistance to chemicals not approved for use within Norway and a lack of systems for detection, traceability and monitoring. According to this model, GMOs with such characteristics do not meet Norwegian policy objectives and/or ethically agreed norms. Therefore, it is not necessary to conduct any further potentially expensive and time-consuming assessments.

Step Two—Evaluation of ethical justifiability

If an application is found to not be in violation of any agricultural and environmental policy objectives or agreed ethical norms, then it would pass to the second step of the public morals review. At this second step, the model advocates the performance of an integrated ethical evaluation on aspects relating to both the product and the process. At this step, it would also be possible for more information to be requested if it is required to complete any component of the evaluation. For the evaluation of ethical justifiability of the product, the existing guidelines for assessing contribution to sustainable development and societal benefit could be used. In addition, it is proposed that for determining ethical justifiability, the product should also be assessed in relation to the other available alternatives (e.g. as currently emphasised in the recommendation of the French High Council for Biotechnologies[129]).

In evaluating the ethical justifiability of the process, different types of techniques of genetic modification can be evaluated. Note that this can include a range of factors of importance and need not be limited to an assessment of risks and/or the degrees of change involved. Other issues of relevance to consider may for example include the impact of the process on genomic integrity, the degree of crossing species or kingdom boundaries that is involved, the underlying attitudes towards human/nature relations being performed, etc. In the evaluation of process, it is proposed that specific attention also be given to the types and degrees of uncertainty associated with the technique and how these may affect ethical justifiability (i.e. connecting to existing notions of precaution and history of safe use). Including uncertainty as part of an ethical evaluation is important since confidence in the available knowledge can significantly impact the acceptability of a new technology and the willingness to accept different levels of risk.

Step Three—Ranking to determine level of risk assessment

The third step of the public morals review would involve using the outcome of the evaluation performed under step two to arrive at an overall ranking of the application as having either a strong, moderate or weak level of ethical justifiability. For example, if during the evaluation at step two, an application receives a yellow rating against at least three of the criteria (and has no red ratings against any cri-

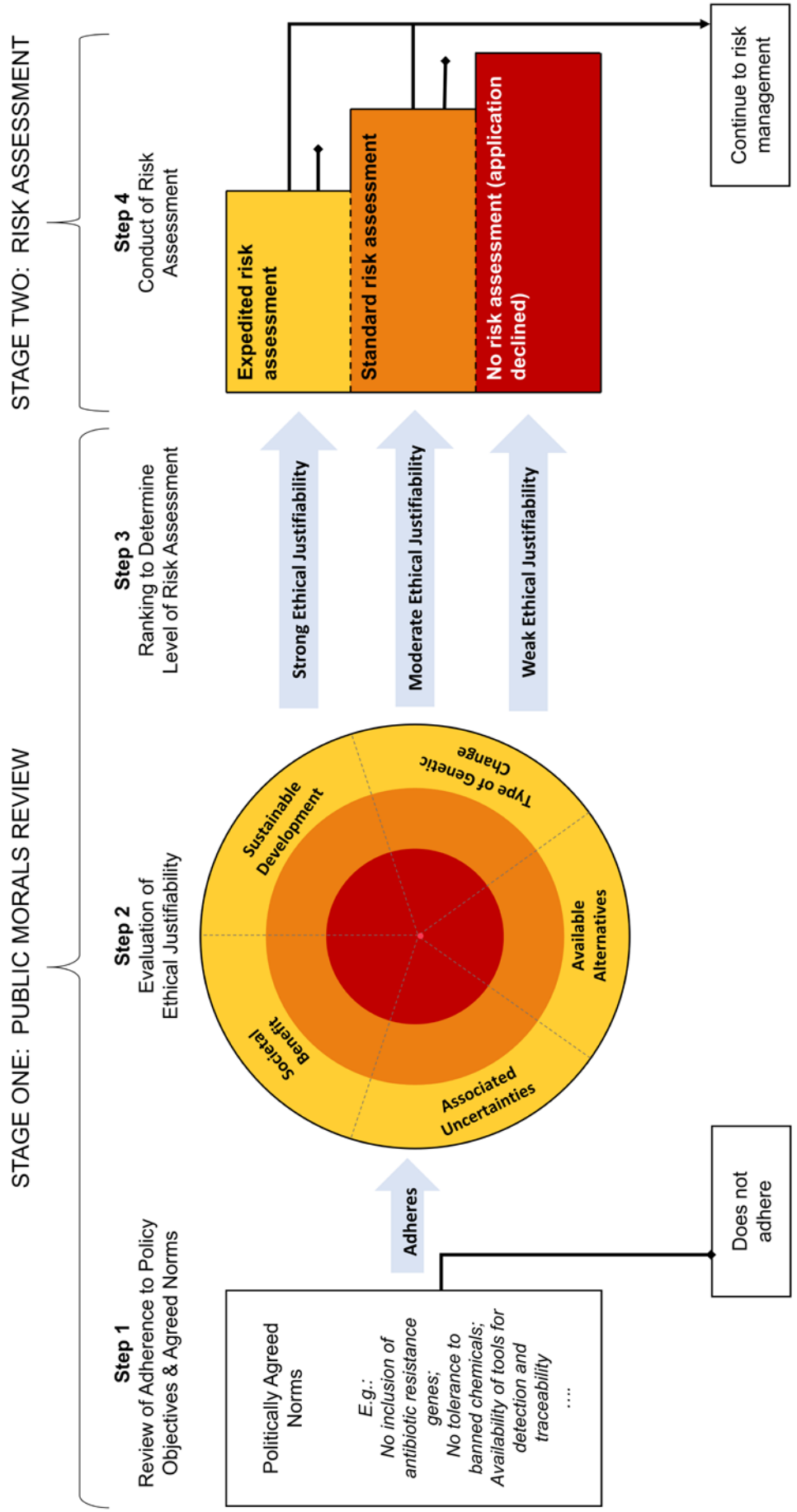

Figure 5: Example of a level-based model based on ethical evaluation.

teria) it may be deemed to have strong ethical justifiability. In contrast, if an application receives three or more red ratings against different criteria during the evaluation in step 2 (and has no yellow ratings) then it may be deemed to have a low ethical justifiability. Based on the overall evaluation and ranking of an application's ethical justifiability, the recommended level for risk assessment may be determined. The intention behind this proposed process is to recognise and support the important role that regulation plays in guiding and promoting development in positive directions, as well as to account for the fact that the level of ethical justifiability can impact the level of risk people are willing to tolerate. This model also indicates that it is not desirable to perform a resource intensive process of risk assessment on products that only have weak ethical justifiability and may therefore ultimately be rejected. Furthermore, for products deemed to be highly ethically justifiable (e.g. in terms of making a strong contribution to sustainable development and/or societal benefit and not involving the use of problematic or ethically unacceptable techniques) it may not be necessary or desirable to go through such extensive and time consuming processes of risk assessment as those performed for less clearly beneficial products.

Stage Two: Risk assessment

In **step four** of the process, the application would move to risk assessment. Here a distinction is made between three different levels: expedited, standard and declined. The standard review effectively comprises of risk assessment as it is performed today, while the expedited level would represent a more accelerated form of review with reduced or different types of data demands. The exact differences between expedited and standard forms of risk assessment requires further (and wider) discussion and articulation. Such differences may be articulated through the development of new dedicated guidance documents. Within this stage of the model, there is always the possibility for applications to pass to a different level if this is deemed appropriate by those performing the assessment, and for more information to be requested if necessary. Following the statement by the Parliament Committee on Business and Industry, the capacity for traceability and labelling would be required regardless of the level of risk assessment.

8.2.3 Advantages of this model

This proposal has the potential advantages of:

a. *Simplicity:* not requiring any changes or exemptions to the existing Gene Technology Act.
b. *Flexibility:* ensuring that all gene technologies are subject to regulation while allowing for varying degrees and intensity of scrutiny.
c. *Conscientiousness:* safeguarding that all organisms developed using gene technologies will be sufficiently assessed according to their contribution to sustainable development, societal benefit and ethical justifiability.
d. *Adaptability:* accounting for the fact that levels of risk acceptability can legitimately vary according to a product's ethical justifiability and contribution to broader society and the environment.
e. *Appropriateness:* emphasising the importance of the specific criteria of the Gene Technology Act that the Norwegian Biotechnology Advisory Board has a mandate to consider (as well as the aspects that EU Directive 2015/412 allows to inform decision making before risk assessment is carried out) and specifically highlighting the role these aspects can play in creating a more nuanced approach to regulation.
f. *Balance:* addressing the call from several actors to more actively consider benefits in regulatory decision making on GMOs.

Furthermore, the model also serves as a potential hybrid form combining the other alternatives discussed in this document. This is because it includes consideration of the type of genetic change but folds it into a more complete evaluation of a broader range of relevant criteria to form the basis of a regulatory system divided into different levels and it also remains open to the possibility of developing new guidance documents for how risk assessment at the different levels should be carried out.

8.2.4 Challenges with this model

Evaluations of societal benefit, ethics and sustainability can affect the level of risk people are willing to accept but they do not necessarily align with the levels of risk a product may pose. For example, what may be deemed to be a very useful and ethically justifiable product for society may

still pose significant environmental problems and risks. Ensuring human health and environmental safety is a foundational aspect of the regulation of GMOs in both Norway and other countries. Therefore, even though an assessment of risk to human health and safety will always be performed for any products approved under this model, one should still evaluate to what extent risk assessment and management are sufficiently safeguarded.

Evaluations of criteria such as contribution to sustainable development, societal benefit and ethical justifiability are often based on assessments that include aspects of health and environmental risk. It will therefore in some cases be challenging to conclude on assessments of the former without first having information and documentation available on the latter.

The objective of the Gene Technology Act is to ensure that the development and use of GMOs takes place in a societally and ethically justifiable manner, in line with the principle of sustainable development and without negative impacts on human health or the environment. To achieve this, it is typical that a process of risk assessment is performed first and given the most weight in decisionmaking. While EU Directive 2015/412 opens for other considerations to be evaluated and inform decision making before risk assessment is conducted, putting an ethical evaluation before the process of risk assessment would indeed challenge existing understandings and typical routines of practice in GMO assessment, and may in that perspective be perceived as unreasonable.

8.2.5 What is required to make this possible?

At the moment, there is no clear single framework for how ethical justifiability is to be understood and evaluated under the Gene Technology Act. There are indications of elements of importance in both Bioteknologinemnda (2009) and the regulations on impact assessment under the Gene Technology Act (2005). However, both of these documents leave room for interpretation and further more specific elaboration. It is, for example, important to recognise that there are various ethical frameworks available to evaluate and determine what is good/bad, right/wrong (see Chapter 4.2). Although the Norwegian Biotechnology Advisory Board has been involved in the development of guidelines for assessing societal benefit and contribution to sustainable development of a GMO, there has not yet been an equally comprehensive process to develop guidelines for assessing ethical justifiability. Similar to how the guidance on sustainable development and societal benefit assessment was developed, the Environmental Agency and/or the Biotechnology Advisory Board could appoint an expert committee to create specific guidelines for assessing the ethical justifiability of GMOs. This committee could also have a mandate to engage members of the public and/or particular interest groups in the process. This work would need to include a detailed consideration of how different ethical frameworks (e.g. consequentialist, deontological, pragmatist, virtue, or care ethics) would assess the acceptability of a range of GM products and processes, as well as what type of framework (singularly or in a symbiotic mix) would sufficiently capture the ethical concerns of Norwegian society, politics and culture.

8.3 Requirements for documentation using a level-based system

If any organisms are to be exempted from the GMO regulations or be subject to simplified requirements for approval/impact assessment, the documentation corresponding to the relevant classification level should always be mandatory. The requirements for documentation must be sufficiently comprehensive to ensure that the processing of the application occurs at the appropriate classification level. Genome sequencing or other relevant methods should be required to detect which changes, both intentional and unintentional, have occurred. A description of the methods used and the trait altered should also be provided. However, a thorough review of which analyses that should be required is needed, since it may be difficult to distinguish between natural variation and any unintended changes that may have arisen due to the production process. For example, gene expression may vary (due to e.g. environmental effects) regardless of whether or not any genetic changes have been made.

9. Labelling requirements

Photo: iStock

One of the central topics of the current debate concerns the consumer's right to choose. In order for a consumer to be able to make knowledge-based decisions, he or she must have access to relevant information about the product.

When GMO regulations were developed in the 1990s, the genetic engineering was very limited, and genetic modification mostly consisted of introducing larger pieces of new DNA to an organism. With all the nuances that come with new gene technologies, such as gene editing and RNA/DNA vaccines, some argue that it is timely to ask what should be labelled.

Studies show that many consumers are sceptical towards genetically modified food. However, they are more positive if the products contribute to more environmentally friendly agriculture,[131] and do not involve the crossing of species boundaries that cannot occur naturally.[132] Today, all production and use of genetically modified products is assessed on the basis of a possible health and environmental risk. If labelling requirements are relaxed in the future, it is crucial that consumers remain confident that products are safe for consumption and that they do not pose a health risk. Consumers also emphasise other aspects, such as environmental considerations, ethics and sustainable development. A general labelling requirement, like we have today, will only inform the consumer that genetic engineering has been used during the production of the product, but does not provide information on what has been changed, health and environmental risk, sustainability, societal benefit and ethical issues, which will vary on a case-by-case basis. Also, general labelling does not indicate which type of gene technology/method that has been used. For example, attitudes towards a plant that is resistant to pesticides may differ from those towards a plant that has increased nutritional content. It is also unclear whether consumers want, for instance, information on the removal of parts of a gene or that DNA which is no longer present in the final product was introduced temporarily during production. There may also be other considerations that consumers regard as important. The question then remains whether labelling is useful or not, and if it is possible to adapt the scheme in a way that reflects such nuances and ensure that the consumer receives relevant information. Whether labelling is mistakenly perceived as a warning about possible health or environmental risks is also an essential question.

Labelling may affect whether gene technology is used to develop new products. Labelling of genetically modified plants and animals as GMOs would make businesses less likely to invest in and use the technology due to consumer skepticism.[104] This issue has been highlighted in a report by The Nuffield Council, an independent body that examines and reports on bioethical issues in the United Kingdom, and by the European Plant Science Organization (EPSO), [134] among others.

Another key question is whether it is possible to comply with requirements for analytical traceability/detection for organisms made using new gene technologies. Current methods for detection of GMOs are based on detecting the presence of introduced/altered DNA. If one cannot distinguish, for example, between changes made with gene editing and those made with methods that are not covered by the regulation, it would be impossible to unambiguously determine the presence of a GMO, and labelling requirements would become difficult to enforce.

This challenge also concerns some products that originate from GMOs, such as oil from rapeseed and soy, but that do not contain DNA. In Norway, the producer must provide documentation to the Norwegian Food Safety Authority that the products are not made from GMOs and that the business has good quality assurance systems for internal control.[135] Corresponding requirements apply in the EU. Particular attention must be paid by producers that import products from countries where GMOs are used. Here, the Norwegian Food Safety Authority recommends using so-called identity-assured traceability (IP traceability). This means that producers must be able to prove that the raw material is kept separate from genetically modified raw materials throughout the value chain, including cultivation, storage, processing and production.

There are no internationally agreed rules for the content of IP traceability systems, but producers set the requirements they deem necessary and assess the documentation, and the Food Safety Authority evaluates whether the system is acceptable.

It is possible to ensure analytical traceability of a product by inserting a genetic ”watermark” into the organism. This was proposed already back in the 1990s. At that point, most stakeholders agreed that this was not a good solution, since it would involve more extensive genetic modification of each organism, which would be contrary to the objectives of minimising the extent of and increasing the targeting of the genetic alteration. The introduction of such a requirement will make it easier to detect a GMO, but will in practice increase uncertainty regarding risk. It will also mean that, in practice, some methods of gene editing cannot feasibly be used. Firstly, it is more technically demanding to insert DNA than to make point mutations, which will lead to a significantly reduced success rate, especially in some types of organisms. Secondly, this involves a risk of destroying the gene by inserting DNA into it, which is necessary to prevent the traceable ”watermark” from segregating from the genetic alteration by further crossing/breeding. Also, there is a risk of additional unintended changes when more modifications are made during the process.

To what extent enforcing traceability and labelling requirements for all organisms regulated by the Gene Technology Act is regarded as necessary should be determined by cost/benefit analyses. The alternatives to equal requirements for all GMOs are exemptions or a level-based system. Traceability requirements can be differentiated according to what is technologically possible or feasible. For example, the requirement can be limited to only apply to products where genetic changes are detectable and possible to distinguish from other genetic variants. Alternatively, document-based traceability can be required regardless of detectability, as for all current food products.

Requirements for traceability, but not analytical detection, are stipulated in §11 of the Food Act and is in line with the EU’s food law (Regulation 178/2002), by which Norway is also bound. The requirement ensures that it is possible to trace a product both in the market and to its origin, should serious health issues arise. The requirements apply to all products, including those not covered by the Gene Technology Act. For example, if pathogenic bacteria are detected in a food product, measures can be implemented to remove the product from the market based on the documented production and distribution processes.

However, labelling and traceability is not just a technical issue, but also a political one. In the spring of 2017, the Norwegian Parliament’s Committee on Business and Industry wrote in their statement that genetically modified organisms should be regulated by the Gene Technology Act and that they should not be approved until guarantees of traceability and monitoring can be made.[136] The statement provided no details about the type of traceability that should be required.

10. Sustainability, societal benefit and ethics: How much is sufficient?

All of the members of the Norwegian Biotechnology Advisory Board argue that assessments of sustainability, societal benefit and ethics should remain a central part of the Norwegian Gene Technology Act. However, the Board believes that the weighting of these criteria should reflect the risk assessment for each specific GMO to a greater extent than today.

When assessing a GMO under the Gene Technology Act, an evaluation of its contribution to sustainable development and that it is societally and ethically defensible is required.

It has been challenging to determine how the criteria for sustainability, societal benefit and ethics should be interpreted in practice when assessing a GMO. The Norwegian Biotechnology Advisory Board has on several occasions contributed to operationalising these criteria. There is currently ongoing efforts among the signatories of the Cartagena Protocol and within the EU to clarify how to understand and assess socio-economic considerations.

In 2010-2012, at the request of the Norwegian Environment Agency, the Norwegian Biotechnology Advisory Board worked to operationalise the criterion of sustainability. The Board has now, together with the Norwegian Environment Agency, launched a new project to operationalise the assessments of societal benefit under the Gene Technology Act.

If approved under the regulation of the Gene Technology Act, a GMO must not represent an unacceptable health or environmental risk, the GMO must be ethically defensible, and "particular emphasis should be placed on whether the deliberate release provides societal benefit and promotes sustainable development". In practice, these regulatory requirements make it more difficult to get approval of a GMO compared to a similar, non-GMO.

With a precautionary approach, stricter regulation of GMOs compared to non-GMOs makes sense. However, one might question whether it is necessary to require GMO products to having to contribute to increased sustainability and societal benefit, since other products are not subject to such requirements for approval. One can further discuss whether it should be sufficient to demonstrate that the product does not pose health and environmental risks, and does not contribute negatively to sustainability, societal benefit and ethics.

The Norwegian authorities' experience with GMO applications thus far suggests that they contain far too little documentation to facilitate an assessment of societal benefit and contribution to sustainable development. This is despite the fact that the criterion of societal benefit represents an opportunity for the producer to argue for the positive aspects of the product. Norway has so far received applications through the EU, and producers perceive the Norwegian market as too small to spend resources on answering control questions that are only required in Norway, some of which cannot realistically be answered.

11. Preliminary views of the Norwegian Biotechnology Advisory Board

Photo: iStock

In this statement, the Biotechnology Advisory Board discusses what should be covered by the Gene Technology Act regulations for deliberate release of GMOs. The Board has not discussed questions about contained use of GMOs (chapter 2 of the Act) and cloning (chapter 3a of the Act).

The Board considers how the release of GMOs should be regulated on an overall and principal level, but without going into detail, since the proposals will have to be thoroughly reviewed and specified by other authorities. Nor has the Board considered any changes that can be implemented by adjusting current Norwegian law or its legal interpretation, as opposed to what may potentially require changes to international legislation and agreements, such as the EEA Agreement, etc.

Regardless of what is regulated by the Gene Technology Act and how this is regulated, the Norwegian Biotechnology Advisory Board unanimously argues that the principle of assessment of the criteria for sustainability, societal benefit and ethics should remain. However, the weighting of these criteria will be discussed. The Board also emphasises that we have a number of other legislative frameworks that will safeguard important considerations. The Food Act prohibits, for example, sale of food and use of ingredients in production that are harmful to humans and animals. The Animal Welfare Act states that breeding, including genetic engineering, is not permitted to promote properties that are detrimental to the animal or ethically irresponsible. In addition, the Nature Diversity Act shall ensure sustainable management of the natural environment through the principles for sustainable use in chapter II, which will be important when decisions are to be made under the Gene Technology Act.

The Biotechnology Advisory Board believes it is very important to facilitate research on gene editing and other new gene technologies, both to acquire knowledge about technical and safety aspects of the technologies, as well as to build competence in Norwegian environments.

11.1 Voting on a level-based approval system

A majority of 18 members of the Biotechnology Advisory Board (Inge Lorange Backer, Cathrine Bjorvatn, Ole Kristian Fauchald, Petter Frost, Kristin Halvorsen, Gunnar Heiene, Arne Holst-Jensen, Torolf Holst-Larsen, Bushra Ishaq, Raino Malnes, Bjørn Myskja, Benedicte Pope, Sonja Sjøli, Birgit Skarstein, May Thorseth, Nils Vagstad, Dag Inge Våge and Fern Wickson) argue that a level-based system for approval/impact assessment for various organisms covered by the Gene Technology Act should be considered.

Of these, 17 members (Inge Lorange Backer, Cathrine Bjorvatn, Ole Kristian Fauchald, Petter Frost, Kristin Halvorsen, Gunnar Heiene, Torolf Holst-Larsen, Bushra Ishaq, Arne HolstJensen, Raino Malnes, Bjørn Myskja, Benedicte Paus, Sonja Sjøli, Birgit Skarstein, May Thorseth, Nils Vagstad and Dag Inge Våge) believe that levels should be based on relevant criteria such as the genetic change that has been made. These members argue that such a system might be appropriate to reflect the different risk levels that can be reasonably be expected for various types of genetic changes, and at the same time allowing for an even more suitable and nuanced assessment of sustainability, societal benefits and ethics. Levels based on genetic change as described earlier in the document is one example of a possible model. A level-based system where the lowest level requires only a notification to the authorities (with feedback before release of the GMO can take place), will ensure that the authorities get sufficient overview of the products, and more extensive impact assessment may be imposed if the type of modification or other circumstances indicate that it is needed. These members also argue that a level-based system with simplified approval requirements will make it easier to utilise the potential of genetic engineering that also meets expectations for sustainability and societal benefit without negative consequences for health and environment. A level-based system will contribute to a less resource-intensive approval process than today, and stimulate the development of more beneficial and sustainable products.

One member (Fern Wickson) argues that all organisms covered by the Gene Technology Act should be subject to approval and impact assessment by the authorities. At the same time, this member acknowledges that it may be relevant to establish a level-based system for approval. This member argues that the type or degree of genetic change in a gene does not necessarily indicate effects at higher levels (a minor genetic change can have major consequences) and therefore does not match the risk level. However, the member acknowledges that societal benefits, contributions to sustainable development and ethical aspects of a GMO can have a significant impact on whether they are considered acceptable and what level of risk one may be willing to tolerate. It is therefore proposed to consider the possibility of a level-based system where an ethical assessment of organisms covered by the Gene Technology Act and their contribution to society and the environment provide the basis for different recommendations on the extent of the risk assessment and how quickly it can be processed. This member believes that such a model will open up for the assessment of benefit and ethical justifiability of a GMO based on different criteria, including but not limited to type of change and technique used. Such a model will ensure that all GMOs are regulated according to the Act, but at the same time provides the opportunity to make the approval process less resource-intensive than it is today, because those applications that are likely to be rejected for ethical reasons will be excluded. In addition, applications that use less controversial techniques and are considered ethically justifiable and significantly beneficial for society and the environment, will be processed faster.

A minority of 2 Board members (Bjørn Hofmann and Bente Sandvig) think that, in principle, the current requirements for approval and impact assessment should apply to all organisms covered by the Gene Technology Act. These members argue that, though it is reasonable to assume that a small and targeted change - where no foreign DNA is introduced - will involve lower risk to health and the environment than more extensive changes, absence of unintended and unpredictable effects cannot be guaranteed. Each organism and product will differ in terms of health and environmental risk, sustainability, societal benefits and ethics, an may therefore be difficult to group in an appropriate manner, but rather should be assessed on a case-by-case basis. These members also believe that we do not yet have the necessary experience with and knowledge about the new methods to allow lowering of approval requirements. However, it may be necessary to clarify the degree of flexibility under existing legislation to adjust the approval requirements. Furthermore, clearer guidelines on risk assessment of certain types of organisms made with specific methods should be developed, and to a greater degree facilitate different data requirements for different types of GMOs. The requirements for assessing organisms where no foreign DNA is inserted can thus become less extensive. The possibility of differentiating between different GMOs should therefore be used more actively than today. Norway should promote the development of guidance documents in the EU for risk assessment of various types of organisms made with gene editing and other new gene technologies.

11.2 Voting on whether organisms produced with conventional methods should be regulated

A majority of 12 members of the Biotechnology Advisory Board (Cathrine Bjorvatn, Ole Kristian Fauchald, Gunnar Heiene, Bjørn Hofmann, Bushra Ishaq, Arne Holst-Jensen, Torolf Holst-Larsen, Bjørn Myskja, Benedicte Paus, Sonja Sjøli, May Thorseth and Fern Wickson) believe that organisms made with certain methods currently exempted

from the Gene Technology Act should be regulated in the same manner as genetically modified organisms, such as mutagenesis, cell fusion and triploidisation. Such methods can, in the same way as genetic engineering, be used to make changes that for all practical purposes cannot occur naturally, and may cause an unknown degree of risk to health and the environment, e.g. through unintended changes. The ethical challenges can also be similar as for use of genetic engineering. However, traditional breeding by crossing should not be regulated under the Gene Technology Act, since this method has a long history of safe use. Including conventional methods under the Act will, however, require a level-based system.

A minority of 8 members of the Biotechnology Advisory Board (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Raino Malnes, Bente Sandvig, Birgit Skarstein, Nils Vagstad, and Dag Inge Våge) believe that all breeding methods currently not covered by the Gene Technology Act should be exempted also in the future. Experience with these methods shows that they do not present any particular risk to health and environment. The current debate, both in Norway and internationally, is concentrated on whether or not certain organisms made with genetic engineering should be exempted from GMO regulation, especially where the genetic changes are equivalent to those achieved by conventional methods. Therefore, from a pragmatic perspective, it would be impractical to subject conventional methods to regulation when already in use, and it would be inappropriate to focus on aspects of the debate that are considered less relevant.

11.3 Voting on whether certain organisms should be exempted from regulation in the Gene Technology Act

The Biotechnology Advisory Board has previously unanimously recommended that RNA and DNA vaccines should be exempted from regulation in the Gene Technology Act. The voting options below concern whether other types of organisms should also be exempted from regulation in the Gene Technology Act.

A majority of 13 members of the Biotechnology Advisory Board (Cathrine Bjorvatn, Ole Kristian Fauchald, Gunnar Heiene, Bjørn Hofmann, Bushra Ishaq, Arne Holst-Jensen, Torolf Holst-Larsen, Bjørn Myskja, Benedicte Paus, Sonja Sjøli, Birgit Skarstein, May Thorseth and Nils Vagstad) believe that in addition to exempting RNA and DNA vaccines from regulation, it is appropriate to treat certain organisms currently regulated by the Gene technology Act in the same way as certain organisms which are currently exempted. This applies to organisms at level 1 of the level-based model and equivalent organisms made with conventional methods, such as mutagenesis. These members argue that point mutations made with gene editing in practice correspond to those made with mutagenesis, and they should therefore be regulated in the same way. These members justify this with the argument that these organisms has not been shown to represent a higher risk than organisms produced by conventional methods or that occur naturally, which have a long history of safe use. Such a principle is also in line with the Board's previous statement on DNA vaccines that recommended equal treatment of vaccines that in practice yield the same result. These members believe that equal treatment is essential, and not whether these organisms are regulated by the Gene Technology Act or not.

A minority of 6 members of the Biotechnology Advisory Board (Inge Lorange Backer, Kristin Halvorsen, Raino Malnes, Bente Sandvig, Dag Inge Våge and Fern Wickson) believe that, with the exception of RNA and DNA vaccines, it is appropriate to keep the scope and definitions set by current regulations unchanged, meaning that all organisms produced by genetic engineering are covered by the Gene Technology Act. These members state that the purpose of the Act is to regulate organisms produced by genetic engineering, and to assess the health and environmental risks, sustainability, socetial benefit and ethical aspects of such products, while at the same time maintaining the precautionary principle as basis for regulation. These members believe that we do not yet have the necessary experience with and knowledge of the new methods to exempt them from the Gene Technology Act. These members also believe that there is an important fundamental ethical distinction between changes that occur naturally and those made by genetic engineering, since the latter contributes to increased reification of nature.

One of the members of the Board (Petter Frost) also believes that it is appropriate to keep the current scope, but that the exemption recently granted for one specific DNA vaccine (Clynav) must apply to all temporary, non-hereditary genetic changes in general. This member justifies with the argument that animals vaccinated with this DNA vaccine is only an example of something that basically falls under the Gene Technology Act's legal definition of GMO, but which generally does not correspond to the biological perception of what a GMO is. Furthermore, this member believes that lack of clearly defined general criteria for what will be considered as GMO results in an unpredictable case-to-case

system that will adversely affect business investments in technology.

11.4 Voting on labelling requirements

A majority of 12 members (Cathrine Bjorvatn, Ole Kristian Fauchald, Kristin Halvorsen, Gunnar Heiene, Torolf Holst-Larsen, Raino Malnes, Bjørn Myskja, Benedicte Paus, Bente Sandvig, Sonja Sjøli, Birgit Skarstein and Dag Inge Våge) believe that all food and feed from GMOs should be labelled, but that there should be a level-based system according to the level at which the GMO is placed. They argue that such labelling will help consumers make more knowledge-based choices. Differentiated labelling will therefore provide an even better basis for choosing. Requirements for traceability, which is a prerequisite for enforcing the labelling requirement, should be reviewed further. For some types of organisms it will not be possible to require analytical traceability without significant disadvantages. For such products, requirements can be document-based traceability, e.g. identityassured traceability, as for other food products. Other solutions should also be evaluated.

A minority of 5 members (Inge Lorange Backer, Petter Frost, Arne Holst-Jensen, May Thorseth and Nils Vagstad) think that the labelling requirement should be differentiated according to the level at which the GMO is placed. They believe that organisms on level 1 should be exempted from the labelling requirement, and justify this with the argument that such organisms will contain very small changes compared to plants and animals from conventional breeding, or changes that theoretically could arise naturally and therefore may be equally acceptable. Labelling may also, incorrectly, be perceived as a warning about possible health or environmental risks. For organisms at levels 2 and 3, labelling should be required, but differentiated according to level. They argue that such labelling will help consumers make more knowledge-based choices. Differentiated labelling will therefore provide an even better basis for choosing. Such a system can help facilitate a desired development using genetic engineering, while largely safeguarding consumer interests. Requirements for traceability, which is a prerequisite for enforcing the labelling requirement, should be reviewed further. For some types of organisms it will not be possible to require analytical traceability without significant disadvantages. For such products, requirements can be document-based traceability, e.g. identityassured traceability, as for other food products. Other solutions should also be evaluated.

A minority of 3 members (Bjørn Hofmann, Bushra Ishaq and Fern Wickson) believe that all food and feed from GMOs should be labelled according to the current requirements. They argue that consumers are entitled to make informed decisions about what food they want to eat and what type of farming and food production they want to support. Regardless of one's own attitude towards genetically modified food, one should respect the preferences of others, and to allow an opt-out option for those that do not want GMOs for ethical reasons. Such a general labelling scheme will be in accordance with international regulations. These members believe that traceability should be required for all organisms covered by the Act.

11.5 Voting on sustainability, societal benefits and ethics

A majority of 13 members of the Board (Inge Lorange Backer, Cathrine Bjorvatn, Ole Kristian Fauchald, Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Bushra Ishaq, Bjørn Myskja, Benedicte Paus, Bente Sandvig, Sonja Sjøli, Birgit Skarstein and Fern Wickson) believe that the requirements for sustainability, societal benefits and ethics under the Gene Technology Act should remain unchanged. These members justify by arguing that this is an important tool for steering the technological development in a desired direction. The members believe that the purpose of the Gene Technology Act is that absence of negative effects of GMOs or GMO products is a necessary but not sufficient condition for approval. In addition, one must also be able to demonstrate the positive contribution of such products to society.

A minority of 7 members (Petter Frost, Arne Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, May Thorseth, Nils Vagstad and Day Inge Våge) believe that the requirements for sustainability, societal benefit and ethics should be differentiated according to the level at which the GMO is placed. In such a system, a positive contribution to sustainability and societal benefit may for example be required for level 3 organisms, since crossing species barriers in a way that cannot occur naturally can be perceived as ethically problematic. On the other hand, a neutral contribution to sustainability and societal benefit for levels 1 and 2 may suffice. They justify this by arguing that those who do not want to buy genetically modified foods because methods that deviate too much from nature may be more willing to accept GMOs that, in practice, correspond to organisms that are currently produced by conventional technology or could have arisen naturally. They further

argue that genetic engineering is not fundamentally more problematic than other technologies if the products have similar traits, and that more stringent requirements for such assessments should not be imposed if there is no risk to health and environment, and it does not contribute negatively to sustainability, societal benefit and ethics. Such a system provides predictability and leaves it up to the individual producer to develop products and choose the production method according to the different levels and the corresponding requirements for contribution to sustainability, societal benefit and ethics. These members also believe that documentation requirements must be made operationally predictable and feasible. må gjøres operasjonelt forutsigbare og gjennomførbare.

11.6 Other societal aspects

In addition to the specific provisions of the Gene Technology Act, other aspects will affect how genetic engineering is used and the societal consequences it may have. This applies in particular to rules for coexistence and access to research data and materials from the producer for independent research. The Norwegian Biotechnology Advisory Board will publish statements on these issues separately on later occasions.

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2018

The Gene Technology Act – Invitation to Public Debate

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