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The Norwegian Biotechnology Advisory Board :

Proposal for relaxation of Norwegian regulations for deliberate release of genetically modified organisms (GMO), with applicability also for EU legislation.

Bioteknologirådet
The Norwegian Biotechnology Advisory Board

INNHOLD

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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, 5deputy members and observers from 7government ministries.

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

Bioteknologirådet

PREFACE AND SUMMARY OF RECOMMENDATIONS

The Norwegian Gene Technology Act is intended to ensure that genetically modified organisms are produced and used in an ethical and societally responsible manner, in accordance with the principle of sustainability and without harmful effects on health and the environment. Very few organisms/ products have been authorised for the Norwegian market under the Gene Technology Act because to date very few applications have fulfilled the requirements of the Act and because there has so far been very little demand for genetically modified organisms (GMOs) from Norwegian producers and consumers.

In recent years, gene technologies have developed significantly. Technologies are now being introduced which are far more precise than previous methods and which have the potential to make a positive contribution to society.

Part of the Norwegian Biotechnology Advisory Board's mandate is to give advice to the government on issues related to GMO regulation. On our own initiative, we have raised the question of whether existing regulations and practices sufficiently facilitate the utilisation of positive aspects of new technological advances, while also addressing associated challenges in a responsible manner. Here, we have prepared a statement on the issue, which has been sent to the Norwegian Ministry of Climate and Environment.

The Norwegian Biotechnology Advisory Board also has a specific mandate for dissemination of information and to promote public debate. During the work with this statement, we have invited public debate and dialogue concerning these issues. The goal was to help raise awareness about gene editing and technological advances in the field, and to encourage a more open and constructive atmosphere for debate concerning the possible societal benefits of genetically engineered organisms. Our aim was also to develop proposals for a sound and robust regulatory framework that will enable the potential of gene technology to be harnessed, whilst at the same time addressing concerns relating to health and the environment, sustainability, societal benefits and ethics.

In this statement, the Norwegian Biotechnology Advisory Board discusses the provisions of the Gene Technology Act concerning the deliberate release of GMOs. However, the recommendations are applicable generally to regulation of GMO, in particular in the EU. The statement focuses on some general issues:

- What should be covered by GMO regulations?
- Should all organisms produced by genetic engineering be covered by GMO regulations, or should some be exempted?
- Should organisms produced using certain methods that are not currently regulated also be covered by GMO regulations?
- What requirements should apply to organisms covered by GMO regulations?
- Should the same requirements apply to all organisms, or can they be tiered?
- What requirements for labelling, traceability and monitoring should apply?
- How should contributions to societal benefits, sustainability and ethics be assessed?

The Norwegian Biotechnology Advisory Board has discussed these aspects at a general level and has opted not to go into extensive detail, since many of the proposals will have to be carefully considered by competent authorities. The Board does not address whether, and if so to what extent, changes to national and/or international legislation and agreements will be required in order to implement the proposals. The Board has also not considered the definitions and terminology used in GMO regulation, as these must be viewed in light of any adjustments to the scope. The statement only concerns the deliberate release of GMOs, not contained use. The recommendations also do not concern the use of GMO medicinal products, which the Board has discussed in a separate statement (1).

Summary of the recommendations:

A joint Board believes it is important to have a forward-looking GMO regulatory framework that allows for technological development and flexibility while simultaneously maintaining governmental oversight and control. This is

particularly important since the total – the accumulated impact of many genetic changes – can be greater than the sum of its parts, particularly given the rapid pace of new product development. The Board therefore recommends not to exempt any genetically engineered organisms with permanent, heritable changes from regulation. However, all Board members believe that requirements for assessment and approval should be differentiated to a larger extent than is currently practiced.

A joint Board recommends that authorities immediately clarify and utilise existing flexibility for differentiated impact assessment of GMOs within the current regulatory framework.

A joint Board recommends that the Norwegian government should appoint an official committee to review proposals for amendments to the regulation of deliberate release of genetically modified organisms in the Gene Technology Act. The committee should consider different ways of differentiating and simplifying the processing of applications for deliberate release of GMOs, including the tiered model proposed by the Board majority (see chapter 8.1).

- A majority of 11 out of 14 members (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Gunnar Heiene, Arne Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, Bjørn Myskja, Sonja Sjøli, Birgit Skarstein and Nils Vagstad) believes that the requirements for the authorisation/impact assessment of GMOs should be differentiated into a tiered system based on the genetic change that has been made. They believe that such a system could be appropriate in order to reflect the different levels of risk that can reasonably be expected for different types of changes, while at the same better ensuring a holistic approach to assessing sustainable development, societal benefit and ethics. At the lowest tier, a duty of notification (with receipt required) may be sufficient, whilst other tiers could have differentiated requirements for approval.
- However, a minority of three members (Bjørn Hofmann, Bente Sandvig and Benedicte Paus) recommend that, in principle, the current requirements for approval/impact assessment should apply to all organisms covered by GMO regulations, but that the opportunity to differentiate between different types of organisms through guidance documents should be utilised more actively.

On the issue of scope of regulations, all Board members agree that organisms with temporary, non-heritable changes, such as RNA and DNA vaccines, should be exempted from GMO regulations. However, opinion is divided on whether the scope should otherwise be maintained or expanded:

- A majority of nine members (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Torolf Holst-Larsen, Raino Malnes, Bente Sandvig, Benedicte Paus, Birgit Skarstein and Nils Vagstad) argue that, for pragmatic reasons, the current scope and definitions of GMO regulations should be kept so that organisms produced by genetic engineering are included, while organisms produced using other methods are excluded.
- A minority of five members (Gunnar Heiene, Bjørn Hofmann, Arne Holst-Jensen, Bjørn Myskja and Sonja Sjøli) recommend that organisms produced with certain conventional methods (such as mutagenesis, triploidisation and cell fusion), which are not currently specifically regulated, should be regulated in the same way as equivalent GMOs. These members justify their position through the principle of equality. However, four of the members (Gunnar Heiene, Arne Holst-Jensen, Bjørn Myskja and Sonja Sjøli) argue that a tiered system should be a prerequisite for including conventional methods.

As regards labelling, a unanimous Board recommend that labelling requirement should be differentiated to reflect relevant differences between organisms and their traits. They argue that differentiated labelling will allow consumers to make more informed decisions and provide a better basis for choosing according to relevant preferences. However, the board members have differing views regarding what should be labelled:

- Eight members (Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Torolf Holst-Larsen, Benedicte Paus, Bente Sandvig, Sonja Sjøli and Birgit Skarstein) argue that all organisms covered by GMO regulations should be labelled according to the differentiated system.
- However, six members (Inge Lorange Backer, Petter Frost, Arne Holst-Jensen, Raino Malnes, Bjørn Myskja and Nils Vagstad) recommend that organisms on tier 1 should be exempted from the labelling requirement, arguing that such organisms will not be significantly different to plants and animals produced via conventional methods such as crossing, or changes that in theory could have occurred

naturally and therefore may be considered equally acceptable. Member Bjørn Myskja presupposes that organisms produced through certain techniques that are currently exempt from GMO regulations will be included for tier 1 to be exempted from labelling requirements.

A unanimous Board recommends that traceability requirements, which are a prerequisite for enforcing the labelling requirement, should be further reviewed. Document-based traceability should be required for all GMOs, e.g. via identity protected (IP) raw materials, as is already the case for food products in general. It may also be appropriate to differentiate requirements for detection (analytical traceability) based on what is reasonable and feasible. The possibility of differentiated requirements regarding monitoring should also be reviewed further, with a view to establishing requirements and practices that may feasibly be applied to organisms with a range of genetic changes.

Regardless of the scope of GMO regulations and how organisms are assessed, the Board members unanimously argue that societal benefit, sustainability and ethics should form part of the assessment. However, there is disagreement about how these requirements should be weighted:

- Seven members (Inge Lorange Backer, Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Bjørn Myskja, Benedicte Paus and Sonja Sjøli) recommend that considerable weight should be placed on whether a GMO contributes positively to societal benefit and sustainability, in addition to being ethically defensible. They argue that this is an important tool for steering technological development in a desired direction.
- Six members (Petter Frost, Arne Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, Birgit Skarstein and Nils Vagstad) recommend that the requirements should be differentiated according to the tiered system, where the absence of negative impacts on societal benefit, sustainability and ethics is sufficient for organisms with genetic changes that do not involve crossing species boundaries or adding synthetic (artificial) DNA sequences. They believe that genetic engineering is principally no more problematic than other technologies if the products have similar characteristics to non-GMO products and do not deviate too much from nature.
- One member (Bente Sandvig) argues that considerable emphasis must continue to be placed on societal benefit, sustainability and ethics, as is currently required under the Gene Technology Act, but that absence of negative impacts is sufficient for all GMOs.

A unanimous Board believes that it is important to facilitate research into gene editing and other new gene technologies, both in order to acquire a knowledge of the technical and safety aspects associated with the technologies and to build expertise in Norway.

Public dialogue

The Norwegian Biotechnology Advisory Board has discussed the issues addressed in this statement for a long time. The issues are challenging and opinions differ about what regulatory frameworks would be most appropriate, both within the Board itself and elsewhere. The recommendations that are presented here also raise many questions. The Board therefore invited a public debate and dialogue in order to obtain input from stakeholders as a basis for further discussion before the statement was finalised. The consultation period lasted from 5 December 2017 to 15 May 2018. The public dialogue involved various activities. For instance, board members and the secretariat took part in several external meetings and conferences in order to present the Norwegian Biotechnology Advisory Board's proposals and participate as a discussion partner. The Board also arranged debate meetings on its own initiative:

- Oslo, 5 December 2017: Preliminary proposals presented.
- Ås, 7 February 2018: In collaboration with the Norwegian University of Life Sciences (NMBU).
- Trondheim, 8 February 2018: In collaboration with the Student Society in Trondheim.
- Hamar, 14 March 2018: In collaboration with Heidner Biocluster.
- Tromsø, 15 March 2018: In collaboration with Biotech North, Tekna and the Helix student association.
- Bergen, 16 March 2018: In collaboration with the Norwegian Institute of Marine Research and the Seafood Innovation Cluster.
- Copenhagen, 2 May 2018: In collaboration with the Danish Council on Ethics.

Anyone who wished to could also send us their views and comments within the deadline of 15 May 2018. The initiative sparked considerable engagement and we received 50 contributions from a wide range of stakeholders. Of these, 34 were from organisations and businesses, while 16 were

from independent scientists or members of the general public. The full comments are presented in Appendix 1 and are also available at http://www.bioteknologiradet.no/a-forward-looking-regulatory-framework-for-gmo/. Here is a summary of the most important aspects:

- Alost all commented on the importance and timeliness of the initiative and the debate about regulation of GMO. Many emphasised that gene technologies such as gene editing can contribute positively to society, for instance through development of products that can give more sustainable agri- and aquaculture. At the same time, many stressed the importance of a precautionary approach, and emphasised that we need more knowledge about and experience with the use of gene editing technology.

- We received a range of questions, comments and suggestions about GMO regulation in general, and our proposal in particular. Comments from industry and industry organisations (especially in agri- and aquaculture) expressed concern about future competitiveness for Norwegian businesses if Norway and the EU maintain a non-differentiated regulatory framework, especially if regulations differ from other countries. Other topics included the relationship with EU legislation, definitions and terms, risk assessment and uses of genetic engineering that had not been addressed in the Board`s preliminary proposal.

- There was broad agreement about many aspects of GMO regulation. In particular, the need for a timely and forward-looking regulatory framework that can be adapted when technologies and knowledge develop, while still safeguarding important considerations. There was also broad support for the purpose of the Norwegian Gene Technology Act; to ensure that the production and use of GMO is ethically sound, beneficial to society, consistent with the principle of sustainable development, and does not pose a threat to health and the environment.

- There was broad agreement about the importance of public trust and consumer choice, and almost all supported labelling of GMOs in general. A few argued against differentiation of labelling. However, most were in favour of differentiation based on the type of genetic change and/or the organism's traits. Justifications were that the consumer will get more relevant information, and that labelling is not useful if products cannot be traced in an effective way.

- A majority thought that societal benefit, sustainability and ethics should still form part of the assessment of GMO. However, there was disagreement about how the criteria should be weighted. Some argued that there should be a positive contribution, while others argued that requirements should be differentiated.

- Many comments, in particular those from industry and academic research, supported a tiered regulatory system where assessments are differentiated according to the genetic change. This way, risk assessments will be more proportional to the risk and more predictable, they argued. Several stressed that GMO regulations will be a significant barrier to using new technologies if approval requirements are not relaxed.

- Many other comments, especially those from farmer`s organisations and environmental organisations, argued that adapting current GMO regulations through guidance documents will give sufficient flexibility. They believed we have limited experience using new gene technologies, and were worried that an expedited assessment or notification is not sufficient to uncover risks.

- A number of independent scientists and members of the general public supported a revision of the GMO regulations, but argued that there should be a system based purely on the traits of the product, in line with Canadian regulations.

The Norwegian Biotechnology Advisory Board hopes this approach has contributed to and will continue to contribute to knowledge building and constructive dialogue about a very important topic. Our ambition is also that these recommendations will be an important contribution to the international debate about how genetically engineered organisms should be regulated.

With this statement, the Norwegian Biotechnology Advisory Board hopes to provide a good basis for shaping a GMO regulatory framework that better allows us to handle the rapid technological development that we are facing.

Kristin Halvorsen
Board Leader

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1. Why are we discussing this issue?

Photo: iStock

The purpose of the Norwegian Gene Technology Act[2] is to ensure that the production and use of genetically modified organisms takes place in an ethical and socially responsible manner, in accordance with the principle of sustainable development and without harmful effects on health and the environment. Among other things, this is about protecting animals and humans from health risks, safeguarding animal welfare, preventing or limiting damage to the natural environment, respecting moral and political boundaries for intervening in natural processes and showing respect for nature's intrinsic value. At the same time, GMO regulations should promote the development of products and technology that can benefit society. Principles such as accountability and transparency about research and use of gene technology can also contribute to positive societal development and public acceptance. Such considerations are particularly important in the face of the significant challenges relating to sustainable development and management of Earth's natural resources in accordance with the UN's sustainable development goals.[3] These principles are also of importance when technology is advancing at a rapid pace and the associated political debates become challenging. Meeting the needs of a growing population in a sustainable manner is dependent on sufficient production of healthy and safe food, as well as societal and political frameworks such as the equitable distribution of resources, infrastructure development, reduction of societal differences, mitigation of climate change and sound trade policies. Genetic engineering can be a vital tool if used for the good of society.

Technologies for genetically modifying plants, animals and microorganisms have been around for over 30 years, and genetically modified plants have been available on the international market for about 20 years. Most genetically modified organisms (GMO[i]) on the global market today are plants that tolerate pesticides and/or produce toxins to control insects. These GMO variants have been developed for large commercial markets. In recent years, a number of new genetic engineering techniques have been developed, which are both simpler and less expensive to use and offer more scope

[i] *In this document, the term 'GMO' is used to refer to one or more genetically modified organisms*

to change the DNA of organisms than previous techniques. In particular, gene editing/CRISPR has been adopted exceptionally quickly, both in academia and in commercial research and development. This has led to an increase in research relating to the development of organisms with many new traits, which in turn is expected to result in an increase in the number of applications for authorisation of such organisms in a five- to ten-year timeframe.[4] This could potentially contribute to the development of products that are beneficial to society, sustainable and ethically defensible. However, such powerful technology could also present many challenges, partly because it offers the ability to create organisms that are very different from those in existence today. Examples are microorganisms with fully synthetic genes which could potentially behave differently in the natural environment than existing microorganisms, organisms that have been created in hobby laboratories outside the control of the authorities ("do-it-yourself biology") or gene drives which are designed to spread genetic changes to large populations of wild plants and animals (see the separate statement from the Board dated 14 February 2017).[5] BOX 1 provides examples of various general applications.

The laws that define and regulate GMO in Norway, the EU and elsewhere in the world were formulated when gene technology was in its early stages of development. As a result of the development of new genetic engineering techniques, there is currently considerable debate globally regarding how organisms created with the technology should be regulated, e.g. concerning whether current regulations are appropriate for ensuring the effective and responsible development of tomorrow's research and products.[13-21] The fundamental principle behind regulation is to ensure safe, societally beneficial, sustainable and ethically responsible use of technology. The legislation must also be feasible to implement, clear and afford a predictable state of law. The Norwegian Biotechnology Advisory Board therefore wished to enter into this debate.

The debate is two-fold: 1) how genetically engineered organisms should be regulated under current frameworks, and 2) how organisms should be regulated in the future. Here, the Norwegian Biotechnology Advisory Board does not address the first question, other than assuming that genetically engineered organisms will be covered by Norwegian and European GMO regulations under the current definitions and scope, unless specific exemptions have been stipulated. In this statement, the Board sets out fundamental views concerning the scope of GMO regulations and what rules should apply to the development and use of the organisms they cover. GMO regulations will define the conditions for the use of gene technology in the bioeconomy of the future, and positive and negative consequences of different regulatory alternatives must be weighed against each other.

BOX 1: EXAMPLES OF GENETIC ENGINEERING OF PLANTS, ANIMALS AND MICROORGANISMS

Food production:
Gene technology can be used to create plants and animals with altered traits, such as improved resistance to disease, higher productivity and improved nutritional content (described in more detail in BOX 3).

Industrial biotechnology:
Genetically modified organisms, particularly microorganisms, are used in a variety of industrial applications. Examples include the production of new types of biofuels, biomaterials and feed and food ingredients.[6]

Medicine:
Genetically modified organisms can be used in human and veterinary medicine. Such GMO medicinal products could be genetically modified viruses that are used to deliver a gene therapy,[7] or genetically modified intestinal bacteria to treat metabolic diseases.[8]

Nature conservation:
A number of research projects aim to use gene technology for various conservation purposes. Examples include increasing the genetic resilience of endangered species (e.g. coral) and reducing pest and invasive species populations.[9] Another rapidly developing area is genetically modified microorganisms that can break down environmentally harmful substances such as plastic, oil or toxins.[10]

Do-it-yourself biology:
A growing application is the use of gene technology in hobby laboratories or for home use.[11] For example, "home kits" to create genetically modified luminous yeast for brewing beer or genetically edited antibiotic-resistant bacteria are sold online.[12] From a legal perspective, such use is considered to constitute deliberate release of GMO and is illegal if not authorised as such.

BOX 2: REGULATION OF GMO IN NORWAY AND THE EU

Regulation of GMO in Norway:

The Gene Technology Act and the Act relating to food production and food safety, etc. (the Food Act)[22] are key laws in the regulation of GMOs in Norway. According to current practice, live (viable) GMOs are regulated by the Gene Technology Act, while dead (processed) GMOs for use in food and feed products are regulated by the Food Act. Live GMOs include genetically modified plants that are cultivated, in addition to the sale, trade and transport of live GMOs. Dead GMOs used for other purposes, such as clothing, are not covered by the regulations.

The Gene Technology Act regulates the production and use of GMO. Its purpose is to ensure that this takes place in an ethically and societally responsible manner, in accordance with the principle of sustainable development and without causing harm to health and the environment. Both deliberate release and contained use of GMO are covered by the Gene Technology Act. Deliberate release is considered to include all production and use which does not take place in contained systems. Authorisation of release of GMO requires that there is no risk of harmful effects for health or the environment. It is also a requirement that considerable emphasis is placed on whether the release offers societal benefits and is likely to promote sustainable development.

The Food Act regulates processed/dead GMOs for use in food and feed products. Examples include flour from genetically modified maize and oil from genetically modified soy. The primary purpose of the Food Act is to ensure that food is safe. The Norwegian regulations under the Food Act largely correspond to the EU regulations concerning genetically modified food under Regulation (EC) No 1829/2003. This Regulation is not currently covered by the EEA Agreement and is therefore not binding for Norway. However, Norway is also involved in the processing of applications under the Food and Feed Regulation in anticipation of this Regulation being implemented into Norwegian law, but without the Government considering cases. Unlike the Gene Technology Act, the Food Act does not enact the assessment criteria of sustainability, societal benefit and ethics.

EU GMO regulation and implementation into Norwegian law:

Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms (the Deliberate Release Directive)[23] and Regulation (EC) No 1829/2003 on genetically modified food and feed (the GM Food and Feed Regulation)[24] are the two main regulations within the EU relating to GMOs. There are also separate regulations concerning labelling and traceability, contained use of genetically modified microorganisms, and transport of GMO across national borders.

The Deliberate Release Directive has been implemented into Norwegian law through the Gene Technology Act, and Norway is therefore affiliated to the EU's authorisation procedures for GMOs under the Directive. GMOs that have been authorised under the Directive are permitted in Norway, unless Norway imposes a ban under the Gene Technology Act. GMOs prohibited in the EU under the Directive are automatically prohibited in Norway. However, the vast majority of GMOs on the market in the EU are authorised under the GM Food and Feed Regulation.

The Norwegian Gene Technology Act differs from EU legislation as regards assessment criteria. In the EU, applications for deliberate release of GMO are assessed for health and environmental risks. When the Directive was incorporated into the EEA Agreement, Norway was granted a permanent exemption through amendments which also enable applications to be assessed according to the criteria sustainability, societal benefit and ethics. The EU legislation has also approached similar assessment criteria. In 2015, the Member States were given the opportunity to restrict or prohibit the cultivation of authorised GMO on their own territory for reasons other than health and environmental risks.[25] Member States can now place emphasis on considerations such as environmental and agricultural policies, town- and country planning, land use, socioeconomic impacts, prevention of GMO mixing with other products, and national policy objectives. The option to impose a ban applies only to cultivation, and not to other uses such as sale and use as food, feed or seed. National restrictions must otherwise be in accordance with the EU's international obligations, including trade agreements with the World Trade Organization.

2. What is GMO?

The Gene Technology Act defines genetically modified organisms as "microorganisms, plants and animals where the genetic composition has been altered through the use of gene or cell technology". The Gene Technology Act therefore currently establishes a clear distinction between organisms produced through gene technology on the one hand and all other conventional breeding techniques (as defined in the footnote) [ii] on the other. However, no distinction is made between the many different forms of GMOs that currently exist. In preparatory works, this is justified through a desire to distinguish between biological processes that occur naturally and those that do not, but emphasis is also placed on having an extensive history of safe use of traditional techniques.[26]

The EU's provisions make a similar distinction in their definition of a genetically modified organism: "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination". However, the Norwegian Ministry of Environment (now the Ministry of Climate and Environment) did not wish to use this definition in the Norwegian Gene Technology Act because they considered it to be too broad: The EU definition would also include mutagenesis (use of chemicals or radiation to provoke mutations), and it would therefore be necessary to specify an exemption for these techniques to keep them outside GMO regulations for pragmatic reasons (mutagenesis had been used as a breeding technique since the 1920s).[26] Moreover, the definition could in the opinion of the ministry be misunderstood, and interpreted as indicating that traditional breeding may also be covered. Organisms created using conventional techniques are therefore not currently regulated as GMOs in either the EU or Norway. However, we do not necessarily have extensive experience using certain techniques that are currently defined as conventional.

Conventional techniques that do not trigger regulation under the Gene Technology Act (see also BOX 3 for further descriptions)
Cross-breeding
Mutagenesis (radiation or chemicals are used to created mutations)
Triploidisation (Pressure treatment gives fish roe an additional set of chromosomes in order to render fish sterile)
Cell fusion within the same species (Combining cells produces extra copies of the genetic material – used in plant breeding)

Genetic engineering techniques that trigger regulation under the Gene Technology Act (see also BOX 3 for further descriptions)
Insertion of new genes from the same or a foreign species using classic genetic modification technology
Gene editing which is used to make more targeted changes either with or without the insertion of new DNA in the organism's own DNA.
Temporary addition of nucleic acids (e.g. RNA/DNA vaccines)[iii]
Regulation of gene expression (e.g. RNAi or epigenetic changes, where nucleic acids are used to modify gene expression, but not the actual DNA-sequence)
Cell fusion between different species

[ii] *In this context, 'conventional techniques' refers to all breeding and processing techniques that are not specifically regulated, as defined by the European Commission's expert group (see https://ec.europa.eu/research/sam/pdf/topics/explanatory_note_new_techniques_agricultural_biotechnology.pdf#view=fit&pagemode=none).*

[iii] *Exemptions have been made from the Gene Technology Act for the specific DNA vaccine Clynav. The authorities currently discuss whether similar exemptions should be made for other DNA vaccines and organisms with other temporary changes.*

BOX 3 – DESCRIPTION OF TECHNIQUES: CONVENTIONAL TECHNIQUES

Cross- breeding: In the case of organisms that reproduce through sexual reproduction, the offspring is a genetic mixture of its two parent organisms. This enables beneficial traits from different individuals to be combined. A genetic trait will therefore be inherited along with other undesirable traits. During the production of the parents' germ cells, a series of genetic changes take place through a process known as 'homologous recombination', where segments of DNA swap places within a chromosome pair (through cutting, swapping and pasting of the DNA by the cell's own molecules) in order to create more genetic variation in the next generation. Genetic variation is also created through spontaneous mutations. Mutation rates vary, but are quite similar within groups of organisms. In the case of higher organisms such as animals and plants, around 0.1 to 100 mutations occur from one generation to the next, depending on the size of the genome.[27] In rice, for example, the rate is around 20 mutations per generation.[28] Some mutations lead to functional changes, which can be either positive or negative for the organism concerned, while most are of little or no significance.

Mutagenesis: Since the 1920s, radiation and chemicals have been used to increase the frequency of mutations, with the aim of achieving more and new genetic variation in cultivated plants. This often occurs through 'double strand breaks' (cuts) in the DNA, which are later repaired by the cell's own repair machinery. Errors during this repair process lead to mutations. When radiation and chemicals are used, many, often hundreds or thousands, of mutations occur at random places throughout the DNA.[29,30] Most mutations are either harmful or have no effect, but sometimes mutations that give desirable traits suitable for further breeding arise. According to an overview from FAO (the UN's Food and Agriculture Organization) and IAEA (the International Atomic Energy Agency), over 3000 plant varieties from over 200 different species in more than 60 countries have been bred in this way and released into the natural environment. Over 1000 varieties are important food plants, including rapeseed, rice and barley, and many are commercially available.[31] The technique is still relatively widely used, with over 600 new varieties registered with the IAEA since the turn of the millennium.[32]

Triploidisation: In the aquaculture industry, triploidisation is used as a technique for rendering fish sterile.[33] By subjecting fertilized fish eggs to high pressure and temperature, the cells gain an extra copy of the entire DNA, i.e. they become triploid. This is a technology with which we do not have extensive experience.

Cell fusion within the same species: Cell fusion is a technique that is used in plant breeding to create new plant varieties by combining cells from different plants.[34] The plant cells that are to be combined are first treated with enzymes to break down the cell wall and then bathed in a chemical solution in order to fuse the cells together. This technique causes the cells to acquire multiple copies of their DNA (polyploidisation) and can for example be used to create sterile plants. It has been used to create varieties of cabbage and broccoli, among other things. Polyploidisation can occur naturally and will normally lead to significant changes in parts of the DNA over relatively few generations.[35] Such changes are not predictable and can be difficult to detect, even with genome sequencing. Like triploidisation, this is not a technology with which we have extensive experience, even though natural polyploidisation is an ancient and well-known phenomenon.

BOX 3 CONTINUED – GENETIC ENGINEERING TECHNIQUES:

Insertion of genes using classic genetic modification technology: The first techniques for genetic modification, which were developed in the 1970s and '80s, are based on isolating and inserting genes in the genetic material of a cell. Various techniques are available for inserting the genes into the cell. In plants, bacteria are often used as carriers of the genetic material, or the material can be transferred using chemicals, electricity or what is known as a 'gene gun'. In animal cells, chemicals or electricity are also used, or the genetic material can be injected through microinjection or transferred using a virus.

Gene editing: Gene editing enables more targeted changes to be made to the genetic material than is possible with classic genetic modification. The process involves enzymes that recognise a specific DNA sequence and create a double-strand break (cut) with the same character as those caused randomly by UV radiation or chemicals, for example. During the subsequent repair process initiated by the cell, DNA can be removed, replaced or inserted in the cut zone, which brings about a specific change. More recent gene editing techniques also enable changes to be made to single bases, without creating a double-strand break, by altering the chemical structure of the base. In this way, it is possible to adjust the sequence of a gene so that, for example, it is identical to a version of the gene that is already present in other individuals of the same species, without any other undesirable traits, such as those associated with traditional cross-breeding.

Temporary transfer of RNA/DNA (vaccines): By inserting bits of RNA or DNA from viruses or bacteria into an animal, it is possible to stimulate an immune response. The technique therefore works in the same way as a vaccine and can produce a similar result to traditional vaccination using peptides or proteins. The RNA/DNA is designed not to be integrated into the DNA of the organism, is not hereditary and disappears over time.

Change in gene expression: Different techniques can affect how genes are expressed, without changing the DNA sequence itself. An example is RNA interference (RNAi), where short RNA molecules bind to and degrade specific mRNA molecules that are intermediate products in the production of proteins and other genetic products. Another example is RNA-dependent DNA methylation (RdDM), where RNA is delivered to cells and modifies DNA methylation (chemical molecules on the DNA), which in turn influences how active the gene is (how much it is expressed).

Cell fusion (between species): In principle, this technique corresponds to that which is used for species-specific cell fusion, but uses cells from different species.

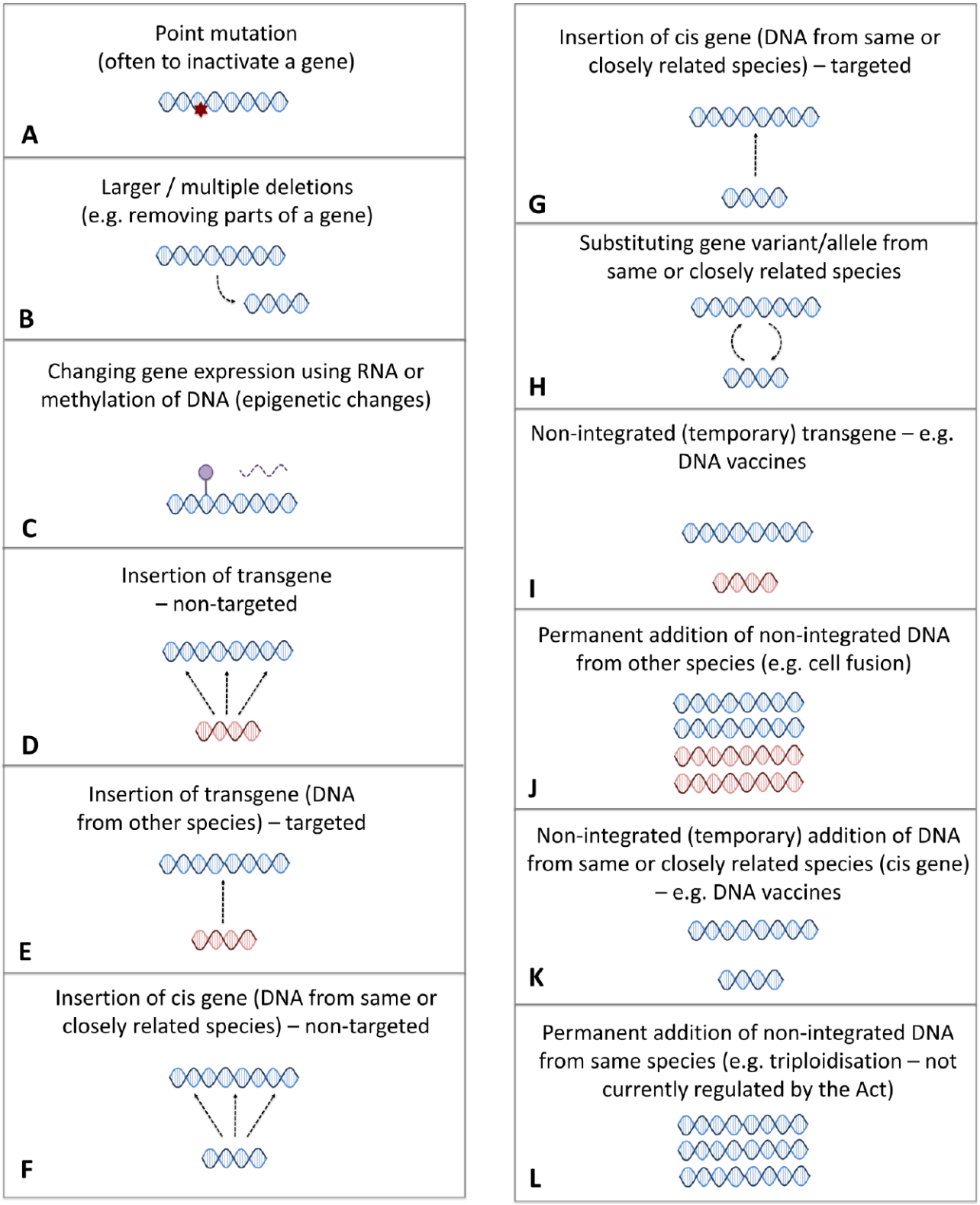


Figure 1: Different genetic engineering techniques can give rise to a broad spectrum of changes (in this document, the term 'point mutation' is used both for single base changes and for the deletion or insertion of a small number of bases (known as 'INDELs'), all of which are common outcomes of both spontaneous mutations and conventional mutagenesis).

3. Are new distinctions needed?

3.1. Similarities between conventional and genetic engineering techniques?

In addition to history of use, the Gene Technology Act is based on a distinction between what can and cannot occur naturally.[26] Genetic engineering now makes it possible to create numerous different changes on a sliding scale, ranging from what can also occur naturally to what absolutely cannot occur in nature or with the use of conventional techniques (see BOX 3 for a description of both conventional and genetic engineering techniques and BOX 4 for a comparison of the techniques published by an expert committee appointed by the European Commission). Studies show that unintended changes can occur both through the use of the new genetic engineering techniques and through conventional techniques, and that this is also dependent on the type of organism.[36] The significance of unintended changes also varies between different types of organisms. In plant breeding, such as mutation breeding, it is common to test large numbers of individuals with many different genetic variants (intentional and unintentional) for agronomic properties such as productivity, stress tolerance and quality. Plants with undesirable traits are rejected, whilst the best candidates are back-crossed repeatedly in order to reduce unwanted variation. In cases where such extensive screening/back-crossing is not possible, precision is more important. One example is the breeding of livestock, where there are limitations on the number of individuals and also important to avoid unintended changes which could have a negative impact on animal welfare. The precision of the new genetic engineering techniques is continually being improved through methodological development,[36-43] and the occurrence of unintended changes is significantly lower than when conventional techniques and classic genetic modification are used.[36,44] However, technique-specific undesirable effects can occur. It has for example been shown in certain cell types that CRISPR is more effective if the control mechanisms for eliminating cells with damaged DNA are inactive.[45] It will be important to take this into account when using the technology, particularly in the field of medicine. Genome sequencing and other analytical techniques make it possible to determine whether undesirable genetic changes have occurred in addition to the intended changes.[46-48]

From a biological perspective, the techniques that are currently exempt from regulation in the Gene Technology Act can also give rise to both intended and unintended genetic changes, large and small, to a much greater extent than targeted genetic engineering techniques. Cross-breeding can produce species-specific genetic combinations which have never previously existed. Radiation or chemical mutagenesis will generate hundreds of random mutations. Triploidisation, a technique used for producing sterile salmon, and cell fusion, a technique used in plant breeding, both cause the organism to acquire multiple copies of the entire genetic material. This can have major consequences for the characteristics of the plant or animal. It can provide a basis for regulating some or all of the conventional techniques as well. On the other hand, experience using such techniques, pragmatic considerations and the fact that they have thus far not been considered genetic engineering techniques may suggest that they should still be exempted from the scope of GMO regulation.

The Gene Technology Act is both technology- and product-based; the technology triggers regulation and a requirement for GMO labelling, but it is the product and its properties that are investigated and assessed. Although there can be significant similarities between organisms produced using conventional techniques and genetic engineering, they are currently regulated differently based on the technology used making them. For example, organisms with mutations created through gene editing are covered by current GMO legislation, while organisms with mutations created through mutagenesis are not. Another example is RNA/DNA-vaccinated organisms, which are defined as being genetically modified, in contrast to organisms that have been vaccinated using recombinant viruses, even though the results are in practice the same. The Norwegian Biotechnology Advisory Board has previously recommended that non-integrative DNA vaccines (Figures 1 I and K) should be exempted from GMO regulation.[49] In accordance with the Board's recommendations, the Norwegian Environment Agency concluded in summer 2017 that fish vaccinated with the DNA vaccine Clynav should not be classified as GMO.[50]

A third example that clearly illustrates the challenges associated with the current definitions is technology to prevent sexual maturation of salmon. This trait can be achieved by inhibiting the production of a specific protein called Dnd.[51] Inhibition of Dnd can be achieved using a number of different techniques, but the end products are regulated differently. A gene-edited salmon where the dnd gene is mutated through gene editing will be defined as a GMO according to the Gene Technology Act. Salmon treated with RNA to inhibit expression of the dnd gene (without altering the gene itself) will also be classified as a GMO. The same effect can be achieved using a molecule known as morpholino, which behaves like RNA, but does not necessarily fulfil the definition of ”genetic material” in the Gene Technology Act because the molecule is not a naturally occurring nucleic acid. This morpholino technology is currently under development in Norway.[52]

As methods other than genetic engineering techniques can also produce unexpected and unpredictable effects, from both a risk and a societal perspective, it is open to question whether both the technique and the characteristic should be triggering factors for regulation. For example, the comprehensive changes that can arise when using conventional techniques such as radiation or chemical mutagenesis, or the degree of “naturalness”, could be used as arguments for stricter regulation of such techniques than today, possibly in line with GMO. The terms ”naturalness” and ”history of safe use” are discussed below, both pivotal premises for the scope of GMO regulation in the light of developments within the field of genetic engineering.

3.2 The term ‘naturalness’

The technological advances that have been built up since the Gene Technology Act was adopted in 1993 raise the question of whether the original distinction between genetic engineering on the one hand, and conventional techniques on the other, still provides the most appropriate basis for regulation. Assuming that the reason for regulating gene technology specifically is that it is unnatural, one objection could be that both natural and manmade changes can give rise to health and environmental risks.

The term ‘naturalness’ is questioned both scientifically and philosophically, and is not unambiguous in the context of genetic modification. Mutations and gene flow between individuals and species both occur naturally and is a driving force for evolution. Viewed in this way, it may be problematic to classify one genetic change produced through genetic modification as being more unnatural than another genetic change.

Nevertheless, there may be relevant differences in the interpretation of naturalness based on the degree of human intervention. Thus, ”natural” may refer to what is not made or controlled by humans, and is meaningful as a background or contrast to what is manmade. ”Natural” then refers to the non-artificial. ”Natural” can also refer to what is normal or happens normally. Both of these meanings commonly underpin public scepticism towards technology in general, and genetic engineering in particular. The term is also used normatively, for example in the assertion that something is good because it is natural. In order for such statements to be valid, justification for why natural is better must be provided.

There is reason to believe that most people do not make an absolute distinction between natural and artificial, but are concerned about degrees of difference[53] and the type of ’unnaturalness’ concerned.[54] From such a perspective, it could be said that different forms of plant and animal breeding are more or less natural, depending on how much humans intervene and control development. The greater the degree of human intervention, the more people are responsible for the outcome and the more thorough the authorisation process should be. This grading of techniques can be justified in several ways, e.g. based on religion, on respect for the sustainability of nature or on scepticism towards human - including scientific - overconfidence. Using such a grading of naturalness as a basis could justify continuing to regulate gene technology in a different way than breeding, because one is less natural than the other. It could also provide a basis for differentiated regulation in line with proposals that are elaborated upon later in this document.

3.3 History of safe use

In general, there are few organisms that have systematically been tested for health and environmental risks. Nevertheless, traditional breeding techniques are considered to be safe, because they have a long history of safe use. The EU also refers to the history of safe use as an argument to exempt organisms produced through mutagenesis using radiation/chemicals from the GMO regulations. The lack of a history of safe use is also the justification for not exempting gene edited organisms from GMO regulations in the EU (see the discussion in section 3.5).

In the absence of experience with organisms produced using genetic engineering, experience of similar organisms

produced using conventional techniques can provide valuable information regarding risks. This may also be of regulatory significance.

However, no organisms or techniques can be considered to be absolutely safe. For example, a traditional food product may trigger allergies in some individuals, or may be toxic if not cooked in certain ways. The term ”history of safe use” has also not been uniquely defined. It has not been determined how long, to what extent or under what conditions an organism or technique must have been in use in order to be considered safe.[55] Depending on how the term is interpreted, it could be argued that certain GMOs have been in use sufficiently long to be covered by it.

A consequence of the current GMO regulations is that organisms produced using techniques which are not defined as genetic engineering, but which influence the genetic material, are automatically exempt, even though we do not have extensive experience with them. An example is triploid, sterile fish. The production technique was developed during the 1980s, but has only recently started to be used in trials in the aquaculture industry. Research indicates that there are challenges associated with the health of the triploid salmon, particularly when growth conditions are less than optimal.[56] However, sterile salmon produced using gene editing (point mutation) seem to do as well as ordinary farmed salmon.[57] Nevertheless, different regulation could result in triploidisation being used to achieve sterility, an attractive characteristic in the aquaculture industry,[58] even though the technique can have substantial adverse consequences for fish health.

It is therefore relevant to ask whether the current distinction between organisms produced using genetic engineering and other techniques is appropriate, if a history of safe use is to be the decisive factor for regulation.

3.4. Experiences with the Gene Technology Act

An important discussion is whether the GMO regulations have worked appropriately.

In Norway, only five types of genetically modified carnations (cut flowers for import) have so far been authorised under the Gene Technology Act. Ten different genetically modified plants are currently banned from sale in Norway, as well as two genetically modified vaccines and one test kit with genetically modified bacteria for detecting antibiotic residues.[59] There are currently no GMOs authorised under the Food Act, but no applications have been submitted under this Act either (with the exception of one case where the application was subsequently withdrawn).

Within the EU, only carnations are currently authorised under the Deliberate Release Directive.[60] The carnations have been authorised for import, distribution and sale as cut ornamental flowers, but not for cultivation. Far more (> 60) GMOs are currently authorised under the Food and Feed Regulation (1829/2003), primarily for food and feed use, including as additives in food and feed products.[61] All of these GMOs are plants: varieties of cotton, corn, oilseed rape, soy and sugar beet. Authorised areas of use are food and feed, as well as products of an authorised GMO, including food and feed additives. The maize MON810 is the only GMO that has so far been cultivated to any significant extent within the EU. Authorisation under the Deliberate Release Directive has now expired, and an application for renewal under the GM Food and Feed Regulation has been submitted. The maize can be cultivated pending the outcome of the process. The maize is already authorised for food, feed and pollen production under the Regulation.
That few GMOs have been authorised in Norway may be perceived in different ways: On the one hand, it could be argued that the regulations have worked well and prevented products that do not fulfil the requirements concerning safety, sustainability, societal benefit or ethics in order to be placed on the market. On the other hand, it could be claimed that the comprehensive requirements for authorisation have meant that only major industrial corporations have been able to adopt the technology, and that smaller businesses simply do not have the resources needed to develop and commercialise products. These views can both be valid and need not be mutually exclusive.

Technological development, blurred distinctions between what should or should not be regarded as a GMO, as well as experiences and knowledge gained since the GMO regulations were introduced, are all factors which contribute to the renewal of the debate concerning how GMOs should be regulated.

3.5. The current debate within the EU

There is considerable discussion globally concerning how organisms produced using new gene technologies should be regulated. In many places, including the United States and parts of South America, the authorities have decided that genetically edited plants which have not had new DNA added to them, are not to be considered as GMOs.

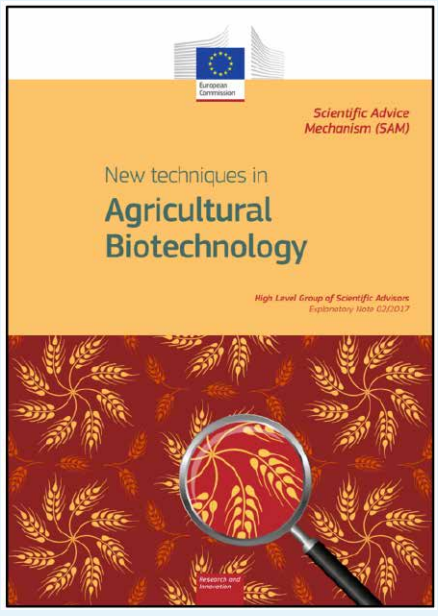
In the EU, these issues have been the subject of discussion

Box 4: A report by the European Commission published in May 2017 compares new gene technologies with classic genetic modification and conventional breeding

A report by the European Commission published in May 2017[36] compares new gene technologies (such as gene editing) with both the classic techniques of genetic modification and conventional breeding techniques based on published scientific studies, overview articles and official statements. The aim of the report was to provide an updated scientific basis for the Commission. However, the Commission's aim was not to provide advice on legislation. The work was carried out by an expert committee consisting of internationally leading specialists in the field of natural sciences, sociology and political science.

The main conclusions of the report are:

- All living organisms undergo genetic changes as a result of various molecular processes (such as errors during DNA replication or mutations), which can occur either spontaneously or upon exposure to environmental factors. This leads to genetic variation.
- All breeding techniques (conventional techniques, classic genetic modification and new gene technologies) utilise such genetic changes, both manmade and natural, to develop organisms with preferred traits.
- There are differences between new gene technologies: Some are more like classic genetic modification, while others have greater similarities with conventional techniques. This is reflected in the broad 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 to one or a few bases), to the insertion of genes. Other techniques can modify gene expression without altering the DNA sequence itself.
- The wide variation in new techniques means that a common grouping would not necessarily be appropriate for scientific or other reasons.
- Differences between techniques with regard to unintended effects and efficacy depend on the extent to which the changes can be targeted and how precisely they can be done. Unlike conventional techniques and classic genetic modification, unintentional changes with new techniques, such as gene editing, are rare. In general, the frequency of unintended effects in organisms produced using new techniques is much lower than with conventional techniques and classic genetic modification. This is currently the subject of many research efforts, as evidenced by the rapidly growing number of publications in the field.
- The precision and efficacy that the new techniques offer means that certain products can only be obtained by using such techniques, and not through the use of conventional techniques or classic genetic modification.
- No conclusions can be made concerning the absolute or comparative risks between techniques. Realistically, risk assessments can only be carried out on a case-by-case basis and will depend on the characteristics of the end product. Genetically and phenotypically similar products produced using different techniques would not be expected to constitute different risks. However, the document does not elaborate on issues relating to risks further.



since 2007.[13,1-7,36,62] The discussions have revolved around how current regulations should be interpreted. The authorities in Sweden, Finland and the United Kingdom have interpreted the current EU regulations as indicating that minor mutations in plants produced through gene editing (Figure 1a) correspond to mutagenesis, and are thus exempt from EU regulation.[63-64] However, the Court of Justice of the European Union concluded in July 2018[65] that all organisms which have had their genetic material altered in ways which do not occur naturally, which covers both genetic engineering and conventional mutagenesis, must legally be considered to be GMOs according to the definition. However, the court maintained that conventional mutagenesis can still be exempted from the regulations because the technique has a long history of safe use. In contrast, the court concluded that we do not have sufficient experience of gene editing and other new technologies to make a similar exception, and thus placed decisive emphasis on the precautionary principle.

Current discussions concern both how the current regulations should be interpreted (the issue on which the European Court of Justice has now ruled) and what future regulatory framework would be most appropriate, as the technological possibilities are different now than when the regulations were originally formulated. The European Commission has itself stressed the importance of a broad debate on the use and regulation of new gene technologies.[66-67] In 2017, the Commission published a report comparing new gene technologies with both classic genetic modification and conventional techniques (see BOX 4), in which they point to blurred distinctions. It is not known whether the European Commission will initiate a broader evaluation of the GMO regulations in the wake of the Court of Justice's judgement.

3.6. Regulation based on technology and/or product?

The main purpose of legislation is to provide regulations as and when necessary, based on health, environment and societal considerations. In Norway and the EU, GMO regulation is triggered by the use of techniques defined as gene technology. However, it is the organism and its characteristics that are assessed and on which requirements are imposed.

Whether it would be most appropriate to regulate on the basis of technology and/or product depends on whether the process itself poses a risk to health and the environment or presents challenges relating to sustainability, societal benefit and ethics. It will also be of importance what kind of regulation will be best suited to cover the current cases.

From a risk perspective, one argument for maintaining technology-based regulation is that we can control the use of technologies with which we do not have much experience. A technology can for example enable more substantial and rapid changes to be made to an organism and its characteristics, with the consequence that the potential harmful effects in the short and long term can be greater than changes made using conventional techniques.

On the other hand, it could be argued that it is the organisms' characteristics, rather than the technique used to produce them, which determine whether or not they pose a risk to health and the environment. With such an approach, the specific change/characteristic should be decisive regarding how they should be handled and what requirements should be imposed regarding risk assessment.[64,68,69]

The latter approach is the basic principle behind the regulations that apply in Canada, which regulate products made using biotechnology as part of the regulations for "new products". The regulations require a risk assessment to be carried out for new plants for cultivation, and new food or feed products, regardless of the technique that was used to produce them.[70] A 'new plant' is defined as a plant with a trait that does not already exist in the plant variety concerned in Canada, or which has a trait that is present in a way which differs from normal variation. 'New food' is defined as food that has been produced using a process that has not previously been used to produce food, products which do not have a history of safe use, and food produced through genetic modification or biotechnology.[71] As a result, both the product's characteristics and the production process can trigger regulation. Whether or not the plant or food is considered to be 'new' is determined on a case-by-case basis.

The risk assessment in Canada follows the same principles as those applied in the EU, with the same general requirements regarding information and what aspects are examined. For plants, the requirements vary from case to case. The plant concerned, its intended use and the environment in which the plant is to be released, will all be decisive factors. Most "new products" have so far been GMOs, but plants produced through conventional breeding have also been assessed and authorised under this system. Gene edited organisms from which DNA has been removed are also covered by the regulation, and one such gene edited oilseed rape has been authorised in Canada.

A more product-based approach is supported in reports and discussion memos published by a number of organisations, such as the European Academies Science Advisory Council

(EASAC),[72,73] European Plant Science Organization (EPSO),[74] European Seed Association (ESA),[75] the Royal Swedish Academy of Agriculture and Forestry (KSLA)[76] and the National Academy of Sciences (NAS) in the US.[77] Others, including environmental organisations, organic agriculture organisations and other civil society organisations want to continue with technology-based regulation.[78-82]

When the agriculture report (Jordbruksmeldingen) was presented by the Government in spring 2017, the industrial committee of the Norwegian Parliament (Storting) stated in its recommendation:[83]

> *The Committee believes that more research must be carried out concerning the new genetically edited GMOs, e.g. the CRISPR technology. More knowledge will be needed before gene edited GMOs can be authorised for use outside contained systems. As with the old GMOs, there is a risk that new, gene edited organisms could disperse in the natural environment and have unintended consequences. The Committee therefore believes that it is necessary to continue to follow a restrictive GMO policy. Gene edited organisms must be regulated through the Norwegian Gene Technology Act, and they cannot be authorised until guarantees have been provided that they are traceable and can therefore be monitored.*

However, the discussion concerns more than risk. Regulation will also be of importance for societal aspects such as sustainability, societal benefit and ethics.

4. Sustainability, societal benefit and ethics - key considerations

The purpose of the Norwegian Gene Technology Act is to ensure that GMOs are developed and used in an ethically and socially responsible manner, in accordance with the principle of sustainable development. Norway was the first country to emphasise these criteria when evaluating genetically modified organisms. More recently, other countries have decided to take into account similar considerations to those adopted by Norway, and EU legislation is now closer to the Norwegian regulations regarding cultivation of GMOs. In 2015, the EU decided that any Member State may restrict or prohibit the cultivation of an EU-authorised GMO for socioeconomic or other reasons (see also BOX 2). The Cartagena Protocol (Article 26 on imports of GMOs) states that Member States may place emphasis on socioeconomic considerations when deciding whether or not to permit a GMO.[84]

4.1. Societal consequences of different regulatory systems

There is currently considerable interest amongst stakeholders in the agricultural and food production sectors in adopting the new genetic engineering techniques, and work is under way on a wide variety of different applications (see BOX 5). In Norway, this is of particular importance for the agriculture and aquaculture industries. If the regulations were to become disproportionately stringent, fewer stakeholders would be likely to adopt the techniques for the production of new plant and animal varieties, partly because it would become too unpredictable, time-consuming and expensive to develop products for the market. The need for relaxation of the Gene Technology Act was emphasised as being decisive by a number of Norwegian industries during the public consultation process of the Norwegian Biotechnology Advisory Board`s preliminary statement (see Appendix 1).

The Gene Technology Act also regulates, inter alia, field trials, which cannot be carried out without specific authorisation. GMO regulations will also have an impact on the competitiveness of stakeholders on international markets. Only a few large industrial companies currently offer GMO plants on any significant scale. It is likely that the current requirements for impact assessment have contributed to there being fewer stakeholders on the international market, because the requirements favour products which are used in large-scale agriculture and large multinational companies with sufficient financial resources to go through the comprehensive processes necessary in order to obtain authorisation. It could be argued that less stringent regulation could promote the development of more niche and socially beneficial products, and that it is the characteristics of the products rather than the technology used in the production process which determine whether or not they are socially beneficial, sustainable and ethically justifiable.

However, regulations that are too weak could lead to the technology being used to make products that are not sustainable, socially beneficial or ethically justifiable. This could also be an argument for technology-based regulation. There may, for example, be challenges linked to the use of a particular technology, or linked to products that can only be produced using a particular technology. If one technique for the production of a domesticated animal could cause suffering to the animal, and another technique for producing a similar animal does not, there may be reason to regulate them in different ways.

Gene technology can be used to produce organisms with more or less favourable intended and unintended characteristics, in the same way as with conventional technologies. Gene technologies are becoming increasingly accessible and enable genetic changes at a higher speed and with a greater scope than has earlier been possible. As a result, the consequences of human intervention in nature could be greater than with other techniques, which could justify technology-based regulation. Another argument for technology-based regulation is if the use of a particular technology results in or changes agricultural practices in ways that do not contribute to sustainable development, regardless of the characteristics of the products.

It could be argued that gene technology, in principle, constitutes an unacceptable intervention in the genetic integrity of organisms and entails a lack of respect for nature, thus crossing biological, moral or political boundaries. The ultimate consequence of such a stance could be to require a ban on all uses of GMO. A more widespread stance is that the extensive use of GMOs could strengthen the development of large-scale industrial agriculture and food produc-

BOX 5: EXAMPLES OF INTENDED TRAITS/ORGANISMS THAT ARE BEING DEVELOPED USING NEW GENE TECHNOLOGIES.

The following is a selection of examples of research and development of organisms using new gene technologies. Some have traits that have also been developed previously, using other technologies. Others have traits that can only be achieved using new gene technologies.

Disease-resistant animals and plants:

- Pigs resistant to the viral diseases Porcine Reproductive and Respiratory Syndrome (PRRS),[85,86] and African swine fever[87]
- Rice,[88] wheat[89] and tomatoes[90] resistant to fungal infections.
- Cucumbers resistant to viral infection[91]
- Citrus fruits resistant to bacterial infection[92]

Plants with altered nutritional content:

- Maize with reduced phytate content (increases absorption of phosphorus in livestock which eats it, thereby reducing phosphate run-off to the environment)[93]
- Potatoes with reduced concentrations of carcinogenic acrylamide following heat treatment[94]
- Rapeseed oil which produces oil with less saturated fats[95]
- Wheat with reduced gluten content[96]
- Rice with a higher content of amylose (which can prevent a variety of diseases, such as diabetes and cardiovascular disease)[97]

Plants with increased productivity and shelf life:

- Tomatoes which flower more frequently (and therefore produce more) per season[98]
- Maize that grows better under drought conditions[99] and rice which produces more grains per plant[100]
- Rice with enhanced storage tolerance[101]
- Browning-resistant apples[102] and mushrooms[103]

Animals with other characteristics:

- Cows without horns (to avoid the dehorning process)[104]
- Sterile farmed salmon (to avoid genetic interference in wild salmon populations)[105]
- Cashmere goats with thicker fur[106]
- Laboratory animals used as models for human diseases in order to study mutations that cause disease, and to develop new medical treatments[107]

Pesticide-resistant plants:

- Rapeseed with increased tolerance to herbicides with the active ingredient sulphonylurea[108]

tion, monoculture and the extensive use of pesticides, which could lead to an undesirable distribution of power and adverse consequences for health and the environment. This could impact on other forms of agriculture and food production, such as organic farming. However, it could also be argued that gene technology offers enormous opportunities for more sustainable operation, e.g. because the technology can reduce the need for disease mitigation and reduce both pre- and postharvest losses.

Previous consumer surveys on attitudes towards GMOs have yielded divergent results. For example, researchers at the National Institute for Consumer Research in Norway (SIFO) concluded that the majority of Norwegian consumers have a negative view of genetically modified food.[109] However, other studies show that there are relevant nuances in attitudes towards the use of gene technology. For example, it is of importance as to whether or not the genetic change crosses species barrier. The product's characteristics are also an important factor.[110-112] That the characteristics and purpose of the product are decisive is also confirmed by recent studies on new gene technologies. For example, a considerable majority (71%) of Britons were positive towards the use of gene technology to improve animal health, while a minority (33%) were positive towards the use of gene technology when the main purpose is to increase the producer's profits. The survey, conducted in 2018 by the Royal Society (the United Kingdom's leading scientific academy) is, as far as we are aware, the only published study which specifically looks at attitudes towards new gene technologies such as gene editing.[113]

A pivotal issue in the discussion concerning GMOs relates to questions regarding intellectual property rights (abbreviated to IPR, i.e. patents, variety protection, etc.), which afford specific exclusive rights to developers of new products or techniques. IPR is not regulated in the Gene Technology Act, but will nevertheless be of importance

regarding which techniques and products are developed and adopted, and the social and ethical consequences products will have when they are released or placed on the market. Intellectual property rights are important instruments for stimulating development and innovation. This can give many societally beneficial products. At the same time, the patenting of genetically modified organisms could lead to unfortunate restrictions on further breeding opportunities and farmers' use of own crop seeds. In practice, ownership issues have also led to indirect limitations on scientists' access to some GMOs, e.g. for independent risk research. Another issue is whether it is ethically problematic to authorise patents for living organisms, irrespective of whether or not they are genetically modified. The patent situation for organisms produced using the new gene editing methods is as yet unclear, and will potentially vary from organism to organism depending on the genetic change that has been made.

4.2. Ethical considerations

As with any technology, modern biotechnologies should be used in an ethically responsible manner, and the legislation which governs its use must reflect relevant ethical considerations. Ethical justifications will always underpin any stance on how this technology should be used, just as it will the wording of the legislation. However, these aspects are not always clearly formulated. Opinions will differ as to what constitutes proper use and acceptable legislation, and for this reason it is essential to clarify these ethical aspects.

A range of ethical stances and philosophical positions will underpin any ethical assessment (see BOX 6).

BOX 6: ETHICS

Consequentialism: A given option may be expected to result in a more desirable outcome than other options, giving us an incentive to choose that option. Such a consideration is based on (a) the premise that something can be inherently good, and (b) the belief that one has an obligation to act in a manner which, all things considered, one assumes will lead to a good outcome. Opinions vary as to what may be considered good. Well-being and self-fulfilment are two common examples. Maximising the good also requires us to make assumptions concerning the likely outcome of a given action. When the consequences of our actions are uncertain, our assessment of the likely outcome will need to take into consideration what is the rational or sensible course of action under uncertainty (see Item 4.1). Consequentialism also encompass the ethics of responsibility, or so-called "future ethics", which asserts that we need to consider the surrounding environment and future generations when we assess the consequences of our actions. This is of particular relevance to sustainable development.

Deontology/duty-based ethics: Actions should not (solely) be assessed on the basis of their consequences, but must also consider the action in and of itself. Punishing a person who has not done anything wrong is wrong, even if it does not result in harm – or even if it results in a positive outcome. We have certain duties that are, in part, independent of the consequences of our actions. One way of understanding such duties is by reference to the fact that all human beings have an inherent value (human dignity) and that we have a duty to act in ways that respect this value. In the same way, one can assign an inherent value to every living being and to nature as a whole.

Relational ethics/ethics of care: The norms that guide our actions are shaped by the fact that we have a particular relationship to human beings or other organisms. This gives us incentives to treat them with particular consideration and respect. This relationship may involve someone taking on a role – e.g. as a healthcare professional or guardian – and thereby assuming an obligation. One form of relational ethics entails stronger commitments to human beings and other organisms which belong to the same community or environment as oneself. A variant of relational ethics is known as care ethics. This approach highlights the importance of placing particular emphasis on the nature and quality of the relationship as well as the key roles played by power, dependence and vulnerability when making a complex assessment of right and wrong.

Virtue ethics: Doing good is not only assessed on the basis of consequences, responsibilities and relationships, but also of character traits. In order to do good, one must strive to be a good person. Good actions are a consequence of good character traits such as courage and mercy. Opinions may differ as to what constitute good character traits, and, as with the preceding ethical perspectives, there are many different ways of defining these traits.

In principle, any ethical or philosophical consideration could form the basis of an ethical assessment of a GMO. Any line of reasoning which seeks to take into account these various factors, requires exercise of judgement. One can also take into account other considerations than those set out above, such as the fundamental values of the general public, bioethics and ecological philosophy. Irrespective of one's political standpoint, it is necessary to explain and specifically define the ethical principles upon which one's stance is based.

Ethical assessments and their operationalisation can potentially vary from one regulatory model to another. Irrespective of which regulatory model is applied, it may be desirable to draw up an appropriate framework for how such assessments should be carried out – something which is currently lacking.

A crucial aspect is that the consumer is able to trust that GMO regulations guarantee safe, sustainable, socially beneficial and ethically sound use of gene technology, while at the same time not placing unreasonably large obstacles in the way of the development of desired products. There is a need for transparency surrounding how the technology is applied, and the consumer needs to be able to make informed decisions. The goal must be to identify a system that facilitates the development of the technology and is used in the best interests of society, in line with the purpose of the Gene Technology Act. In order to achieve this goal, it is necessary to compare different regulatory models.

It may be questioned whether the scope and definitions of the Gene Technology Act should be retained in their present form, or if amendments should be made which will result in certain organisms produced via genetic engineering to be exempted from regulation, and/or whether organisms currently not regulated by the Act may be included. One might also ask whether different requirements should apply to different types of organisms. Irrespective of what approach is taken to regulation, appropriate distinctions must be made. Such distinctions may be based on the type of genetic modification, the scope of modification(s), the trait modified, risk to health or the environment and/or other considerations such as sustainability, societal benefit and ethics. Again, this may depend on which rules or approval requirements that apply.

The following chapters initially describe the current system for authorisation of GMOs, followed by presentation of and discussions on some possible alternative strategies.

Photo: iStock

5. The current system for authorisation of GMOs

Before a GMO can be authorised, an assessment must be made of whether it poses a risk to health and the environment. This is statutory both in Norway and in the EU. In Norway, an assessment regarding sustainability, societal benefit and ethics must also be carried out. Labelling and traceability requirements come in addition to the authorisation system of GMOs.

5.1. Risk assessment and risk management

Under current legislation there is a clear division of labour between bodies which assess risk scientifically (risk assessors), such as the European Food Safety Authority (EFSA), the Norwegian Scientific Committee for Food and Environment (VKM) and bodies whose task it is to advise on and reach political decisions on what to do in the event that a risk arises (risk managers), such as the Norwegian Food Safety Authority, the Norwegian Environment Agency and the Norwegian Ministry of Climate and Environment.

Quantified risk analysis entails assessing risk by combining the likelihood that damage will occur and the severity of the potential damage. Risk assessors must also account for uncertainty and lack of knowledge.

Outside of decision theory, however, there is a great deal of ambiguity surrounding the terms ”uncertainty” and ”risk”. Both terms refer to a situation in which there is uncertainty surrounding the outcome of an action. At least three types of uncertainty exist:

- There is uncertainty about what outcome an action will result in, but the probability distribution across possible outcomes is known. In the language of decision theory this is known as risk. Possible outcomes are known, but their probability distribution is not. This is known as uncertainty. Neither the outcomes nor their probabilities are known. This is the highest level of uncertainty.
- When making decisions in the presence of risk, it is generally considered rational to maximize the expected value. The expected value of the various options is calculated based on the estimated probability and the predicted outcome value. This approach is not applicable in cases where there is uncertainty and lack of knowledge.
- A key principle of rational action in situations of uncertainty is the maximin rule. In order to apply this rule, one merely requires estimates of the value of different outcomes, and not their probability. One then selects the option which has the best minimum outcome – which is to say, the option that will result in the least severe consequences in a worst-case scenario. This is a reasonable approach when there is little to gain and a great deal to lose by choosing a risky option. Yet if there are significant potential benefits, it would seem unwise not to take them into consideration when comparing alternative options.

In hybrid situations where the probability of the various outcomes is partly known, one can select the option which has the lowest probability of resulting in the worst possible outcome.

On the basis of an overall assessment the risk managers will determine what is an acceptable level of risk, what to do if a risk arises, and what should be done in the event of lack of knowledge or scientific disagreement. In this context the precautionary principle forms a key basis for legislation.

5.1.1. The precautionary principle

The precautionary principle is a key prerequisite for legislation on genetic engineering, both in Norway and in the European Union. The precautionary principle regulates actions in cases of doubt or uncertainty. This principle is referred to in the preparatory work for the Gene Technology Act. It is pointed out that the wording of the Act, i.e. that the production and use of a GMO must be carried out ”without adverse effects to health and the environment”, has been chosen in order to emphasise the aim of assessing health and environmental risks in advance of release and to avoid potential adverse effects, and that the precautionary principle should guide decisions. The preparatory works of the Act outline how this principle is to be understood:

> *The Ministry wishes to emphasise that the precautionary principle does not mean that all use of gene technology is automatically considered hazardous. If, however, following a specific assessment, there is rea-*

sonable doubt concerning risk, this would be an argument against its use.[114]

The precise meaning of "reasonable doubt" leaves room for interpretation. In the comments to the objects clause it is stated that the precautionary principle should form the basis of the assessment of detrimental impacts on human and animal health and the environment, and that ethical considerations will have to be emphasized when applications for authorisation of a GMO are to be assessed.

The precautionary principle is considered one of several principles within the concept of sustainable development. In Section 9 of the Norwegian Nature Diversity Act,[115] application of the precautionary principle is described as follows:

When a decision is taken in the absence of sufficient knowledge of what impacts it may have on the natural environment, specific efforts should be made to avoid potential significant harm to biodiversity. Where there is a risk of serious or irreversible harm to biodiversity, lack of knowledge may not be used as justification for postponing or failing to implement protective measures.

The risk assessment must be based on both quantitative and qualitative criteria, which entails e.g. assessing whether an adverse impact is irreversible, and whether an adverse impact could prove disastrous even if no damage occurs in the short term. If we apply the precautionary principle, there are a range of measures that can be implemented to address uncertainty. These may include imposing a permanent ban, a moratorium (a time-limited ban to allow time for knowledge to be gathered), a step-by-step strategy (with clearly-defined milestones for each step), a go-slow strategy (whereby a limited activity is followed up via a targeted follow-up programme, e.g. in the context of research) or a monitoring strategy (a more comprehensive activity followed up via a special monitoring programme and reporting system, but taking into account the principle of reversibility). Once a measure has been implemented the goal should be to minimise uncertainty, for instance by conducting research or requesting further data on any areas of uncertainty.

However, the precautionary principle can be understood in various ways. As such it may be appropriate to define criteria for what level of knowledge is sufficient to justify abandoning the precautionary approach, in order to ensure that this principle does not, in practice, become a strategy whereby it is never possible to authorise a GMO. Flexible regulations, which allow for requirements for documentation and safety measures to be adjusted in step with an increasing knowledge base, will also be in line with the basic principle of a precautionary approach.

5.1.2. EU guidelines on health and environmental risk assessment

The EU has prepared guidance documents for environmental and health risk assessment of genetically modified plants, microorganisms and animals.[116] These documents provide guidelines on how applicants can evaluate the impact a GMO has on the environment or human health, and set out why specific data or methods are recommended for a risk assessment. A key principle when assessing GMOs is that they must be assessed on a case-by-case basis, due to the fact that each GMO is different in terms of the potential risks it poses. For this reason, the information which is requested may vary depending on the type of GMO and the modified traits, the intended use, the environment into which the organism is to be introduced, and whether any other GMOs are present in the environment into which it is to be introduced. A further principle is that genetically modified plants must be considered on a step-by-step basis. This means that initial trials must be conducted in laboratories, followed by small-scale field studies, followed in turn by large-scale field studies. Given that the ecosystems in question are so complex, it is difficult to predict all potential outcomes in advance.

The guidance documents provide recommendations on methods and what should be measured. In some cases, GMOs have been authorised despite the fact that they did not meet all of the requirements set out in the guidance documents. Within the EU there have been extensive discussions about whether the methods applied are adequate to measure the relevant factors, and also whether some of the recommendations may perhaps be unnecessary. Amendments have been proposed and the guidance documents have been updated intermittently.

Specific guidelines stipulate that GMO organisms must be studied in comparison to non-GMO organisms. This approach is based on the fact that non-genetically engineered plants have a history of safe use for humans and animals, while the biology of non-genetically modified plants is already known. For instance, when conducting an environmental risk assessment, a genetically-engineered plant must be compared to the nearest non-genetically modified related species in the same ecosystem conditions.

For the purpose of an environmental risk assessment, information may be obtained from field studies, descriptions of

the composition of the plant at a molecular level, descriptions of the nutritional content of the plant, ecotoxicological tests, modelling and/or literature reviews. A monitoring plan must also be prepared which can be implemented in the event that a GMO is authorised, in order to gather information about the consequences of its introduction. Furthermore, the guidance documents provide guidelines for what should form a basis for comparison, what kind of environment the GMO is introduced into, and long-term impacts.

Risk assessment of GMOs should comprise the following six steps:[117] 1) Problem formulation, including hazard identification, 2) Hazard characterisation, 3) Exposure characterisation (the exposure various organisms will be subjected to), 4) Risk characterisation, 5) Strategies for managing risk, and 6) Holistic evaluation of risk.

5.1.3. Risk assessment of organisms produced via genome editing and other new gene technologies under current regulations

Some international institutions have proposed ways of assessing health and environmental risks of GMOs produced via new gene technologies, without proposing how to regulate the technologies themselves. As previously described, a risk assessment comprises several steps, with an initial identification of any differences, after which one establishes whether these differences pose any potential hazards and then determines the risk, i.e. the probability that an undesirable event will occur, multiplied by the consequences.

In 2012 EFSA published a report on risk assessments of plants with new DNA introduced using site-directed mutagenesis (this report concerns technologies developed prior to CRISPR), and EFSA recommends that they should be assessed on the basis of existing criteria.[118] However, this report does not apply to plants where no new DNA has been introduced.

In a report from 2015, researchers from GenØk Centre for Biosafety likewise concluded that the same points should be included when assessing the risks posed by gene-edited organisms with mutations obtained using gene technology, so-called site-directed mutagenesis (CRISPR etc.) and oligonucleotide□directed mutagenesis (ODM).[119] It was furthermore pointed out that, given that the technologies in question are so new, and not all of the molecular mechanisms are known, the assessment of unintended effects entails a degree of uncertainty. It was recommended that a case-by-case assessment should be conducted of each organism together with a mapping of all of the genes, proteins etc. (so-called '-omics' methods: genomics, proteomics) in order to detect unintended changes. Other researchers are however of the opinion that organisms produced using gene technology present no greater risk than corresponding organisms produced via other methods.[18, 19, 36]

Researchers have pointed out that even though changes in the DNA are small, they may have significant impact, especially if a metabolic pathway is deactivated or is rendered more or less effective as the result of a change to an enzymes' ability to bind to other proteins.[120] It is also possible that a large genetic change will have little impact, depending on what kind of change it is. For instance, the duplication or inversion of segments of genetic material, which are events that can occur naturally, when using conventional methods or when using gene technology, can occur without obvious phenotypic effects.[121] There is broad consensus that the size of the genetic change does not determine the extent of the phenotypic effect.

As the technologies used for detecting differences evolve, it can also become possible to detect differences that hitherto have been undetectable.

The Norwegian Scientific Committee for Food and Environment (VKM), which is the Norwegian body that assesses the potential health and environmental risks posed by GMOs, has itself initiated a project entitled "Gene-edited organisms – potential consequences for food safety and biodiversity".[122] The project commenced in February 2018 and is expected to be completed in June 2019. The Norwegian Scientific Committee for Food and Environment will focus on what consequences gene-edited plants and animals used in food production may have for human and animal health, animal welfare and biodiversity. The project will focus on matters of particular relevance for Norway.

5.2 Assessment of sustainability, societal benefit and ethics

The Norwegian Gene Technology Act stresses that the production and use of GMOs covered by the Act must take place in an "ethical justifiable and socially acceptable manner", and "in accordance with the principle of sustainable development". GMOs must furthermore have no adverse effects on health and the environment. These are national requirements that are additional to the requirements set out in EU Directive 2001/18/EC on the deliberate release of GMOs into the environment. The Norwegian Biotechnology Advisory

Board has a particular responsibility to assess sustainability, societal benefit and ethical matters with respect to GMOs assessed under the Gene Technology Act. The regulations relating to impact assessment pursuant to the Gene Technology Act[123] set out a number of control questions that can be posed to applicants to enable the Norwegian authorities to assess whether a GMO complies with these three criteria. Furthermore, at the request of the Norwegian Environment Agency, the Norwegian Biotechnology Advisory Board has drafted guidance reports on how assessments of sustainability and societal benefit can be carried out. The report "Insect-resistant genetically modified plants and sustainability" was published in 2011,[124] followed by the report "Pesticide resistant genetically modified plants and sustainability" in 2013.[125] In addition, in 2018 the Norwegian Biotechnology Advisory Board completed an operationalisation of the assessment criterion societal benefit.[126]

As such, a key issue in this context is what useful products these new technologies can provide us with, and whether they can provide us with products of an equal or better quality than what is already available via alternative approaches. This may have a bearing on whether consumers will accept such products, and on future demand for these products. People are normally willing to accept greater risks and uncertainties provided that a product provides clear benefits to society or to the individual consumer.

Societal benefit assessments concern aspects particular to Norway and the near future. Both advantageous and disadvantageous effects should be assessed. Increased productivity, improved nutritional content, reduced levels of hazardous substances and increased shelf life are among the traits that can be more relevant than those of GMOs authorised to date. It is not simply a matter of what benefits the product will have for the applicant, the individual manufacturer or the consumer, but also how it will impact third parties.

In order to assess sustainability, it is necessary to broaden the temporal and spatial perspective of the assessment compared with that of a typical health and environmental risk assessment, and take into account societal and economic circumstances. This assessment will have a global and long-term focus. This will further entail assessment of conditions in the country in which the organism is cultivated, with a particular emphasis on issues of key relevance in a north/south perspective. Current issues may concern food safety, animal health and animal welfare, living conditions and profitability for farmers, living conditions and profitability in production areas, access to further breeding of plants and animals, property rights with respect to seeds, plant varieties and animals, coexistence, and freedom of choice for consumers.

The requirement that the production and use of GMOs should take place in an ethically justifiable manner may apply to changes which impact individual animals' welfare or integrity, species' integrity or matters of environmental ethics that impact the ecological balance or the relationship between man and nature. There may also be a focus on whether new technology/new products accord with prevailing values among the general public and take into account disadvantaged societal groups, or how these factors impact the distribution of power. This may apply to the properties, production and use of the product.

Assessments of sustainability, societal benefit and ethics are made on the basis of questions posed to the applicant concerning aspects deemed relevant to the product in this context. Additionally, if documentation on similar products is available, this should be utilised, along with any other available knowledge. However, the operationalisation of these assessments is not clearly defined, and is subject to discussion (see Chapter 10). Objections to these assessment criteria concern, among other things, the fact that the documentation necessary to facilitate a comparison of products may be difficult or impossible for the applicant applying for authorisation of a product to obtain.

5.3. Labelling, traceability and monitoring requirements

The king of Norway may issue regulations concerning the labelling of products consisting of or containing genetically modified organisms or products derived from cloned animals.

A regulation pursuant to the Gene Technology Act sets out the requirements for labelling, transportation, import and export of GMOs (Regulation of 2 September 2005 No. 1009).[127] This

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[iv] *Document-based traceability means tracking a product through all stages of the production and distribution chain via accompanying documentation.*

[v] *Detection/analytical traceability means tracking by means of methods for establishing the presence of a specific organism/product, in this context an organism which has undergone a genetic change obtained through the use of gene technology.*

requires that an authorised GMO product must be labelled indicating that it contains GMOs. Labelling must be provided either on the packaging unit or in the accompanying document or notice. Provided that the end product does not contain genetically modified organisms, there is no requirement for products manufactured using gene technology to be labelled. Examples of this are proteins or other substances that are produced from genetically modified bacteria. Processed foods and animal feed produced from GMOs where DNA is not present in the end product are covered by the Norwegian Food Act and must be labelled.[128]

The preparatory work of the Gene Technology Act specifies that, from a consumer point of view, it is primarily the health and environmental aspects of living genetically modified organisms that are relevant, while the method of production is not in itself a determining factor for the properties of the end product.[26] The aspect which is most often emphasised in current discussions on labelling is the consumer's and the farmer's freedom of choice, i.e. that consumers should be entitled to choose what kind of food they want to eat, or what types of farming they would like to support. However, it is unclear whether consumers perceive labelling as a warning about possible health and/or environmental risks, despite the fact that a key condition for a product to be authorised is that such a risk does not exist.[129, 130]

As a general rule food and animal feed is subject to the principle that the producer and seller of the product is responsible for ensuring that it is safe to consume. Traceability regulations for food production allow the manufacturer to be held accountable for their products. EU and Norwegian regulations stipulate requirements for the traceability of GMOs. This is laid down in Article 4 of Directive 2001/18/EC on the deliberate release of GMOs into the environment, which is incorporated into the EEA agreement and is binding for Norway, and in Regulation (EC) No. 1830/2003, which does not currently form part of the EEA agreement. These provisions require states to ensure document-based traceability,[iv] methods of detection (analytical traceability)[v] and the labelling of GMOs which have been authorised. Detection requirements do not however apply to GMO-derived products that do not contain DNA, such as oils from GMO plants, while traceability and labelling requirements do apply to these products. The impact assessment regulations pursuant to the Norwegian Gene Technology Act further stipulate requirements for information on monitoring plans, including methods for tracing the genetically modified organisms, monitoring of impacts and methods of detecting transfer of the introduced genetic material to other organisms. This makes it possible to validate hypotheses in an environmental risk assessment regarding potential adverse effects, to identify the incidence of any adverse effects and, in the event that any arise, to implement measures. However, detection requirements may be difficult to enforce with respect to many of the organisms produced by means of new gene technologies (see the discussion in Chapter 9).

In their regulatory guidelines for genetically modified food, the Norwegian Food Safety Authority makes a number of recommendations concerning documentation and documentation requirements for genetically modified food and animal feed on the Norwegian market. To date no GMOs have been authorised pursuant to the Norwegian Food Act. Given that a different situation pertains on the global market, the Norwegian Food Safety Authority states that when importing products manufactured from raw materials, a significant proportion of which (worldwide) comprise genetically modified organisms such as soya, maize and rapeseed, it is highly probable that genetically modified products will enter the Norwegian market unless businesses take specific precautions to prevent this. Businesses must therefore check the documentation that accompanies the raw materials in question and request information from the supplier on what procedures are in place to prevent the introduction of GMOs.

For this purpose, the Norwegian Food Safety Authority recommends the use of so-called identity preserved (IP) raw materials. This means that the manufacturers must be able to document that the raw material has been kept separate from genetically modified raw materials throughout the entire supply chain, i.e. during cultivation, storage, processing and production. There are no internationally prescribed rules for the content of raw material identity preserved systems, but the manufacturers stipulate such requirements as they deem necessary and assess the documentation, while the Norwegian Food Safety Authority verifies that the system is acceptable.

Various regulatory requirements apply to the monitoring of GMOs depending on whether the GMO product in question

is to be marketed or whether the release instead concerns e.g. field trials of a GMO, routine release of a GMO from contained use facilities, or disposal of GMO waste. Annex 3 (monitoring plan) of Section 13 of the impact assessment regulations123 sets out general principles for monitoring in addition to more specific requirements for the design of the plan itself. It is for instance stated that the monitoring plan must include a detailed assessment of each individual case. The plan must be drafted on the basis of the environmental risk assessment and take into consideration the characteristics of the GMO in question, the scope of its expected use and the specific environmental conditions in which it is expected to be released. General monitoring should be carried out and where necessary combined with more specific monitoring focusing on any adverse effects highlighted by the environmental risk assessment. With respect to specific monitoring, this should be carried out over a sufficient period of time to allow for delayed and indirect impacts to be detected. Existing routine monitoring procedures such as monitoring of agricultural cultivars can be employed. Further requirements set out in the Annex include the need for systematization of monitoring and for a clear division of responsibilities.

6. Alternative directions forward

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Given the ongoing discussions concerning which regulations should apply to GMOs, assessment of different regulatory options is timely. Relevant questions to consider include what is to be regulated and how, what ethical considerations are taken into account in various options and the implications the various options may have for society and the environment.

Regarding what should be covered by GMO regulations, there are three main options:

1. Retaining the current distinction between organisms produced using gene technology and those produced via all other methods (conventional methods)
2. Including currently exempt organisms/methods under GMO regulations
3. Exempting certain organisms produced using gene technology from GMO regulations

No less important than determining what is to be regulated is how it is to be regulated. A central matter is whether uniform overall authorisation/impact assessment requirements should apply for all organisms covered by GMO regulations, or whether a tiered framework is more appropriate. In order to determine this, it is first necessary to determine the purpose of a tiered system, what considerations are important, and what consequences the respective options will have. While the consequences may be small with respect to health and environmental risk assessments, they may prove to be significant when it comes to assessments of sustainability, societal benefit and ethics, or vice versa.

There is likewise a need for clarification of how much flexibility there is for adapting the authorisation requirements under the current regulations. For a more in-depth discussion of the flexibility in the Gene Technology Act and the EU's GMO regulations, see Chapter 11, 'Flexibility under current regulations'. If parts of the GMO regulations are to be amended, it will also be necessary to clarify whether these amendments should be made within the scope of the regulations with definitions (which organisms should be defined as genetically modified organisms, or what the regulations should cover if it should cover more than gene technology) or in the individual provisions of the laws.

The following chapters describe various options for differentiating the system for authorisation of various types of GMOs. Initially a description is given of the possibilities for differentiation under the current Gene Technology Act. Alternative proposals for tiered regulation that requires changes to current practice are then outlined.

7. Differentiation between different types of genetically modified organisms under the current Gene Technology Act

7.1 Differentiation for deliberate release via guidance documents

In principle the current regulations allow for differentiation between various types of GMOs, for instance via requirements for approval, impact assessment and labelling. No specific tiering of different uses of GMOs is stated in the law text, other than making a distinction between deliberate release and contained use. In practice there is a differentiation of risk assessment of, among other things, microorganisms and plants through provisions and guidance documents.

The impact assessment regulations of the Norwegian Gene Technology Act allow for differentiation between different types of GMOs, and it is emphasised that similar or the same amount of information will not necessarily be required in all instances, and that there may potentially be significant differences in terms of what information is required.

Sections 13 and 15 of the regulations refer to Appendix 1 on the content of the impact assessment, where it is stated that:

> *Not all the points included will apply to every case. An individual application shall therefore address only the particular subset of considerations that is appropriate to the specific case. The level of detail required in response to each subset of considerations is also likely to vary according to the nature and the scale of the proposed release.*
>
> *Future developments in genetic modification may necessitate adapting this Appendix to technical progress or developing guidance notes on this Appendix. Further differentiation of information requirements for different types of genetically modified organisms, for example single-celled organisms, fish or insects, or for particular use of genetically modified organisms like the development of vaccines, may be possible once sufficient experience with notifications for the release of particular genetically modified organisms has been gained in the EEA.*

EFSA has prepared guidance documents for risk assessment of genetically modified plants, microorganisms and animals. The guidance document for genetically modified animals also includes specific chapters detailing further specification of genetically modified mammals, birds, fish and insects. Guidance documents have also been prepared which do not relate to specific biological groups, but instead to other key matters. Examples are guidelines for the testing of animal feed and assessment of the allergenicity of plants. The guidelines set out detailed requirements for information that the applicant must provide. Norway – via the Norwegian Scientific Committee for Food and Environment (VKM) – also participates in the process of designing such guidelines, and VKM makes use of the guidance documents in its health and environmental risk assessments.

The risk assessment must address the matter of whether a GMO is detrimental to human and animal health or to the environment. The documentation submitted together with the application and the trials conducted must be sufficiently comprehensive to be able to answer this question. Not all of the guidance documents' recommendations concerning trials or data that need to be provided are relevant in all cases. The applicant should initially assess what is required on the basis of the guidance document, after which risk assessors and risk managers determine whether sufficient documentation has been provided in each individual case.

A differentiation of GMOs beyond what is stipulated in current legislation and practiced in EFSA's guidance documents may be made on the basis of a range of criteria. Differentiation criteria will include the nature and degree of genetic modification, various functional properties, ethical considerations and contribution to sustainable development, as well as risk factors such as the potential for dispersal. When it comes to differentiation on the basis of genetic modification, it is conceivable that the criteria will include degree of presumed risk and ethical considerations. For instance, fewer requirements might apply to organisms with genetic modifications that do not involve the insertion of foreign or artificial DNA than for organisms for which the modifications entail crossing of species

barriers or the insertion of artificial DNA sequences. As previously mentioned, functional properties/purposes comprise a further basis for the classification of GMOs. Thus, it is possible to apply different requirements for information required for a GMO with a particular potential for societal benefit which also contributes to sustainable development compared with an organism which does not have such qualities. Examples of this include disease-resistant plants and animals and plants whose cultivation properties have been adapted to cope with climate change. The question of which criteria are most suitable for the classification/differentiation of GMOs must be clarified in collaboration with relevant professional bodies.

The specific task of differentiating different GMOs under current regulations and via guidance documents might conceivably be carried out in a number of ways. One possible approach, where appropriate, is to carry out a preliminary classification of different types of GMOs. For instance, species which pose a proven/demonstrable risk of dispersal and species which do not present a likely risk of dispersal can be assigned to separate categories subject to specific requirements. Another example is gene edited organisms where no foreign DNA has been inserted. In these organisms, there is no inserted gene to investigate, and they can therefore be assigned to a category with fewer requirements than apply to other GMOs.

Another possibility is for guidance documents to clearly set out which requirements must be met in order to increase the likelihood that the application will be authorised. In other words, provided that the requirements are met, the applicant can expect approval of the application.

It is also possible to develop a system based around meetings between developers and authorities, where guidance is provided on which requirements will apply in order for authorisation to be granted.

All of these approaches – preliminary classification, clearly-stated requirements and a preliminary guiding statement – will serve to make the process more predictable and thereby ensure more appropriate use of resources on the part of the developer. As new knowledge and experience is acquired, a key task will be to revise guidance documents on risk assessments, together with associated information requirements.

7.2 Tiered system for authorisation of contained use of genetically modified organisms

One example of a tiered system of differentiation is the regulations governing contained use of genetically modified organisms. These include separate regulations governing plants, animals and microorganisms. All three groups are subject to tiered classification, albeit each according to different criteria. Specifically, a distinction is made with respect to the extent of the measures required to prevent the organisms from spreading outside of laboratories/greenhouses/livestock facilities. The question of whether approval should be required or whether notification is sufficient is likewise subject to differentiation.

The regulation on contained use of genetically modified plants provides for three tiered levels based on the plants' ability to establish themselves outdoors, their ability to disperse and their ability to discharge pollen.[132] The user must carry out a preliminary assessment of the risk of harm to people, animals, plants or the environment in the event of the organism establishing itself and dispersing outdoors and in an agricultural context. This preliminary assessment will determine which requirements for containment measures and containment levels apply. An assessment must also be made of societal and ethical aspects of the activity, with a particular emphasis on the purpose of the activity.

Regulations on the contained use of genetically modified microorganisms set out four levels or classes of containment according to the level of risk they pose:[133] 1) no risk or insignificant risk, 2) minor risk, 3) moderate risk and 4) major risk. With certain exceptions, classes 1 and 2 only require notification, while classes 3 and 4 require approval. The user must carry out a preliminary assessment of the risk of illness or harm to people, animals, plants or the environment, and on that basis classify the activity. When determining classification, it may be helpful to refer to Council Directive 90/679/EEC (on the protection of workers from risks related to exposure to biological agents at work) as well as to international or national classification systems such as WHO, NIH etc. The preliminary assessment determines which containment measures and containment levels are considered appropriate for protecting human and animal health and the environment. In some cases, it will be necessary to assess ethical and societal factors, as well as animal welfare considerations. All classes are subject to requirements for contingency plans, supervi-

sion, safety measures for waste management etc.

Regulations concerning contained use of genetically modified animals set out three categories based on the requirements for containment measures: a) vertebrates, b) invertebrates and c) aquatic animals.[134] The user must carry out a preliminary assessment of the risk of illness or harm to people, animals, plants or the environment. This preliminary assessment will determine what requirements for containment measures apply. In particular the applicant must assess societal and ethical factors, including factors relating to the genetic modification of vertebrates and the production and use of genetically modified animals for sale or use in foodstuffs, and in some cases animal welfare. Purposes and ethical aspects beyond animal welfare are to be assessed separately. Experimentation with genetically modified animals for scientific purposes, which is authorised under Section 13 of the Norwegian Animal Welfare Act,[135] is subject to a duty of notification. All other activities require authorisation.

8. A tiered system for approval also for deliberate release of GMOs?

A major international debate is currently ongoing about whether certain genetically modified organisms should be exempted from GMO legislation. This is particularly relevant where no new DNA has been introduced into the genetic material of an organism, such as point mutations obtained via genome editing technology and temporary, non-heritable changes. Proponents of such exemptions argue that, from a scientific perspective, such organisms are not likely to pose a greater risk than similar organisms produced in a conventional manner, nor to present greater challenges to sustainability, societal benefit and ethics. Reference is also made to the fact that current approval systems are time-consuming and costly for the manufacturer. A review of all GMOs which had undergone risk assessment in the EU in the period 1998 to 2015 indicated that the approval process took on average almost five years,[136] while two US studies indicate that the approval process alone cost manufacturers between 10 and 30 million dollars depending on the specific product and where the application was submitted.[137,138] Conversely, those who oppose the exemption of such organisms from GMO regulations believe that we have insufficient knowledge of or experience with the new techniques to be able to determine what risks they entail, what societal benefits or disadvantages they will result in, or what consequences they will have for sustainable development and ethical aspects.

An alternative solution is to introduce, to a greater extent than is currently possible under the Gene Technology Act, differentiated requirements for impact assessment and approval of deliberate release of GMOs according to a tiered model. This will help reduce costs and time spent on development and authorisation, while at the same time ensuring that the authorities largely retain oversight of products and can intervene when necessary.

Similar arguments were used when amendments were made to the Norwegian Nature Diversity Act's regulations on the release of alien organisms in 2014. This opened for a tiered regulation. According to the regulation relating to alien organisms (Regulation No. 716 of 19 June 2015) certain uses of specific alien organisms is permitted without assessment, in other cases authorisation is required, but for some uses of specific organisms a notification is sufficient. Notification is sufficient for contained use of some freshwater organisms, marine plants and fish in aquariums and of the buff-tailed bumblebee for the purpose of pollination in greenhouses. The notes on the regulation state that the notification system will provide the public authorities with oversight of the import or release of the organisms in question, and that it will provide an opportunity to conduct general environmental impact assessments and potentially impose different regulations and requirements.

By applying a similar line of reasoning, it may be possible to outline a differentiated approval system for the deliberate release of GMOs. However, it may be appropriate to avoid making these regulations too detailed, which would risk rendering the operationalisation of the provisions unwieldy or particularly difficult to grasp. At the same time, regulations should be sufficiently differentiated to provide different levels of control. It may also be appropriate to stipulate general principles of tiering in the Act, while specific criteria for the different tiers are detailed in accompanying regulations. This will facilitate easier and more rapid adaptation of regulations to new developments.

Some of the key issues discussed by the Board in what follows include:

- Should there be tiered assessements?
- How should sustainability, societal benefit and ethics be taken into account?
- Should the organism be labelled?
- Should different tiering systems be applied to e.g. plants, animals and microorganisms?

Tiering assumes that appropriate distinctions are made between various groups or classes, based on the type of genetic modification, the extent of the modification(s), the trait modified, the use of the organism, risk to health or the environment, sustainability, societal benefit and ethics and/or other criteria. If, in specific cases, circumstances warrant a more thorough assessement than what applies to the assigned class, there should be an option to reassign the organism to a higher tier. Furthermore, clarification is needed about what should trigger such a reassignment, and who makes such decisions.

The following chapters outline and discuss proposals for tiering at a general level. The various members of the Board have differing views on the model and the accuracy of the descriptive and normative elements it comprises. Individual members' views are specified in their recommendations (chapter 12).

The proposed tiering is based on what type of genetic changes have been made to an organism and a principle of equal treatment of similar organisms irrespective of production method. Type of genetic change here refers both to the extent of the change and the characteristics that result from the modification. The purpose is to adapt the risk assessment requirements to better reflect a presumed level of risk, thereby simplifying and facilitating a smoother authorisation process. Assessment of sustainability, societal benefit and ethics will be required on all tiers. This model retains the option for a case-by-case assessment by allowing impact assessment requirements to be increased when needed. The model allows for parallel assessment of health and environmental risk, sustainability, societal benefit and ethics in order to guarantee efficient processing of applications and ensure that the decision is reached on a holistic basis. This is in keeping with the intention behind the new administrative procedures for GMOs covered by the Gene Technology Act, which were established by the Norwegian Ministry of Climate and Environment in July 2017. The purpose of the new procedures is to ensure faster and more predictable assessment of whether an EU-authorised GMO should also be authorised in Norway.

8.1 Tiering on the basis of the specific genetic change

Tiering the regulation of genetically modified organisms can be done in several ways. One possibility is a three-tiered system, based on the presumed need for impact assessment.

Such a system could for instance be based on some 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 the use of genetic engineering in sustainable, socially beneficial and ethically defensible ways. An emphasis is placed on whether the genetic change could be obtained via other methods that are not covered by GMO regulations, and thereby the likelihood that the modification entails risks that are particular to gene technology, whether the changes can occur naturally, and taking sustainability, societal benefit and ethics into account at all levels of the model. The model sets out the following key tiering criteria:

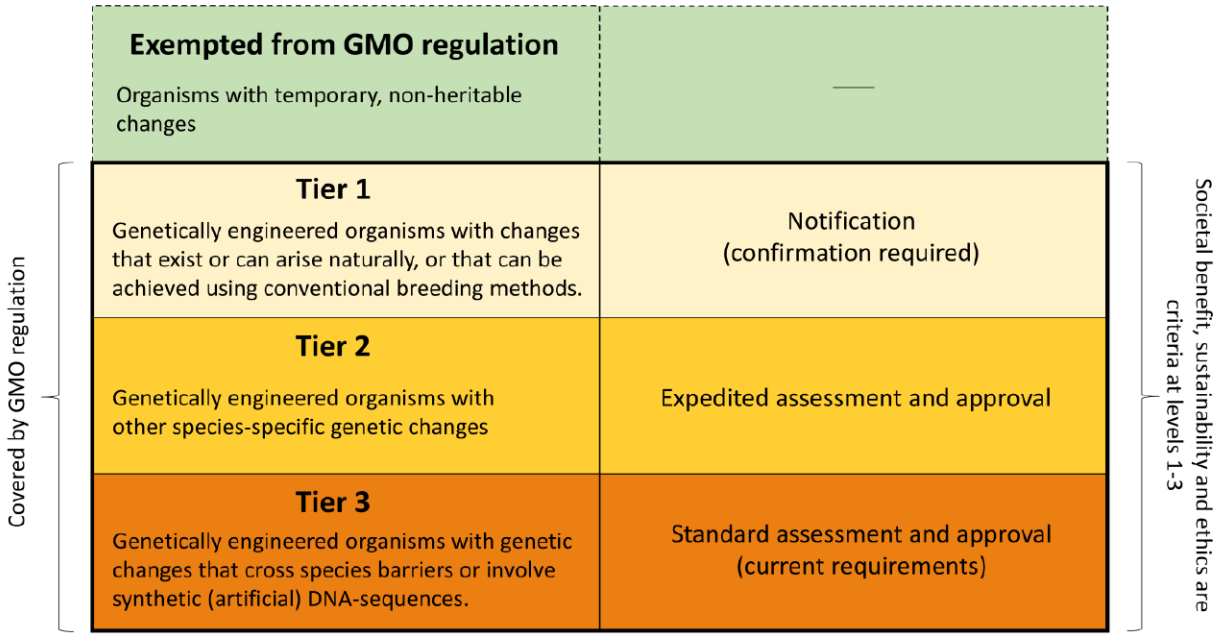

Figure 2: Example of principles of tiering based on the genetic change. In this example, regulation is triggered by the use of genetic engineering, but depending on the nature of the modification, the organism may not necessarily be covered by the Act or defined as a GMO.

- Whether or not the end product contains new DNA (novel traits).
- Whether or not genetic sequences from other species have been introduced (transgenes).
- Whether the modification has been made to body (somatic) cells or germ cells (i.e. hereditary).
- Whether the modification is permanent or temporary.

A precondition for tiering is the option of reassigning an organism to another tier at any given time if warranted by factors relating to the genetic modification, the trait or the organism.

Tier 0 / Exemption – Organisms with temporary, non-heritable changes.

Assuming that specific organisms covered by GMO regulations are to be exempted, the main criteria for this category could be that no new genetic material is present in the end product, irrespective of whether nucleic acids have been used in the production process, and furthermore that the modifications are temporary and non-heritable. The decision not to regulate fish vaccinated with the DNA vaccine Clynav as GMO is an example of this approach pursuant to current regulations.

In some cases, DNA has been introduced during parts of the production process without this resulting in permanent changes to the end product. Such organisms could be exempted from GMO regulations on the basis of the proposed criteria. One example of this is the fruit of plants that have been grafted onto a genetically engineered rootstock. It is highly unlikely that genetic material will have been transferred from the root to the grafted plant and thence to the fruit.[139,140] The rootstock itself will however be classified as a GMO. Another example is where new DNA has been temporarily integrated into the product or organism, and subsequently completely removed. One example of this is transgenes which are present during, and influence some aspects of, the plant's development but are not inherited through the germ cells.[141] Another example is a selectable marker (e.g. an antibiotic resistance gene) that has been inserted during the development of a plant, but subsequently removed.[142]

The Norwegian Biotechnology Advisory Board has previously recommended that, for these reasons, RNA- and DNA-vaccinated organisms should not be regulated by the Gene Technology Act (Figure 1/3 I and K). This is in line with the aforementioned decision of the Norwegian Environment Agency not to classify fish vaccinated with the DNA vaccine Clynav as GMO.[143] Along the same lines of reasoning, other methods for genetic modification may potentially also meet these criteria (e.g. certain forms of RNAi and epigenetic changes which are not heritable (Figure 1/3 C)).[vi]

Tier 1 – Organisms with changes similar to those obtained via conventional methods.

New gene technologies present a range of opportunities for making genetic changes that can also be obtained via other methods that are not specifically regulated, such as crossing or mutagenesis. If it can be documented that no off-target changes have arisen in an organism produced via gene technology, and the modified variant also exists naturally or would be possible to make using non-regulated methods, authorisation of the organism without a requirement for comprehensive impact assessment may be appropriate. The rationale for this is that any risks associated with two similar end products will largely be independent of the methods used to produce them. In cases where it is likely to be particular challenges relating to risk, sustainability or ethics, the regulations should allow the authorities to reassign the organism to a higher tier.

One example of this is organisms with point mutations[vii] which have arisen naturally or have been obtained via mutagenesis or gene editing (Figure 1/3 A). Gene editing has for instance been used to make pigs that are resistant to Porcine Respiratory and Reproductive Syndrome Virus (PRRSV),[85] oilseed rape which is resistant to pesticides of the class sulphonylurea,[108] and sterile salmon,[105] through small mutations. Another example is where one gene variant is substituted for another, either through breeding or via gene editing

[vi] *The consequences of temporary changes to gene expression through the use of nucleic acids do not fundamentally differ from those resulting from changes to gene expression through the use of chemicals, medicines etc. The hereditariness of changes to gene expression obtained via the use of nucleic acids will nonetheless vary. As such it may be difficult to generalise with respect to this category, given that heritability is one of the tiering criteria in the model.*

[vii] *In this context, the term 'point mutation' is used both for single base changes and for the deletion or insertion of a small number of bases (so-called 'indels'), all of which are common outcomes of both spontaneous mutations and conventional mutagenesis.*

(Figure 1/3 H). Dairy cattle with the polled gene variant that renders them hornless have been made via gene editing, and can also be obtained through traditional breeding.[104]

Nevertheless, it may be reasonable to require that the applicant documents which changes have occurred and accordingly that the organisms are reported to the authorities with accompanying documentation on intended and unintentional changes that have arisen. In contrast to what was previously the case, this is now relatively easy to do by means of genome sequencing. Self-assessments of health and environmental risk should also be required. Applicants should also give an account of relevant aspects related to sustainability, societal benefit and ethics. All documentation should be assessed by the regulatory authorities in order to ensure that the requirements have been met. The authorities may also base their assessment of all the criteria on other documentation, where available. For instance, in the case of organisms on tier 1 there may be a duty of notification with a confirmation of receipt required, but without any requirement for specific authorisation.

Tier 2 – Other genetic changes within the species

Gene technology can be used to obtain various types of changes in an organism's DNA. Examples include the removal of large segments of DNA (Figure 1/3 B), such as rice with a large chromosomal deletion where ten different genes involved in disease resistance have been removed,[144] or the insertion of genetic elements (genes, parts of genes or regulatory elements) that provide additional species-specific characteristics (Figure 1/3 F, G and L), such as potatoes with genes transferred from a wild potato that provides resistance to late blight.[145] In such cases it may be necessary to conduct a risk assessment for health and safety reasons. It would nevertheless be appropriate to lower the requirements in cases where DNA has been removed, or the introduced genetic material (giving both temporary and permanent, targeted and non-targeted changes) is derived from the same or a closely-related species (which has a different variant of the same gene), since species integrity is maintained and traits are already established. It is natural to assume that a simplified impact assessment will uncover whether such organisms pose significant threats to health and the environment. Such genetic modifications may also pose fewer ethical challenges than crossing of natural species barriers. Nevertheless, an assessement of sustainability, societal benefit and ethics should be carried out. Organisms on tier 2 may have simplified requirements for approval and impact assessment.

Tier 3 – Organisms with permanently introduced DNA from other species or synthetic (non-naturally occurring) DNA (transgenes)

In cases involving the permanent introduction of DNA from other species or synthetic (non-naturally occurring) DNA, current regulations and requirements for authorisation and impact assessment may be appropriate, irrespective of whether or not the insertion is targeted or not (Figure 1/3 D, E and J). For instance, it is currently mandatory to conduct field trials and to monitor how the organism behaves in and interacts, over time, with the environment into which it is introduced. One must also document that the changes are stable across multiple generations. Introducing novel genes that do not occur naturally in the species can warrant placement on tier 3 because there may be an increased risk to health or the environment, and/or because crossing species barriers may be more ethically challenging. This would apply both to transgenic organisms, e.g. plants with genes transferred from bacteria to make them tolerant to pesticides, and organisms obtained via cell fusion between different species. Gene drives will also be placed on this tier. A higher level of risk may warrant increased requirements for sustainability, societal benefit and ethics compared to tiers 1 and 2. Organisms on tier 3 may be subject to current requirements for authorisation and impact assessment.

An example of how such a model might look in practice is illustrated in Figure 3. Here, it is not the method applied that defines which tier an organism is assigned to, but rather the genetic change that has been made. For instance, an organism in which CRISPR is used to make a point mutation will be assigned to tier 1 (unless specific circumstances warrant a reassigment to a higher tier), while an organism in which CRISPR is used to insert a new gene that does not already exist in the species will be assigned to tier 3. There may also be other tiering criteria (see boxes 7 and 8).

8.1.1 Advantages and disadvantages of the model

There are both advantages and disadvantages to this kind of tiered model. One of the advantages of tiering in a similar way to that which currently applies to contained use of GMOs and the release of alien species is that the extent of the impact assessment and authorisation requirements may better correspond with expected risks and other relevant criteria. For instance, in most cases it will be reasonable to assume that a small number of targeted changes will entail a lower and more predictable risk than would be the case for random and substantial changes that impact large biological systems with multiple unknown, unintended effects.36 In cases where significant consequences can be expected to arise from small genetic changes, reassignment of the organism to another tier will be the appropriate course of action. The smaller the

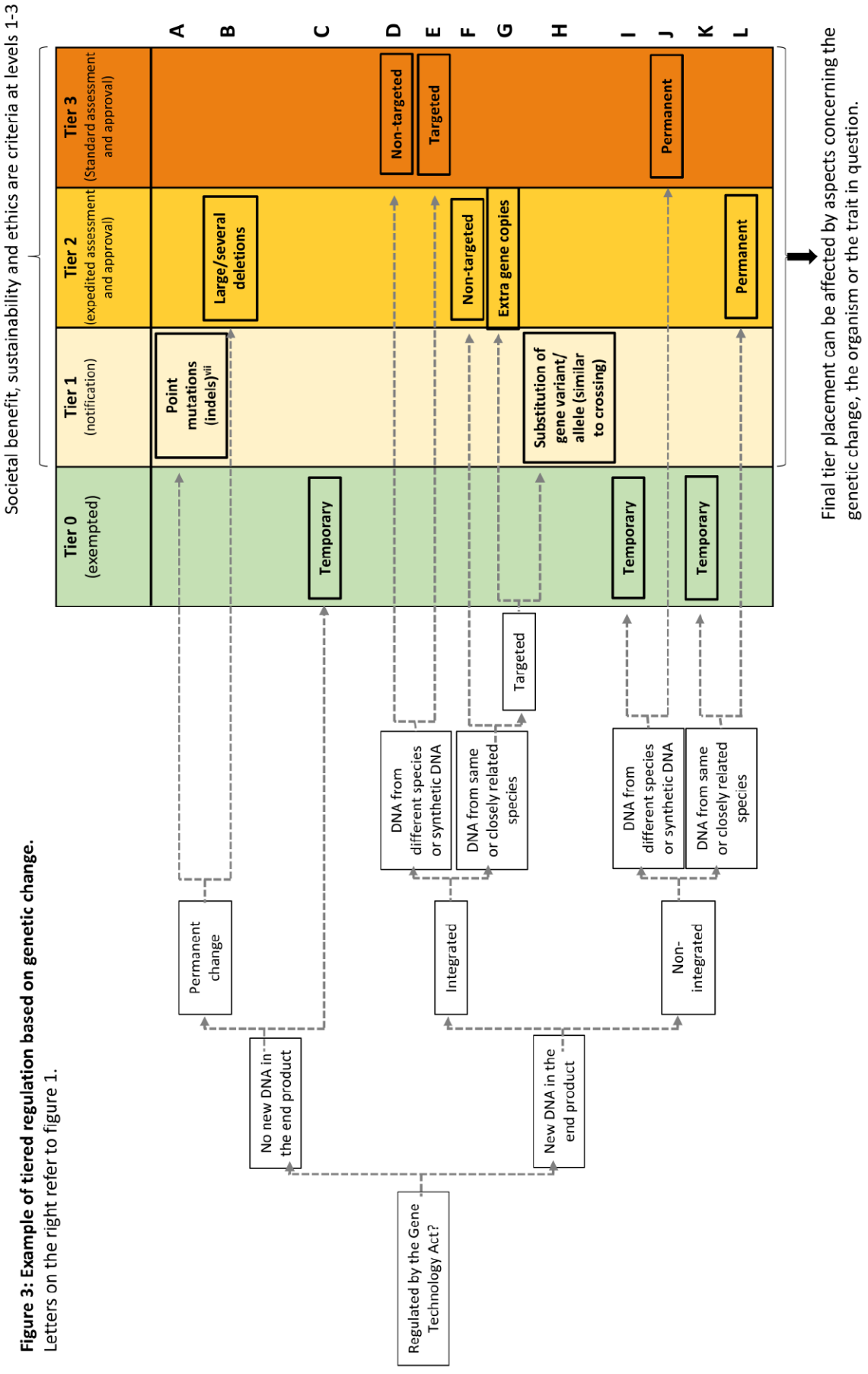

Figure 3: Example of tiered regulation based on genetic change.
Letters on the right refer to figure 1.

change, and the more targeted it is, the easier it will be to predict and assess the consequences. When the impact assessment or the genetic change itself become less predictable, there is a greater need for more comprehensive documentation and assessment. For this reason, it may be appropriate to limit duty of notification (tier 1) to organisms with minor/a limited number of changes, for which a preliminary assessment of the consequences is feasible. Nevertheless, a prerequisite for placement on tier 1 is, in all cases, that the organism/change can also be obtained via conventional methods[146] or can arise naturally.[147] This ensures that all organisms assigned to this tier are equivalent to those currently exempt on the basis of a "history of safe use". That a trait is already present in a species, and therefore known and already integrated into the ecosystems in question, also tends to reduce the level of risk. In this regard, a simplified risk assessment (for tiers 1 and 2) may be sufficient provided that a genetic change does not cross species barriers.

In the coming years, it is anticipated that many products will be developed, for which authorisation will be sought. Thus, it is essential to facilitate appropriate handling of applications.[4] A tiered system has the potential to save government resources, thereby ensuring that resources are directed to areas where the need is greatest. A similar rationale underpins the tiering of the regulation of release of alien species pursuant to the Norwegian Nature Diversity Act. Tiering also has the potential to provide developers of new products with a greater degree of predictability, something which is frequently a deciding factor when determining whether to invest in development and marketing. Hence, the threshold for adopting the technology could potentially be lowered, which might facilitate more societally beneficial and sustainable products. The criteria sustainability, societal benefit and ethics will apply to all levels of the model (tiers 1-3), and will be subject to assessment by the authorities that receive the application. A tiering approach which includes a notification as a minimum requirement will ensure that the authorities have a comprehensive overview of all products, and safeguards the principle of a case-by-case assessment. This also facilitates implementation of measures to limit damage in the event that an organism or product were to result in adverse consequences, as is currently possible according to sections 20 and 21 of the Gene Technology Act, and also for alien species regulated by the Norwegian Nature Diversity Act and all foodstuffs according to Section 11 of the Norwegian Food Act. This approach could strengthen public confidence more than exempting such organisms from the regulations.

The principal rationale for the government's recent adoption of new administrative procedures for the assessment of GMOs in Norway was to streamline and simplify the process. In short, this means that the Norwegian authorities now only assess a GMO once, and in parallel to the process in the EU. This allows Norway to make decisions on cases immediately after the EU. It is emphasized that this will save considerable resources and time during the processing of applications in Norway. Tiered assessments will be possible to conduct within the proposed deadlines, and could potentially further simplify and streamline the process.

Compared to the current situation, tiering will imply a relaxation of the approval requirements for products on the lowest tiers. Regulations in EU and Norway are based on an intent to regulate new technologies with which we have little experience, and require that the precautionary principle should be applied. Accordingly, an evaluation should be made of whether not carrying out a full risk assessment of plants and animals produced via methods with which we have little experience is in line with the purpose of the regulations and with the precautionary principle. Another question is whether a notification or expedited impact assessment inspires sufficient public trust.

A further challenge posed by a tiered system is that the number of factors to consider in order to establish whether the organisms should be reassigned to another tier can become so large that it begins to resemble a standard case-by-case assessment. This may in turn render the process less predictable. Assuming that a tiered system is deemed appropriate, it will be necessary to set out clearly defined criteria for how to classify each GMO, together with specific requirements for impact assessment and risk evaluation on each tier. Among other things, defining which genetic changes can occur naturally – which is a proposed criterion for tier 1 – may prove difficult. For instance, transferring genes between species (using gene technology) should be placed on tier 3, despite the fact that the transfer of genes between species can also occur naturally. Here, we assume the same understanding of naturalness that currently underpins EU GMO regulations, i.e. genetic changes arising through natural breeding or natural recombination without the use of gene technology. Determining the dividing line between tiers 2 and 3 may potentially also prove challenging, given that species boundaries are not always clearly defined. Box 7 (fewer tiers) discusses possibilities for simplifying tiering by reducing the number of tiers.

Additionally, from a risk perspective, classification according to type of genetic change may prove challenging. A number of factors make it difficult to establish predefined levels of requirements: Potential risk to health and the environment will depend on both intended and unintended changes, the genetic background of the modified organism, whether the organism in question is a plant, an animal or a microorganism, and the environment into which the organism is to be released. Furthermore, the ethical challenges may not necessarily

correspond to the proposed tiers. These are aspects that could potentially be used as arguments for an alternative or more detailed approach to tiering (see Box 8 (further differentiation)).

In order to ensure sufficiently flexible regulations, it may be appropriate to have the tiering principles in the Act itself, while specific criteria for different tiers are detailed in supplementary regulations.

The question is whether or not the benefits of introducing a tiered system outweigh the disadvantages, and whether aspects relating to public health, the environment, societal benefit, sustainability and ethics are sufficiently addressed. It will be essential to conduct a thorough and weighted evaluation of the advantages and disadvantages of tiering.

BOX 7: FEWER TIERS

One of the challenges posed by the three-tiered model is that it can become too unpredictable or complex, or there may be difficulties in establishing clear distinctions between tiers. One alternative approach is to further simplify the system by decreasing the number of tiers to two.

One option is to merge tiers 2 and 3, i.e. all changes that do not occur naturally or which cannot be obtained via conventional methods (as illustrated under a) in the figure below). This way, the challenge of clearly defining species boundaries can be circumvented.

Another option is to only differentiate between genetic changes that already exist within the species (which therefore theoretically can be crossed into the organism), and all other changes (as illustrated under point b) in the figure below). Such a model was proposed by several Norwegian breeding organisations during the public consultation. They did however argue that the requirements for impact assessment on the highest tier should be lower than they currently are.

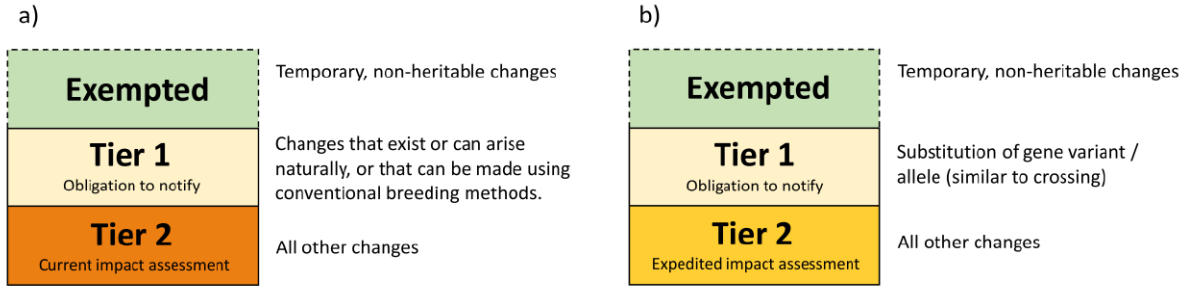

Figure 4: Examples of tiered regulation with fewer tiers.

8.1.2 Approval or obligation to notify

Introducing a notification and self-declaration system (tier 1) may lead some developers to argue for a lower classification than what applies to a specific product. The intention may be to avoid having to conduct trials that demonstrate how a GMO behaves in the environment into which it is to be released, or trials that indicate whether the consumption of a GMO poses a health risk to humans or animals. By documenting that the entire DNA sequence of the organism has been mapped, the developer may argue that the trait is known and tested, or that the gene variant is known from similar organisms (e.g. a close genetic relative), and as such has already been trialled and has a history of safe use. The manufacturer must also give an account of factors relating to sustainability, societal benefit and ethics (see Chapter 11), which will determine whether the notification requirements have been met. Legislative frameworks and associated regulations must clearly state what documentation must be included in the notification and which organisms qualify. Competent authorities, according to their defined areas of responsibility, will then determine whether the notification is complete (the Norwegian Food Safety Authority or the Norwegian Environment Agency on the recommendation of the Norwegian Scientific Committee for Food and Environment and the Norwegian Biotechnology Advisory Board). This will be in line with the new administrative procedures for applications under the Gene Technology Act as specified by the Norwegian Ministry of Climate and Environment in summer 2017.[149] An obligation to notify implies that the notification is made public pursuant to the Norwegian Freedom of Information Act/Environmental Information Act, a public consultation will probably not be feasible.

Various types of notifications exist: (i) notification without

BOX 8: FURTHER/ALTERNATIVE DIFFERENTIATION

While certain principles concerning the genetic change form the basis of a general tiered model (Figure 2), it may be appropriate to consider additional differentiation criteria for impact assessment requirements. For instance, different classes of organisms may pose very different challenges.

Potential for spreading or gene flow in the environment

A relevant aspect in this context is the organism's potential for spreading to the environment and the probability of it mating with related wild species and thereby introducing new gene variants into the ecosystems. Microorganisms and insects (and similar taxonomic groups) largely comprise species that have the potential to spread in the environment in a rapid and uncontrolled manner. Accordingly, one option is to place all genetically engineered microorganisms and insects on tiers 2 and 3, where approval is required before release can take place. In these cases, all genetic changes within the species (or closely related species), including those that correspond to changes that can be made via conventional methods or which are naturally occurring, will as a rule be assigned to tier 2. Changes that cross species barriers or involve the introduction of synthetic DNA sequences will be assigned to tier 3.

Animals and plants, which generally present a lower risk of spreading to the environment than microorganisms and insects, may generally be classified in accordance with the fundamental principles of tiers 0, 1, 2, and 3. This will apply to many crops conventionally grown in Norway such as potato plants, grain crops, fruit trees, etc. as well as livestock such as cattle, pigs and poultry. By contrast, specific varieties/species/families that pose a high risk of spreading to the environment may be classified according to the same principles as microorganisms and insects. Examples of this include rapeseed or grasses, both of which easily spread in the environment. The same may apply to marine organisms, including fish and other marine animals, unless they are sterile and thus not able to interbreed with related wild species in the event of deliberate release or escape from aquaculture facilities. Genetically engineered species that are not already present in Norwegian ecosystems (alien species), for which the risk of spreading and impact on local ecosystems are unknown, can also be placed on tier 2 or higher. GMO medicinal products, which contain genetically modified organisms to be used for medical treatments, should however be considered subjected to separate regulations (see statement).[1]

Experience of use

Experience with different types of changes, technologies and products may over time result in the gradual adjustment of classification practice. One option is to place organisms with changes similar to previously authorised GMOs on tier 1 where they are subject to a notification. For instance, a cis-genetic late blight resistant potato variety (with resistance genes transferred from wild potato) may be subject to notification provided that another late blight resistant potato with similar genetic changes has already been approved (originally on tier 2). This builds on similar principles as regulation of so-called "biosimilar medicines", where a medicine with very similar mechanisms of action as an already authorised medicine is authorised on the basis of existing risk assessments.[148]

Ethical defensibility

Another means of differentiation is to make a preliminary assessment of ethical aspects of a GMO, which is then used to determine the scope of the risk assessment the organism will be subjected to. If the product is not ethically defensible, the application may be rejected without any risk assessment. See Annex 1 for further details.

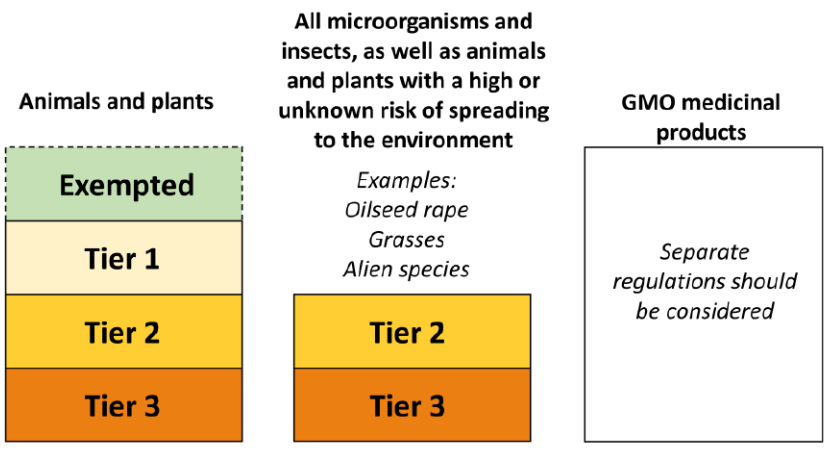

Figure 5: Example of additional differentiation based on potential for spreading to the environment

receipt required before the action can be implemented, (ii) notification with receipt required before the action can be implemented (the receipt confirms that the conditions for notification have been met), or (iii) notification with the option of imposing ad hoc requirement for approval should the authorities consider this necessary.

With respect to contained use of genetically modified animals, the sender may implement the activity immediately after submitting the notification provided that approval has been granted pursuant to Section 13 of the Norwegian Animal Welfare Act concerning use of animals in clinical trials. The authorities do however have the option of requesting further information if deemed necessary.
Provisions concerning notification for contained use of microorganisms of classes 1 and 2 are specified in the regulation on genetically modified microorganisms:

> *Once the competent authorities have received a notification or application, they should investigate whether*
> *1) the notifications/applications comply with the requirements set out in the regulation,*
> *2) the information submitted is accurate and complete,*
> *3) the preliminary assessment and the contained use class are correct,*
> *4) the containment measures, other precautionary measures and waste and emergency measures are adequate.*
>
> *If necessary, the competent authority may ask the user to provide supplementary information, to change the conditions surrounding the planned contained use, or to reassign the enclosed use to another class. In such cases, the competent authority may require that any scheduled contained use is postponed, or that contained use which is already underway is temporarily suspended or terminated until the competent authority has given its consent on the basis of the submitted supplementary information or changes to conditions surrounding the contained use.*
>
> *Once the certifying authority has received the information required in order to certify that the assessments and the information are complete and correct, the certifying authority will confirm the receipt of, or request the submission of, a complete notification or application.*
>
> *If the competent authority subsequently receives information that may have a significant impact on the risks of the contained use, the competent authority may require the user to change the conditions of the contained use, or temporarily suspend or terminate it.*

The handling of notifications for release of alien species under the Norwegian Nature Diversity Act is based on the same principles as that of contained use of genetically modified organisms.

Certain specific measures regulated by the Norwegian Nature Diversity Act are subject to an explicit requirement that the sender must have received feedback before implementing the activity, and the authorities have the option to change the conditions of the activity if this is deemed necessary. One example of this is agricultural activities:

> *Section 55. (duty of notification for agricultural measures)*
> *Agricultural measures that impact selected natural habitats and which do not require authorisation must be reported to the municipality before the measure is implemented. Prior to implementing the measure, feedback from the municipality must have been received. The municipality must assess the measure pursuant to the provisions set out in paragraphs 2 and 3 of Section 53. If the municipality considers that the measure may result in the deterioration of the extent and ecological condition of the natural habitat, the municipality may refuse the measure or lay down more specific instructions concerning how the measure is to be implemented pursuant to Section 11(1) of Act No. 23 of 12 May 1995 relating to Land (the Soil Conservation Act).*

Similarly, one argument for proposing a notification system for the deliberate release of certain genetically modified organisms, rather than exempting them from the regulations, is that the authorities maintain overview and control and the option to change classification. In the same manner as for certain activities regulated by the Norwegian Nature Diversity Act, it may be stipulated that, prior to release, the user must have received feedback from the authorities. If all organisms that qualify for notification are to be automatically authorised for release unless otherwise reported, i.e. if no feedback is required, it may be appropriate to impose a delay / time limited moratorium (e.g. 30 days) on the release. This will serve to ensure that the authorities have sufficient time to assess whether a GMO has been correctly classified and, where applicable, inform the sender of any decision concerning reassignment to another tier. For instance, reassigning an orga-

nism to a higher tier is appropriate if the authorities consider that the organism does not in fact meet the requirements for a notification, or if other circumstances warrant a more thorough assessment (see Box 9 for examples).

With respect to research and use of higher animals, particular ethical considerations must be taken into account. Section 25 the Norwegian Animal Welfare Act prohibits breeding, including via gene technology, which (i) alters the animal's genetic material in a way that negatively impacts its physical or mental functions, or that passes on such heritable traits, (ii) reduces animals' ability to exercise natural behaviour, or (iii) invokes ethical objections in the general public. Furthermore, Section 10 of the Regulation on Animal Experimentation stipulates approval requirements for all research, including applied research, involving higher animals. The purposes for which animals may be used in applied research are limited to (i) avoiding, preventing, diagnosing or treating disease, poor health or other abnormal conditions or their impacts, in humans, animals or plants, (ii) evaluating, demonstrating, adjusting or altering physiological conditions in humans, animals, or plants, or (iii) improving animal welfare, including the conditions under which livestock are produced. This includes research on animals produced using gene technology. A notification system has already been imposed for the contained use of genetically modified animals in research provided that the use has been approved under the Norwegian Animal Welfare Act. Approval under the Animal Welfare Act may also be an appropriate precondition for notifications of release of genetically modified animals on tier 1.

8.1.3 Documentation requirements/terms for different tiers

Documentation consistent with the assigned tier should always be provided when specific organisms are to be exempted from approval requirements, or where simplified requirements for approval and impact assessment apply. The requirements for such documentation must be sufficiently comprehensive to ensure that the classification of the organism and the corresponding impact assessment is appropriate. For instance, genome sequencing or other equivalent relevant methods should be mandatory at all levels in order to demonstrate which intended and unintended changes have arisen. A description of production methods used and novel or altered traits should also be mandatory. However, which aspects are relevant to investigate should be carefully evaluated since it can be difficult to distinguish between natural genetic variation and unintended changes that may have resulted from the production method. For example, a scientific paper that demonstrated that CRISPR could cause thou-

BOX 9: EXAMPLES OF THE REASSIGNMENT OF GENETICALLY MODIFIED ORGANISMS TO A DIFFERENT TIER

One possible reason for increasing requirements for assessment and approval is a suspicion of potential health risks. Gene editing can for instance be used to make small genetic changes in potatoes, such as point mutations, which may affect the amount of acrylamide formed when the potatoes are exposed to high heat. Acrylamide is potentially carcinogenic when consumed in large doses. By introducing an inactivating mutation into the gene, it is possible to lower the amount of acrylamide, thereby providing a health benefit. In contrast, mutations that have a reasonable likelihood of increasing gene activity pose a potential health risk. On the basis of the genetic modification, both would be assigned to tier 1 in the proposed model. In the latter case, however, a more thorough assessment and stricter requirements for authorisation would be appropriate, as would reassignment of the organism to a higher tier.

Another example of a factor that may prompt reassignment to a higher tier is a high risk of spreading in the environment – either because a genetic change is likely to impact the organism's potential for spreading or because the organism is a plant which spreads very easily in the first place. Another example is a genetic change that increases the organism's competitiveness in other ways. It may be desirable to assess such cases more thoroughly and require specific approval. Likewise, increased tolerance to pesticides may necessitate a more thorough assessment, especially in cases where the change in question may result in significant changes to agricultural practices or pose increased health risks. The accumulated impacts of releases over time can also necessitate an assessment of the genetic modifications in a wider context, and therefore a reassignment of an organism to a higher tier.

In some cases, it may also be appropriate to reassign an organism to a lower tier. For instance, a genetic deletion assigned to tier 2 may, in practice, be expected to have the same impact as a point mutation on tier 1. In some cases, products may be expected to be very similar to other, previously assessed and approved organisms, in which case it may be appropriate to reassign the product to a lower tier. This could potentially save resources for both the developer and the authorities.

sands of unintended DNA cuts in mice was later retracted because of major methodological weaknesses and conclusions that the findings in all likelihood were the result of natural genetic variation.[150] Another example is the use of various -omics technologies, which are able to measure variation in a range of biological parameters, in order to study the effects of genetic changes. One challenge in this context is that gene expression can potentially vary widely from organism to organism irrespective of any genetic changes made. A meta-study that evaluated 60 relevant research papers concluded that gene expression is affected to a much larger extent by traditional crossing than by genetic modification, and furthermore that much of the variation can be attributed to environmental factors such as geography, sampling time and agricultural practices.[151] It is therefore uncertain whether such data are meaningful in the context of risk assessment.

Documentation and requirements for impact assessment must be specified for each tier when a tiering model is to be operationalised. These requirements must be defined and drafted by competent authorities. This task lies outside the mandate and competence of the Norwegian Biotechnology Advisory Board. Nevertheless, some general options are outlined below, and in greater detail in Annex 2.

Tier 1 (Notification):
On this tier, required documentation may include information on the methods used, which genes/traits have been changed, intended and unintended changes, the specific organism that has been modified, the environment into which the organism is to be released, and experimental data, where available. A self-assessment of health and environmental risks, sustainability, societal benefit and ethics should also accompany the notification.

The information provided must be sufficiently comprehensive and detailed to fulfil the conditions for classification. The more information is available, the greater the likelihood the classification/tier will be upheld. Prior to release the sender must have received feedback from the authorities confirming that the requirements have been met. If the conditions are not fulfilled or circumstances have come to light that warrant a more thorough assessment, the organism will be reassigned to a different tier.

Tier 2 (expedited impact assessment):
Stricter documentation requirements apply for tier 2 than for tier 1, and the application must be approved by the authorities prior to release. However, it may be appropriate to limit the requirements for tier 2 compared with tier 3, given that no new dominant traits that are not already present in the species or closely-related species are introduced. Requirements for field trials and toxicity testing, as well as documentation requirements for specific release conditions and recipient environments could potentially be lower compared to requirements for organisms on tier 3.
If a genetic change assigned to this tier may reasonably be expected to result in specific risks that will not be sufficiently addressed in an expedited assessment, additional requirements may be imposed, or alternatively the organism may be reassigned to tier 3.

Tier 3 (current requirements for impact assessment):
Generally, an impact assessment of a GMO must currently include information and documentation on a range of aspects related to health and environmental risk, societal benefit, sustainability and ethics. In the tiered model, the same requirements will apply to organisms on tier 3, where DNA sequences not previously established in the species or a closely-related species have been introduced. Both the impact assessment regulations of the Gene Technology Act and EFSA's guidelines include requirements for the content of environmental and health risk assessments. The impact assessment regulations of the Gene Technology Act also set out control questions that the applicant can be asked in order to clarify the product's impact on the criteria societal benefit, sustainability and ethics. Guidance documents for these criteria have also been prepared (see also chapter 5.3).

9. Challenges posed by current labelling, traceability and monitoring requirements

Regulatory requirements for labelling, traceability and monitoring of genetically modified organisms are summarised under chapter 5.3. One of the most central aspects in discussions on this subject is the consumer's right to choose. In order for consumers to be able to make informed decisions they require access to relevant information about the product. Labelling, traceability and monitoring are also important means of ensuring accountability and the option to intervene in the event that something goes wrong.

In the 1990s, when GMO regulations were drafted, the possibilities of genetic engineering were limited, and mainly involved transferring large fragments of DNA to an organism. The many nuances made possible by new gene technologies such as gene editing and RNA/DNA vaccines may warrant a re-evaluation of what should be labelled and the content of the label.

Studies indicate that many consumers are sceptical of genetically modified food. However, consumers are more positive when the products in question contribute to more environmentally friendly agricultural production,[110] and do not involve crossing of species boundaries that does not occur naturally.[54] Currently, all production and use of genetically modified products is assessed on the basis of its potential health and environmental risks. Any future relaxation of the labelling requirement must ensure that consumers can trust that the product is safe to eat and does not pose a health risk. Other aspects that are important to consumers include environmental considerations, ethics and sustainable development. The general labelling requirement that currently applies only indicates whether gene technology has been used in the making of the product, but does not provide any information on what genetic changes have been made, health or environmental risks, sustainability, societal benefit or ethical aspects, all of which will vary from product to product. Nor will general labelling reveal anything about the type of gene technology or method used. For example, attitudes to a plant that is pesticide resistant may be very different than attitudes to a plant that has an improved nutrient content. Furthermore, it is unclear whether consumers would want information on e.g. the absence of parts of a gene or temporary insertion of DNA that is not present in the final product. Consumers may also prioritise other considerations. The question then is whether or not labelling is helpful and whether it is possible to tailor the scheme to reflect these nuances and ensure that the consumer is provided with relevant information. Labelling has the potential both to mislead and inform the consumer. The potential for labelling to be mistakenly interpreted as a warning of potential health or environmental risks is therefore a key issue. The Norwegian Food Safety Authority considers it generally misleading to claim that a foodstuff does not contain a given ingredient that the foodstuff in question does not typically contain or that is not permitted for use in the product.

Labelling may impact whether gene technology will be prioritised in the development of new products. Labelling of genetically modified plants and animals currently acts as a deterrent to commercial investment in gene technology due to fear of consumer scepticism.[152] These issues have been highlighted by the European Plant Science Organization (EPSO)[153] and in a report produced by the Nuffield Council, an independent bioethics advisory body in the UK.[154]

Another key question is whether it will be possible to comply with the provisions concerning detection (analytical traceability) with respect to organisms produced using new gene technologies. Current methods of detecting GMOs are based on demonstrating the presence of introduced/modified DNA. In principle, any genetic change can be detected provided that the DNA sequence in question is known, and the genetic variant is not already present in the species/varieties/individuals with which the organism is compared. For instance, if changes made with gene editing and other methods or those already present in the variety/species are indistinguishable, definitive detection will be impossible and the labelling requirement more difficult to enforce. It will likewise become increasingly difficult to comply with monitoring requirements if it is not possible to demonstrate whether or not a given genetic change originated from a GMO. These issues are also highlighted in a technical report

produced by the European Commission's internal Joint Research Centre (JRC).[155] The JRC states that enforcing GMO regulations is a very difficult matter with respect to gene edited crops, and that gene edited products will make it more difficult to maintain zero tolerance of unauthorised GMOs on the European market. The JRC states that detection of both minor genetic changes affecting one or a small number of base pairs and of more extensive changes is difficult to manage. The report also emphasises that challenges associated with detection may also impact the clearance time for food and feed for entry into the EU.

The difficulty of demonstrating the origins of a genetic change also applies to a number of products currently produced from GMOs that do not contain DNA, such as oil from rapeseed and soy. In such cases, detection requirements within the EU apply to the genetically modified organism from which the product is derived, while document-based traceability is sufficient with respect to the product itself. Similar rules apply in Norway.[131]

Comprehensive document-based tracing systems already exist. One example is an identity preserved system (IP system), as described in Chapter 5.3. This system has been developed by the industry itself, and in the context of GMOs is used to ensure that products are GMO-free. The IP system is based on the requirement that the identity of a product must be verified throughout the entire production and distribution chain, from seed to final processed product.

Detection can be guaranteed by introducing a "genetic watermark" in the organisms DNA. This approach was first proposed in the 1990s. At that time most stakeholders agreed that it was an inappropriate solution which would involve more extensive genetic modification of each organism, contrary to the aim of ensuring that modifications made are as targeted and limited as possible. The introduction of such a requirement will facilitate easier detection of GMOs, but will in practice increase the uncertainty about risk. It would also mean that certain gene editing methods cannot realistically be used. Firstly, inserting DNA is technically more difficult than making point mutations, which will result in a substantially reduced success rate, particularly in certain types of organisms. Secondly, inserting DNA into a gene – which is necessary in order to ensure that the traceable watermark does not segregate from the genetic change during further crossing/breeding – can potentially render the gene non-functional. An additional modification can potentially also result in further unintended changes.

The question of whether traceability and labelling is considered a necessity for all organisms covered by GMO regulations will depend on the weighing of costs and benefits. The alternative to uniform requirements is to make exemptions or introduce a differentiated system. Traceability requirements can be differentiated according to what is technologically feasible. For instance, the detection requirement could be limited to products with genetic changes that can be definitively detected. Alternatively, document-based traceability could be required irrespective of whether the changes can be detected, as currently applies to all food products.

Requirements for traceability, but not detection (analytical traceability, is laid out in Section 11 of the Norwegian Food Act and its regulations which follows from EU Regulation (EC) No. 178/2002, by which Norway is bound. This requirement is intended to ensure that any product can be traced, both on the market and with respect to is origin, in the case of serious health problems. This requirement applies to all products, including products not regulated as GMO. For instance, if it is demonstrated that a foodstuff contains pathogenic bacteria, steps can be taken to remove the product from the market on the basis of production and distribution documentation.

Norwegian and EU GMO regulations require that genetically modified organisms are monitored in order for them to be authorised. There are specific requirements for the contents of a monitoring plan. This way it is possible to map the consequences of the release and implement measures in the event of adverse effects. Monitoring is however dependent on the ability for detection and traceability. In cases where it is not possible to distinguish a gene edited organism from other organisms, enforcing provisions for monitoring becomes challenging. When detection (analytical traceability) is not possible, document-based traceability may prove essential for monitoring GMOs.

However, labelling, traceability and monitoring is not just a technical issue, but also a political one. In the spring of 2017, the Standing Committee on Business and Industry of the Parliament of Norway (Stortinget) made a recommendation that gene edited organisms should be regulated by the Gene Technology Act and should not be authorised until it can be guaranteed that they are traceable and therefore can be monitored.[83] The recommendation provides no details on what type of traceability should be required.

A further challenge to labelling, traceability and monitoring

are the varying definitions of GMOs used in different parts of the world. For example, gene edited plants to which no new DNA has been added are defined as GMOs in Norway and the EU but not in the United States. Enforcing provisions on labelling, traceability and monitoring for such imported products will be a highly demanding task for the EU given that US legislation does not require documentation of how such products are made. This may also have implications for international trade agreements (WTO).

9.1 Differentiation of labelling, traceability and monitoring requirements?

Generally, there are several ways to differentiate requirements for labelling, traceability and monitoring of different GMOs within a tiered model.

9.1.1. Tiered labelling requirements

There are various approaches to tiered/differentiated labelling. For instance, it is possible to:

- Provide information on what trait has been modified and any benefits to the product
- Provide information on what technology has been used to make the product
- Make a terminological distinction between gene edited and genetically modified products
- Employ a system of colour-coding by tier
- Label the product with a neutral QR code via which those interested can obtain information on the product

model. Such information allows detection of GMOs provided that the gene variant is not already present in the species/other products. However, it is not possible to establish with certainty that an organism on tier 1 has been produced using gene technology given that, by definition, such changes can also occur naturally or be obtained via conventional methods. As such, one alternative is to limit the requirement to document-based traceability on tier 1. By contrast, organisms on tiers 2 and 3 may be subject to a requirement for availability of detection methods. Derogation from this requirement may be considered for organisms on tier 2 which in exceptional cases prove to be indistinguishable from other products, provided that the applicant can present convincing arguments for doing so.

9.1.3. Tiered monitoring requirements

Tiered requirements for monitoring and containment is currently applied to the authorisation of GMO field trials in the Netherlands. As further evidence becomes available that a GMO poses no threat to health or the environment, the requirements decrease. Similarly, requirements for monitoring and containment can increase gradually from tier 1 to tier 3 in the tiered model. Given that organisms on tier 1 are not considered to pose a greater risk than equivalent organisms produced via other methods, the need for monitoring and containment may be limited. In the case of organisms on tier 2, where risks can be more unpredictable, the need may be greater. However, since these organisms have no new dominant traits, the need may be lower than on tier 3.


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10. Sustainability, societal benefit and ethics

When assessing GMOs under the Gene Technology Act, Norway places an emphasis on sustainability, societal benefit and ethics, as well as health and environmental risk. For cases involving deliberate release of GMOs, the authorities will place considerable emphasis on whether the release is of benefit to society and promotes sustainable development. The assessment of societal benefit, sustainability and ethics means that in practice, more stringent requirements apply to GMOs than equivalent non-GMOs.

Determining how the criteria sustainability, societal benefit and ethics should be interpreted in practice has proven challenging when assessing GMOs. The Norwegian Biotechnology Advisory Board has on several occasions assisted in operationalising these criteria (see chapter 5.2). Likewise, the work to determine how ”socioeconomic considerations” should be understood is currently underway in the EU and under the Cartagena Protocol.

From a precautionary perspective, stricter regulation of GMOs than of non-GMOs is understandable. At the same time, the emphasis on sustainability, societal benefit and ethics is open to question, given that other products are not assessed according to the same criteria. Should it be sufficient to document that a GMO does not pose a risk to health and the environment and does not have a negative impact on sustainability, societal benefit and ethics? Or should organisms produced using gene technology be required to have a positive impact?

The Norwegian authorities' experience is that mostly, GMO applications contain little documentation necessary to facilitate an assessment of a GMO's societal benefit and contribution to sustainable development. This is the case despite the fact that the societal benefit criterion in particular provides developers with an opportunity to highlight the positive aspects of the product they have developed. This may be due to the fact that Norway has so far received applications via the EU, and that the developers in question regard Norway as too small a market to justify spending resources on answering particular questions relating to specific Norwegian requirements. Another possibility is that the developer is unable to answer some of the questions posed.

11. Flexibility under current regulations

The Gene Technology Act and its regulations allow for differentiated assessment of different GMOs (see the earlier discussion in Chapter 7.1). The only explicit tiering set out in the Act itself is a distinction between deliberate release and contained use. Nevertheless, the Act provides scope for differentiation by allowing for different information to be required for different GMOs. As such, the extent and type of information provided by applicants may vary from case to case.

In principle, the Gene Technology Act allows for a notification in two cases:

- The King may, through regulations, determine that deliberate release as set out in sections 9(g) and 9(h) is permitted without prior approval provided that specifically stated conditions are met, e.g. requirements for specific packaging and labelling of products. Such deliberate release may instead be subject to a duty of notification (import and transport).
- The King may, through regulations, determine that the deliberate release of specific types of genetically modified organisms into specific environments is permitted without approval pursuant to paragraph 1, point 1. Such deliberate release may instead be subject to a duty of notification.

The preparatory work[26] further specifies that this shall apply where relevant experience indicates that the use does not pose a risk to health and the environment. The question is whether it can be argued that we have experience with the types of genetic changes on tier 1, since the same changes can be obtained via conventional methods.

With respect to flexibility under EU GMO regulations, the deliberate release directive (Directive 2001/18/EC) also allows for derogation from standard procedures. Article 7 of Part B, which concerns field trials (the deliberate release of GMOs for purposes other than marketing), provides scope for derogation from standard procedure. This is also confirmed in article 16 of Part C concerning the marketing of GMOs. The passage in question states that: " A competent authority, or the Commission on its own initiative, may make a proposal on criteria and information requirements to be met for the notification, by way of derogation from Article 13, for the placing on the market of certain types of GMOs as or in products". Differentiation and derogation from these requirements may be granted for a single GMO or groups of GMOs, and any requirement can in theory be omitted.

If such derogations from the standard procedure are proposed by an EU Member State or by the European Commission, the matter must be decided by the EU authorities pursuant to current provisions. However, there is no precedent in this area since a derogation of this kind has not previously been requested by the European Commission or Member States, according to an expert on European legislation with whom the Norwegian Biotechnology Advisory Board has been in contact.[156]

In the question of whether requirement for approval or a duty of notification should apply, the directive stipulates that all applications must be approved. This requirement likewise applies to gene edited organisms, in compliance with the recent ruling by the EU Court of Justice. A duty of notification is not permitted. Thus, in order to implement a notification system, the directive must be amended.

The directive does not allow for derogation from any GMO labelling requirements either, with the exception of accidental contamination (a maximum of 0.9% GMO of each food/animal feed ingredient). Differentiation is nevertheless already used for detection and tracing of products derived from GMOs that do not contain DNA (such as oils), even though they are required to be labelled.

The provisions of the directive apply to all EU Member States. Implementation of the provisions is however carried out by the individual EU Member States. As such, the details are set out in national legislation, and this allows for somewhat different application of the provisions within the framework of the directive. One example of this is the Dutch policy regarding information requirements for field trials with genetically modified organisms. According to a Dutch expert on the topic,[157] this flexibility is used to divide field trials into three categories, each subject to differing infor-

mation requirements regarding risk and the organisms' traits. On the lowest level the requirements for documentation on risk is lower than on higher levels, and authorisation for multiple varieties and multiple genetic changes may be granted on the basis of a single application. Conversely, the requirement for monitoring and containment is higher for the lowest level because risk is not well documented. The trial must also be limited in scale. The requirements for containment decrease as information on risk increases, and the scale of the trial may increase.

In the view of the Norwegian Biotechnology Advisory Board, the flexibility under Norwegian and European GMO legislation has not been comprehensively mapped.

12. Recommendations by the Norwegian Biotechnology Advisory Board

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In this statement, the Norwegian Biotechnology Advisory Board discusses the provisions of the Gene Technology Act concerning the deliberate release of GMOs. However, the recommendations are applicable generally to regulation of GMO. The statement does not concern contained use of GMOs (Chapter 2) or cloning (Chapter 3a). The recommendations also do not apply to the use of GMOs in medicinal products, which has been discussed in a separate statement.1 Nor does the Board go into detail regarding the unregulated use of gene technology, such as do-it-yourself biology and bioterrorism. The challenges associated with such use are not fundamentally a question of legislation, but rather of how provisions are enforced.

The Board has discussed how deliberate release of GMOs should be regulated at a fundamental level and has opted not to go into detail, since many of the proposals will have to be carefully considered by competent authorities. The Board does not address whether, and if so to what extent, changes to national and/or international legislation and agreements will be required in order to implement the proposals.

Regardless of the scope of GMO regulations and how organisms covered are regulated, the Board members unanimously agree that societal benefit, sustainable development and ethics should form part of the assessment. The weighting of these criteria will however be discussed. The Board also emphasises that a number of other regulations safeguard important considerations. For instance, the Norwegian Food Act prohibits the sale of food and the use of ingredients for production that are harmful to human and animal health. The Norwegian Animal Welfare Act prohibits breeding, including via the use of genetic engineering, to promote traits that have a negative impact on the animal or are not ethically defensible. In addition, the Norwegian Nature Diversity Act safeguards sustainable management of the natural environment via the principles of sustainable use set out in Chapter II of the Act, which come into play when a decisions under the Gene Technology Act are to be made.

The Norwegian Biotechnology Advisory Board considers it a matter of great importance to facilitate research on gene editing and other new gene technologies, both in order to acquire knowledge about technical and safety aspects of these technologies and to build competence in Norwegian research environments.

In light of political and scientific disagreements about what should and should not be covered by the Gene Technology Act and the EU directive, the Norwegian Biotechnology Advisory Board urges the authorities to set out clear guidelines on how the term ”history of safe use” is to be under-

stood, what evidence is required in order for organisms to be considered safe, and whether it should be based on the organisms' traits and/or the production method used.

The Norwegian Biotechnology Advisory Board thinks that, in principle, it would be interesting to consider a strictly product-based model of regulation along the lines of the system used in Canada, but has for pragmatic reasons chosen not to pursue this discussion, since such a model is considered impossible to implement under EU's existing technology-based framework. The following majority proposal is nonetheless more product-based than current regulations.

A joint Board recommends that authorities clarify and utilise existing flexibility for differentiated impact assessment of GMOs within the current regulatory framework as soon as possible.

A joint Board recommends that the Norwegian government appoint an official committee to review proposals for amendments to the Gene Technology Act's provisions concerning the deliberate release of GMOs. This committee should assess different ways of differentiating and simplifying the processing of applications for the release of GMOs, including the tiering approach proposed by the majority.

12.1. Recommendations for a tiered system for authorisation of GMOs

A majority of 11 board members (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Gunnar Heiene, Arne Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, Bjørn Myskja, Sonja Sjøli, Birgit Skarstein and Nils Vagstad) recommend a tiered system for approval/impact assessment of different organisms covered by GMO regulations. These members argue that tiering should be done according to relevant criteria such as the genetic change that has been made. These members believe that such a system may be appropriate to reflect the different levels of risk that may reasonably be assumed for different types of changes, while at the same better ensuring a holistic approach to assessing sustainable development, societal benefit and ethics. Tiering based on the genetic change as described earlier in this document is an example of a possible model. A tiered system where organisms on the lowest tier are subject to a duty of notification (and the option of reassignment to a higher tier where authorisation is required) will ensure that the authorities keep an overview of the products, which enables further impact assessment when warranted by the type of modification or other circumstances. These board members furthermore justify the recommendation of a tiered system on the basis that simplified authorisation requirements will make it easier to harness the potential of genetic engineering in ways that also meet expectations regarding sustainability and societal benefit without having adverse impacts on public health and the environment. Tiering will make the approval process less resource-intensive than today, and will stimulate the development of sustainable and societally beneficial products.

A minority of three board members (Bjørn Hofmann, Bente Sandvig and Benedicte Paus) recommend that, in principle, the current requirements for approval/impact assessment should apply to all organisms covered by GMO regulations. These members base their view on the fact that, while it may seem reasonable to assume that a small, targeted change that does not involve the insertion of foreign DNA will pose a lower risk to health and the environment than more extensive changes, this is in fact not always the case. A small change can have significant consequences, and the possibility of unintended effects cannot be excluded. Each organism and each product will differ in terms of the risk it poses to public health, the environment, sustainability, societal benefit and ethics, making it difficult to pre-assign products to defined groups in an appropriate manner. These members believe that we currently lack the necessary experience with and knowledge about new methods to justify subjecting groups of organisms to merely a duty of notification. On the basis of these considerations, this minority consider that the current case-by-case assessment remains the best approach, but that simplification of the process should be done where possible and desirable. In the view of the minority, possibilities for greater flexibility exist within the existing legislative framework than is currently practiced. Applying differentiated requirements for different types of GMOs will highlight the fact that GMOs can be very different and constitute a range of products, and that requirements for impact assessment should potentially differ. Furthermore, this minority emphasises that the Norwegian government recently simplified the administrative procedures for applications under the Gene Technology Act (facilitated under Directive 2001/18/EC). This minority nevertheless considers it key to clarify what level of flexibility for tailoring requirements for approval exist under current provisions of the Gene Technology Act and EU legislation. Once this flexibility has been clarified (in Norway and the EU), a review of current guidelines should be conducted to ensure that they provide a sufficiently clear indication of which requirements apply to GMOs. Where appropriate, new guidelines should be drafted. This applies to organisms produced by both gene

editing and other forms of gene technology. Like the majority of the board members, the minority acknowledges that gene editing has the potential to provide us with new products that safeguard the principles of societal benefit, sustainability and ethical justifiability, and consider it appropriate for regulations to facilitate the participation of minor stakeholders in this development. At the same time, in the view of the minority, it would be advantageous both for the industry and for consumers to know that every single product is subject to individual approval. The need to facilitate industry activities must be balanced against the need for consumer confidence in products that come on the market.

12.2. Recommendations for scope of regulations

On the issue of scope of GMO regulations, the Board has discussed whether specific organisms produced using gene technology should be exempted. The Board has furthermore voted on whether organisms produced via certain conventional methods that are currently not subject to specific regulation should be covered by GMO regulations.

In line with earlier recommendations, the Norwegian Biotechnology Advisory Board unanimously recommend that RNA- and DNA-vaccinated organisms should be exempted from GMO regulations. In contrast, the Board argues that no organisms with permanent heritable genetic changes obtained via gene technology should be exempted. The Board furthermore unanimously argues that organisms produced by conventional crossing should remain outside GMO regulations. Otherwise, opinions are divided on the question of scope.

A majority of nine board members (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Torolf Holst-Larsen, Raino Malnes, Bente Sandvig, Benedicte Paus, Birgit Skarstein and Nils Vagstad) recommend that, with the exception of temporary, non-heritable changes such as RNA and DNA vaccines, the current scope and definitions of GMO regulations should be kept so that organisms produced by genetic engineering are included, while organisms produced using other methods are excluded. These members argue that the purpose of the Act is to regulate organisms produced with gene technology, and that health and environmental risks, sustainability, societal benefit and ethics must be assessed, with the precautionary principle as a basis for regulation. History of use of conventional methods indicates that such organisms pose no particular risk to health or the environment. The current debate, both in Norway and internationally, concerns whether or not certain organisms produced via genetic engineering should be exempted from GMO regulation, especially in cases where the genetic changes are equivalent to changes that can be obtained using conventional methods. As such, from a pragmatic point of view, it would be impractical to impose new regulations on conventional methods when they are already in use, and it would be inappropriate to focus on a debate that is not regarded as particularly relevant.

A minority of five board members (Gunnar Heiene, Bjørn Hofmann, Arne Holst-Jensen, Bjørn Myskja and Sonja Sjøli) recommend that organisms produced using certain conventional methods that are currently exempt from GMO regulations, such as mutagenesis, triploidisation and cell fusion, should be governed by GMO regulations in the same way as equivalent GMOs. These members justify their position on the basis of the principle of equality. Like genetic engineering, such methods can be used to make genetic changes that, for all intents and purposes, cannot occur naturally, and can result in an unknown level of risk to health and the environment, for example through unintended changes. Such methods may furthermore pose similar ethical challenges as those posed by genetic engineering.

- Four of these five members (Gunnar Heiene, Arne Holst-Jensen, Bjørn Myskja and Sonja Sjøli) nevertheless argue that the risks posed by genetically modified organisms are no greater than those posed by equivalent organisms obtained via conventional methods or naturally occurring organisms – i.e. organisms that have a long history of safe use. Therefore, it would not be a necessary or appropriate use of resources to do a complete assessment of organisms with simple, species-specific changes, and a tiered system is therefore a prerequisite for including conventional methods.
- In contrast, one of these five members, Bjørn Hofmann, argues that all organisms covered by GMO regulations must be handled equally. At the same time, existing flexibility within the current regulatory framework must be utilised to differentiate requirements for different types of GMOs. This will highlight the fact that GMOs can be very different and constitute a range of products, and that requirements for impact assessment should potentially differ.

12.3. Recommendations for labelling, traceability and monitoring

All 14 board members (Inge Lorange Backer, Petter Frost, Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Arne

Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, Bjørn Myskja, Benedicte Paus, Bente Sandvig, Sonja Sjøli, Birgit Skarstein and Nils Vagstad) recommend that labelling requirement should be differentiated to reflect relevant differences between organisms and their traits. They argue that differentiated labelling will allow consumers to make more informed decisions and provide a better basis for choosing according to relevant preferences. Such a system has the potential to facilitate a desirable development of gene technology while at the same time safeguarding consumer considerations.

- Eight board members (Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Torolf Holst-Larsen, Benedicte Paus, Bente Sandvig, Sonja Sjøli and Birgit Skarstein) recommend that all organisms covered by GMO regulations should be labelled in accordance with the differentiated system.
- However, six board members (Inge Lorange Backer, Petter Frost, Arne Holst-Jensen, Raino Malnes, Bjørn Myskja and Nils Vagstad) recommend that organisms on tier 1 should be exempted from the labelling requirement, arguing that such organisms will not be significantly different to plants and animals produced via conventional methods such as crossing, or changes that in theory could have occurred naturally and therefore may be considered equally acceptable. Labelling furthermore has the potential to be misinterpreted as a warning about potential health or environmental risks. Organisms on tiers 2 and 3 should be subject to labelling requirements, but differentiated in a way that reflects differences between the respective tiers. Member Bjørn Myskja presupposes that organisms produced through certain techniques that are currently exempt from GMO regulations will be included for tier 1 to be exempted from labelling requirements.

All 14 members of the Board recommend that traceability requirements, which are a prerequisite for enforcing the labelling requirement, should be further reviewed. Document-based traceability should be required for all GMOs, e.g. via identity preserved (IP) raw materials, as is already the case for food products in general. The manufacturer should also be required to document the DNA sequence of the genetic change that has been made. In cases where the change differs from existing products/organisms, it will be feasible to apply requirements for detection (analytical traceability). In cases where the genetic change does not differ from existing products/organisms, it will not be possible to impose a detection requirement without significant disadvantages. For such products, a requirement for document-based traceability may be sufficient. Other solutions should also be evaluated. Possibilities for differentiated monitoring requirements should also be reviewed further, with a view to establishing requirements and practices that may feasibly be applied to organisms with a range of genetic changes.

12.4. Recommendations for sustainability, societal benefit and ethics

Regardless of the scope of GMO regulations and how organisms are assessed, the Board members unanimously argue that societal benefit, sustainability and ethics should form part of the assessment. However, there is disagreement about how these requirements should be weighted.

A majority of seven members (Inge Lorange Backer, Kristin Halvorsen, Gunnar Heiene, Bjørn Hofmann, Bjørn Myskja, Benedicte Paus and Sonja Sjøli) recommend that considerable weight should be placed on whether a GMO contributes positively to societal benefit and sustainability, in addition to being ethically justifiable. They argue that this is an important tool for steering technological development in a desired direction. These board members consider absence of negative effects a necessary but insufficient condition for approval of a GMO. The products positive contributions to society must also be demonstrated.

A minority of six members (Petter Frost, Arne Holst-Jensen, Torolf Holst-Larsen, Raino Malnes, Birgit Skarstein and Nils Vagstad) recommend that the weighting of requirements for sustainability, societal benefit and ethics should be differentiated according to the tiered system. In such a system, a positive contribution to sustainability and societal benefit may be required for organisms on tier 3, since crossing species barriers in a way that cannot occur naturally is considered ethically problematic. For products/organisms on tiers 1 and 2, however, an absence of negative effects on sustainability and society, as well as being ethically justifiable, may be sufficient. These board members base their views on an assumption that consumers who do not wish to buy genetically modified food because it is produced using methods considered unnatural may more readily accept GMOs that in practice are equivalent to organisms produced via conventional technology or that occur naturally. Additionally, they believe that genetic engineering is principally no more problematic

than other technologies if the products have similar characteristics to non-GMO products, and therefore that assessment requirements should not be more stringent, provided that they pose no risk to health or the environment and do not negatively impact sustainability, societal benefit or ethics. Such a system provides more predictability, and allows individual developers to make decisions about which products to develop and to select production methods according to different tiers and associated requirements for sustainability, societal benefit and ethics. These board members furthermore stress the importance of making requirements for documentation operationally predictable and feasible.

A minority of one board member (Bente Sandvig) recommends that considerable emphasis should be placed on whether the deliberate release is beneficial to society, promotes sustainable development and will be carried out in an ethically responsible manner in accordance with current legislation. This board member argues that genetic engineering is principally no more problematic than other technologies if the products have similar characteristics to non-GMO products, and therefore that assessment requirements should not be more stringent, provided that they pose no risk to health or the environment and do not negatively impact sustainability, societal benefit or ethics.

12.5. Other societal factors

In addition to the specific provisions of GMO regulations, other factors will also impact the way gene technology is applied and what societal consequences this may have. This is especially relevant with respect to regulations for coexistence and access to research data and materials from developers for independent research. The Norwegian Biotechnology Advisory Board will address these factors in separate statements at a later time.

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Annex 1: Summary of tiering based on a preliminary ethical evaluation

The framework presented in this model proposes a 2-stage / 4-step process. The two stages are (i) an initial public morals review that forms the basis for (ii) a subsequent risk assessment. The first stage of public morals assessment (i) involves three steps: 1. Review of foundational political requirements in the form of policy objectives and politically agreed norms; 2. A comprehensive evaluation of ethical justifiability, including not only the type of genetic change but also other relevant factors such as societal benefit and sustainability, and 3. Determination of an ethical justifiability ranking (i.e. 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 assigned tier (i.e. expedited, standard or declined). Each of the steps in the process of this model is illustrated in Figure 1.

1. A more detailed description of the evaluation process

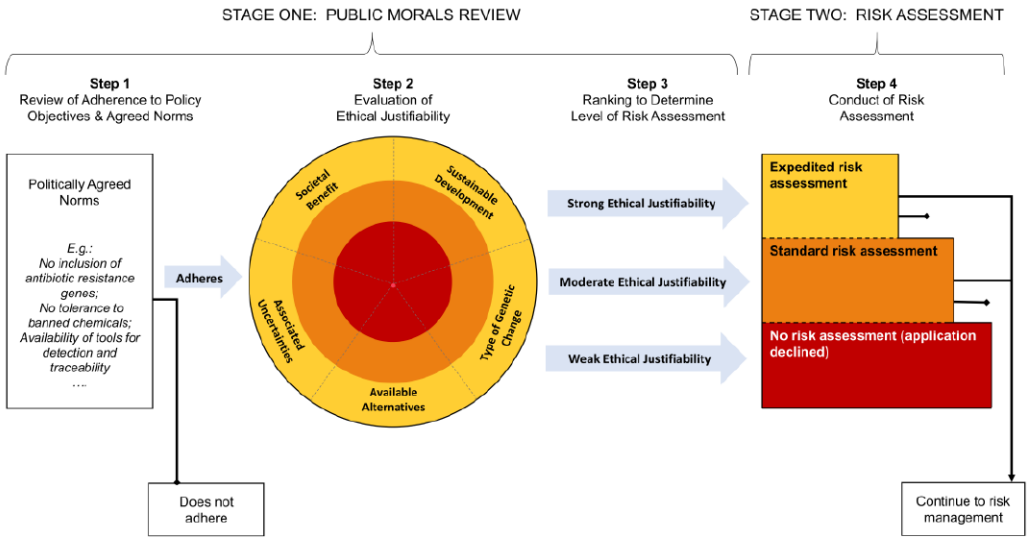
1.1. Stage 1: Public morals review

Step 1 – Review of adherance to policy objectives and agreed norms

In the first step of stage 1 of a public moral assessment, 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 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 2 — Evaluation of ethical justifiability

If an application is found not to be in violation of any agricultural and environmental policy objectives or agreed ethical norms, then it would progress 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 parts of the assessment. 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 the product should



Figur 1. Eksempel på nivådeling basert på en forhåndsvurdering av etikk

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).[1]

In evaluating the ethical justifiability of the process, different types of techniques of genetic modification can be assessed. Note that this can include a range of important factors 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 of species or kingdom boundaries, 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 3 — Ranking to determine level of risk assessment

The third step of the public morals review would involve using the outcome of the assessment performed in 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 step two evaluation, an application receives a yellow rating (Figure 1) for at least three of the criteria (and has no red ratings for any criteria) it may be deemed to have strong ethical justifiability. In contrast, if an application receives three or more red ratings for different criteria during the evaluation in step 2 (and has no yellow ratings) then it may be deemed to have 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 to go through such extensive and time consuming processes of risk assessment as those performed for less clearly beneficial products.

1.2. Stage 2: Risk assessment

In step 4 of the process, the application would move to risk assessment. Here a distinction is made between three different tiers: expedited, standard and declined. The standard review effectively comprises 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 requirements. The exact differences between expedited and standard forms of risk assessment requires further (and wider) discussion and articulation. Within this stage of the model, there is always the possibility for applications to be transferred to a different tier 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,[2] traceability and labelling would be required regardless of the level of risk assessment.

A more detailed description of this model was included in the Biotechnology Advisory Board`s preliminary statement on future regulation of GMOs. Comments were also received during the public consultation period, and the model was generally not supported. Therefore, this model is not included in the final statement. See the preliminary statement for supplementary information on this model.[3]

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Annex 2: Further details on proposals for data requirements in a tiered system based on the genetic change

Tier 1 (notification):
GMOs with genetic changes similar to those that can also be obtained via conventional methods or can arise naturally, will be assigned to this tier. The data requirements might include the following:

- Description and relevant details of the method used. For example, for gene editing with CRISPR this might include information on the specific enzyme used (and of any modifications to improve efficiancy/precision), structure and sequence of sgRNA with algorithmic predictions of the probability of off-target cuts, whether a plasmid or ribonucleoprotein (RNP) is used, methods for delivering CRISPR molecules into cells (embryo microinjection, Agrobacterium for plant tissues, chemical transfection in cell cultures etc.), documentation on the presence/abscence of off-target cuts (sequencing data), documentation on the absence of temporarily introduced nucleic acids (e.g CRISPR plasmids) in the end product.
- Information on the gene/trait that has been modified: the relevant DNA sequence, a summary of existing literature/knowledge about the gene/gene variant/ DNA region (including impact on molecular interactions and biochemical signalling pathways, phenotypic effects etc.).
- Information on the modified organism: for example, what is known about its potential for dispersal and its allergenicity?
- Information about the environment that the GMO will be released into (e.g. agricultural practices, biotopes, safeguards against escaping/spread etc.)
- Any other relevant information, including experimental data if available.
- Preliminary assessment/self-assessment of health and environmental risks: Based on information obtained from the previous five bullet points: are there any circumstances that may impact health or environmental risks, e.g. potential for dispersal or the level of allergens?
- Societal benefit, sustainability and ethics: both positive and negative consequences should be addressed. This will apply to, among other things:
    - The production process: For example, ethical challenges may arise if cloning of mammals is part of the process.
    - The actual gene/trait that is changed: for example, food products with a healthier nutritional content may be favourable in a societal benefit or public health context.
    - The modified organism: for example, there may be ethical issues related to animals: Can the genetic change affect the intrinsic value of the animal? Can the change impact animal welfare in a positive way, e.g. improved animal health and reduced need for culling, dehorning, castration etc.?
    - Effects of deliberate release on health and the environment: for example, disease resistance in plants and animals expected to reduce pesticide use/use of antibiotics may be regarded positively from a sustainability perspective, while genetic changes that introduce antibiotic resistance or lead to increased pesticide use may be considered as negative, depending on case-specific conditions.
    - Societal effects of the release: can the product contribute to solving a societal problem? Which product benefits and costs may arise? Can the product contribute positively to the economy through for example improved value creation and increased employment? Will the product increase production costs? Is the product useful for the consumers?

Tier 2 (expedited impact assessment):
This tier includes GMOs where no new traits that are not already present in a species or a closely related species are introduced. The requirements for impact assessment may be reduced compared to organisms on tier 3 where DNA sequences not present in the species or closely related species are introduced. For example, requirements for toxicity testing may be considered removed, since no foreign sequences/allergens are introduced. Reducing requirements for documentation on specific release conditions and recipient environments, such as individual time-points for release, the duration of the release, preparations of the place for release etc., may also be considered.

One way of facilitating more research may be to simplify the requirements for field trials. For example, approval may be granted for groups of GMOs that are very similar, e.g. different varieties of a plant with the same genetic change, or different genetic changes that give the same phenotype within one plant variety. In this way, it will be easier to perform comparisons of different plant variants (risks, effects, productivity etc.) without having to apply for approval of each GMO. Another way of simplifying or shortening the authorisation process for field trials might be to exempt organisms on tier 2 from the requirement of a public hearing specifically for field trials. This will require

amendments to existing legislation. Further differentiation of the requirements for deliberate field trials based on the organism`s potential for dispersal might also be considered (see Box 8 in the main document on further/alternative differentiation).

Tier 3 (standard impact assessment):
Tier 3 includes GMOs where DNA sequences not previously established in the species or in closely related species are introduced. Generally, an impact assessment of a GMO must currently include information on several aspects related to health and environmental risks, societal benefit, sustainability and ethics. The tiering model sets out corresponding requirements for GMOs on tier 3. Briefly, an impact assessment must include the following, as exemplified here for GM plants:

An environmental risk assessment:[1]

1. Persistence and invasiveness of the GM plant itself, or of relatives with which it can interbreed (e.g. how easily it will establish in recipient environments and outcompete other plants).
2. Plant-to-microorganisms gene transfers (e.g. antibiotic resistance genes)
3. Interactions of the GM plant with target organisms (organisms that the GM plants are intended to impact, e.g. certain plant pests).
4. Interactions of the GM plant with non-target organisms (organisms that the GM plants are not intended impact, e.g. other insects than plant pests), including selecting relevant species and relevant functional groups (e.g. organisms in a certain position on the food chain) for risk assessment.
5. Impacts of the specific cultivation, management and harvesting techniques that are used. This also includes the production systems and the environment in the cultivation area.
6. Effects on biogeochemical processes (e.g. uptake of CO2 by plants, formation of soil organic matter, evaporation of water and transformation of nitrogenous compounds).
7. Effects on human and animal health.

A health risk assessment:[2]

1. Characteristics of the donor organisms and recipient plants
2. The genetic modification and its functional consequences for the plant.
3. Agronomic and phenotypical characteristics of the GM plant, i.e. cultivation traits and observable traits in the plant.
4. Compositional characteristics of the GM plants and derived food and feed.
5. Potential toxicity and allergenicity of gene products (proteins, metabolites) and the whole GM plant and its derived products.
6. Dietary intake and potential for nutritional impact.
7. Influence of processing and storage on the characteristics of the derived products.

A substantial part of the documentation must be based on extensive safety testing, e.g. through feeding trials with laboratory animals and field trials.

1. EFSA (2010) Guidance on the environmental risk assessment of genetically modified plants. www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1879.pdf

2. EFSA (2011) Guidance for risk assessment of food and feed from genetically modified plants. https://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2150.pdf

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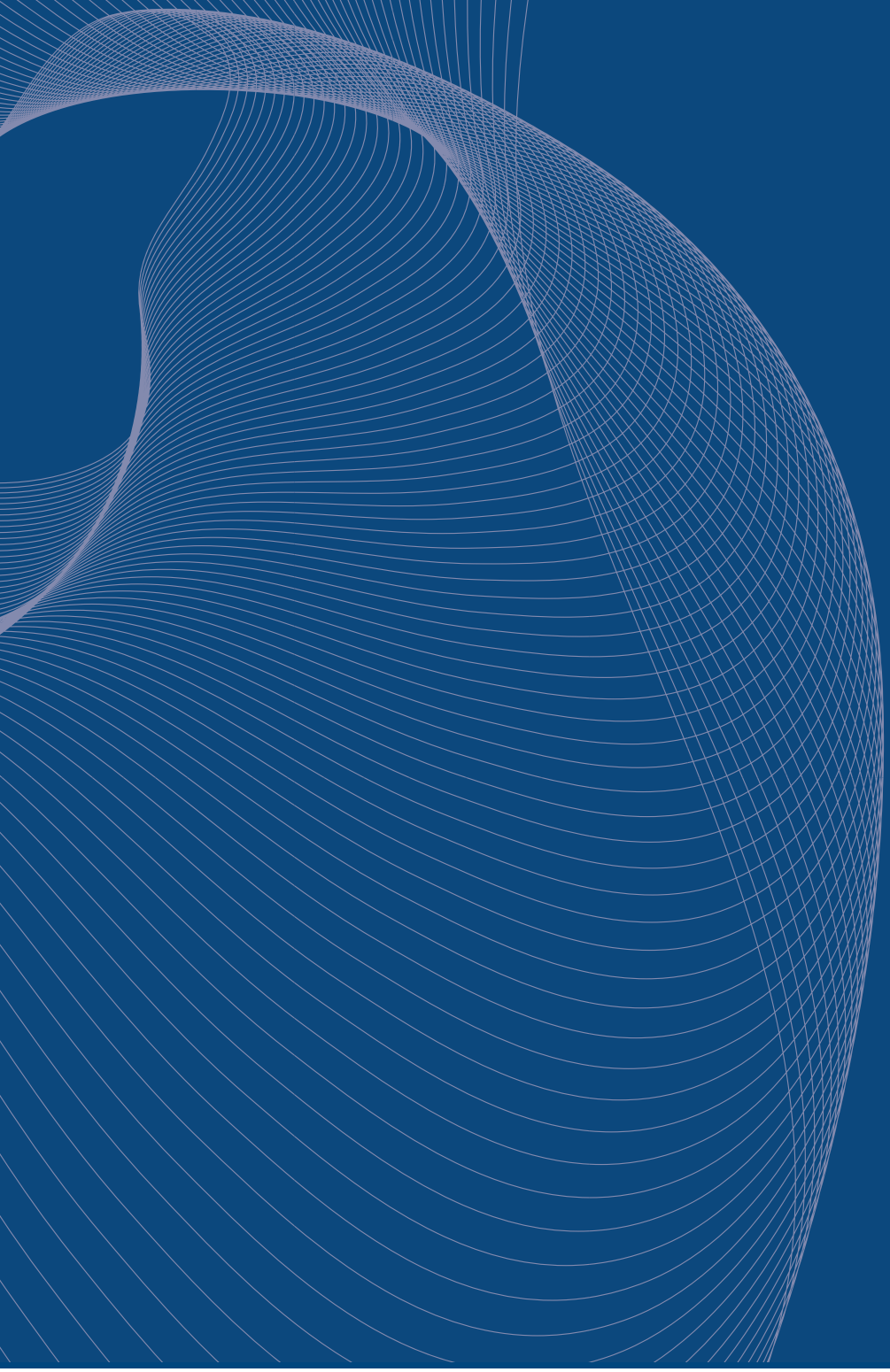

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