The Norwegian Biotechnology Advisory Board

Proposal for revision of the Norwegian Gene Technology Act

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Online virtual workshops on regulatory approaches for agricultural and food/feed applications of animal biotechnology
Session II: Regulatory approaches for genome edited animals – September 23rd 2020

Veterinærinstituttet
Norwegian Veterinary Institute

The Gene Technology Act (Genteknologiloven) regulates contained use and release of GMOs

- Law entered into force in 1993
  - almost unchanged since

- Is it adequate for present technological and political realities?
  - especially in light of genome editing?

Definitions of GMOs in Norway and EU (Directive on Deliberate Release)

Norway

genetically modified organism: a microorganism, plant or animal in which the genetic material has been altered by means of gene or cell technology.

EU

'genetically modified organism (GMO)' means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

- *Interpretation in several EU countries before July 2018: organisms with CRISPR-induced point mutations are not GMOs.*
- *European Court of Justice in July 2018: gene-edited organisms are GMOs.*

Assessment criteria for GMOs in the Gene Technology Act

Sustainability

Societal benefits

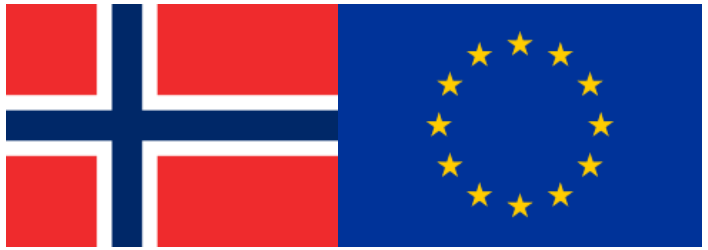
Ethics

Non-safety criteria:

Health

Environment

Safety criteria:



Contemporary debate:

- **Gene editing renewed the debate on GMO regulation**
- **Black & white discussion:**
  - Apply current regulation & practice also to new techniques?
  - Exempt some organisms/techniques from GMO regulation?
- **The Biotechnology Advisory Board* – on its own initiative – suggested a novel approach to regulation**
- **Basic idea: the *type* of genetic change in most cases provide clues to identify and assess the associated risks**

* Proposal developed by the NBA board 2014-2018. A new board was nominated in 2019, presently discussing…

Question motivating the proposal:

How can we utilize the potential of gene technology, …

… while paying adequate attention to concerns for:

- Health
- Environment
- Benefits to society
- Sustainability
- Ethics?

The Board wanted to approach the question from an elevated, principled angle

«Proposal for a relaxation of the legislation on release of genetically modified organisms»

A level-based approach within the current general regulatory framework

Board leader Kristin Halvorsen handed over the proposal to the minister of climate and the environment Ola Elvestuen on December 4th 2018

Principled and/or regulatory distinction of gene modification types

is not a novel idea:

Transgenic organisms—time for conceptual diversification?

Kaare M. Nielsen

Recent advances in genetic engineering have made it possible to effect previously unattainable genetic changes in most organisms subjected to breeding[1]. The altered organisms into which hereditary (that is, genetic) material from another organism has been introduced are referred to as transgenic or genetically modified organisms (GMOs)[2]. Wide use of these process-based terms has resulted in little appreciation for the sources, extent, and novelty of the genetic modifications made in GMOs. Not surprisingly, indiscriminate scientific, public, and regulatory scrutiny based on misleading conceptual assumptions have developed into negative perceptions of GMOs, particularly among European citizens[3,4]. I hypothesize that the failure to establish, from the onset, explicit terminology to categorize the various applications of gene technology in breeding have contributed to this skepticism and to rejection of the technology by many consumers.

The current practice of process-based categorization of GMOs is biologically imprecise and does not accurately reflect the nature of the introduced genotypic changes. As the terms enforce focus on the process, rather than the product, of the technology, they obstruct the potential to subdivide and conceptually expand the categories of products derived through gene technology–based breeding (see below). We propose the adoption of alternative categories that would shift focus to a product-based perception of gene technology, allowing conscious differentiation in the perception of GMOs based on the sources of the genetic changes introduced.

The extent to which transgenic organisms differ from traditionally bred organisms underlies much of the controversy surrounding the use of GMOs[5]. In seeking a scientifically sound resolution, the key factor is a clear, accurate understanding of the context of the specific genetic changes introduced. Generally, the release and use of GMOs with simple nucleotide changes are likely to generate few ecological concerns beyond those faced by the organisms' traditionally bred counterparts. However, species-foreign genes, synthetic genes, and other genetic changes have been introduced into GMOs, and some deviate substantially (genetically, biochemically, and physiologically as well as in ethical, regulatory, and public perceptions) from what classical, selection-based breeding has achieved[6,7]. These organisms have genetic compositions that do not reflect evolutionary processes occurring under natural conditions[8–10].

Consider, for instance, the genome of a representative transgenic variety of corn carrying the gene encoding *Bacillus thuringiensis* toxin (*Bt*), which contains functional recombinations and synthetic modifications of DNA fragments from four different bacterial species (from the genuses *Agrobacterium*, *Streptomyces*, *Bacillus*, and *Escherichia*), additional prokaryotic mobile elements (bacterial plasmid), and regulatory sequences from a virus (cauliflower mosaic virus) and a rice plant[11]. The known natural mechanisms generating genetic variability in higher eukaryotes cannot combine, functionally enhance, and propagate DNA sequences derived from several unrelated organisms within the time scale achieved by genetic engineering. Therefore, genotypes achieved by genetic engineering can be conceptually different from those arising naturally or from classical selective breeding, thus warranting further classification.

The genetic distance between the engineered organism and the source of the new genetic variation would be a functional criterion for assessing the novelty of the introduced genetic changes. A more precise and explicit nomenclature based on the genetic distance associated with the introduced genetic modifications is illustrated in Table 1.

The five categories of GMOs suggested are defined by their biological relevance, reflecting the level of genetic relatedness between the donor and the recipient organisms, and thereby indicate the broad potential for the engineered trait to evolve spontaneously[12]. The focus of most current engineering has been on adding or altering phenotypic traits conferred by single genes, often with little understanding of the biochemical and cellular interactions of the gene product within the new genetic background[13–15]. The proposed divisions implicitly consider the biochemical networks through their evolutionary distance from the introduced trait. The categorizations address many of the ethical, religious, and public concerns raised, by allowing a conscious and conceptual diversification of current and future developments in gene technology assisted breeding.

At the center of many objections to GMOs is concern about the introduction of genetic material from distantly related organisms, such as the insertion of animal DNA into crop plants. To meet such concerns, relevant

Table 1. Proposed categories for organisms currently designated 'transgenic' or 'genetically modified'

Categories	Source of genetic modifications	Genetic variability via conventional breeding	Genetic distance
Intragenic	Within genome[a]	Possible	Low
Famigenic	Species in the same family[b]	Possible	↓
Linegenic	Species in the same lineage[c]	Impossible	
Transgenic	Unrelated species[d]	Impossible	
Xenogenic	Laboratory-designed genes[e]	Impossible	High

[a]From directed mutations or recombinations; the extent of modification also reflects those arising in classical, selection-based breeding.
[b]Taxonomic family; the extent of modification also reflects those arising from applying cellular techniques in classical breeding.
[c]Phylogenetic lineage; recombination of genetic material beyond what can be achieved by classical breeding methods.
[d]Contains recombined DNA from unrelated organisms. Reflects the genetic composition of most GMOs commercialized today.
[e]For which no naturally evolved genetic counterpart can be found or expected (for example, synthetic genes and novel combinations of protein domains from various species).

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ARTICLES

Time for a New EU Regulatory Framework for GM Crops?

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Abstract In recent years, the EU legislation on genetically modified (GM) crops has come under severe criticism. Among the arguments are that the present legislation is inconsistent, disproportionate, obsolete from a scientific point of view, and vague in terms of its scope. In this paper, the EU GM legislation (mainly the "Release Directive", 2001/18/EC) is analysed based on five proposed criteria: legal certainty, non-discrimination, proportionality, scientific adaptability, and inclusion of non-safety considerations. It is argued that the European regulatory framework does not at present satisfy the criteria of legal certainty, non-discrimination, and scientific adaptability. Two ways of reforming the present legislation toward greater accommodation of the values expressed through the proposed criteria are briefly introduced and discussed.

Keywords GM crops · Genetic engineering · EU Release directive · Legislative techniques · Legal principles · Sustainability

EMBO *reports*

viewpoint

Cisgenic plants are similar to traditionally bred plants

International regulations for genetically modified organisms should be altered to exempt cisgenesis

Henk J Schouten, Frans A. Krens & Evert Jacobsen

The testing and release of genetically modified organisms (GMOs)—in particular GM plants—is tightly regulated internationally to prevent any negative effects on the environment or human health. However, these regulations are based on transgenic organisms and do not discriminate between transgenic plants and cisgenic plants, although we believe that they are fundamentally different (see sidebar). Now, cisgenic plants fall under regulations designed for transgenic organisms, possibly because there have not yet been any applications for the approval of the deliberate release of cisgenic plants into the environment.

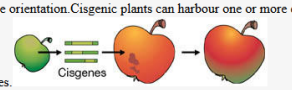
> **If the current international GMO regulations … continue to fail to differentiate between cisgenic and transgenic plants, the use of cisgenesis could be seriously hindered**

Although transgenesis and cisgenesis both use the same genetic modification techniques—namely the introduction of one or more genes and their promoters into a plant—cisgenesis involves only genes from the plant itself or from a close relative, and these genes could also be transferred by traditional breeding techniques. If the current international GMO regulations, which are mainly based on the process of transferring transgenes, continue to fail to differentiate between cisgenic and transgenic plants, the use of cisgenesis could be seriously hindered. Only Canada now has a product-based rather than a process-based regulation system, and therefore has the legal possibility to control cisgenic plants less strictly than transgenic plants. Any restrictions on cisgenesis could block or delay further research on improving crop varieties, particularly as an increasing number of functional genes from crops and their crossable wild relatives are being isolated and are becoming amenable to cisgenesis. We argue that cisgenic plants are fundamentally different from transgenic plants, and should therefore be treated differently under GMO regulations.

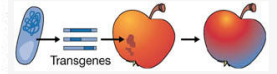
traits. No changes in fitness occur that would not happen through either traditional breeding or natural gene flow. Similarly, cisgenesis carries no risks—such as effects on non-target organisms or soil ecosystems, toxicity or a possible allergy risk for GM food or feed—other than those that are also incurred by traditional breeding. This is the fundamental difference between cisgenesis and transgenesis. Consequently, the deliberate release and market introduction of cisgenic plants is as safe as the release and market

Definitions of key terms in relation to plants

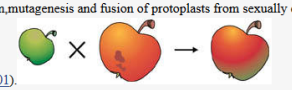
Cisgenesis is the genetic modification of a recipient plant with a natural gene from a crossable —sexually compatible—plant. Such a gene includes its introns and is flanked by its native promoter and terminator in the normalsense orientation.Cisgenic plants can harbour one or more cisgenes, but they do not contain any transgenes.



Transgenesis is the genetic modification of a recipient plant with one or more genes from any non-plant organism, or from a donor plant that is sexually incompatible with the recipient plant. This includes gene sequences of any origin in the anti-sense orientation, any artificial combination of a coding sequence and a regulatory sequence, such as a promoter from another gene, or a synthetic gene.



Traditional breeding encompasses all plant breeding methods that do not fall under current GMO regulations.As the European legal framework defines GMOs and specifies various breeding techniques that are excluded from the GMO regulations,we use this framework as a starting point, particularly the European Directive 2001/18/EC on the deliberate release of GMOs into the environment (European Parliament, 2001). Excluded from this GMO Directive are longstanding cross breeding, in vitro fertilization, polyploidy induction,mutagenesis and fusion of protoplasts from sexually compatible plants (European Parliament, 2001).



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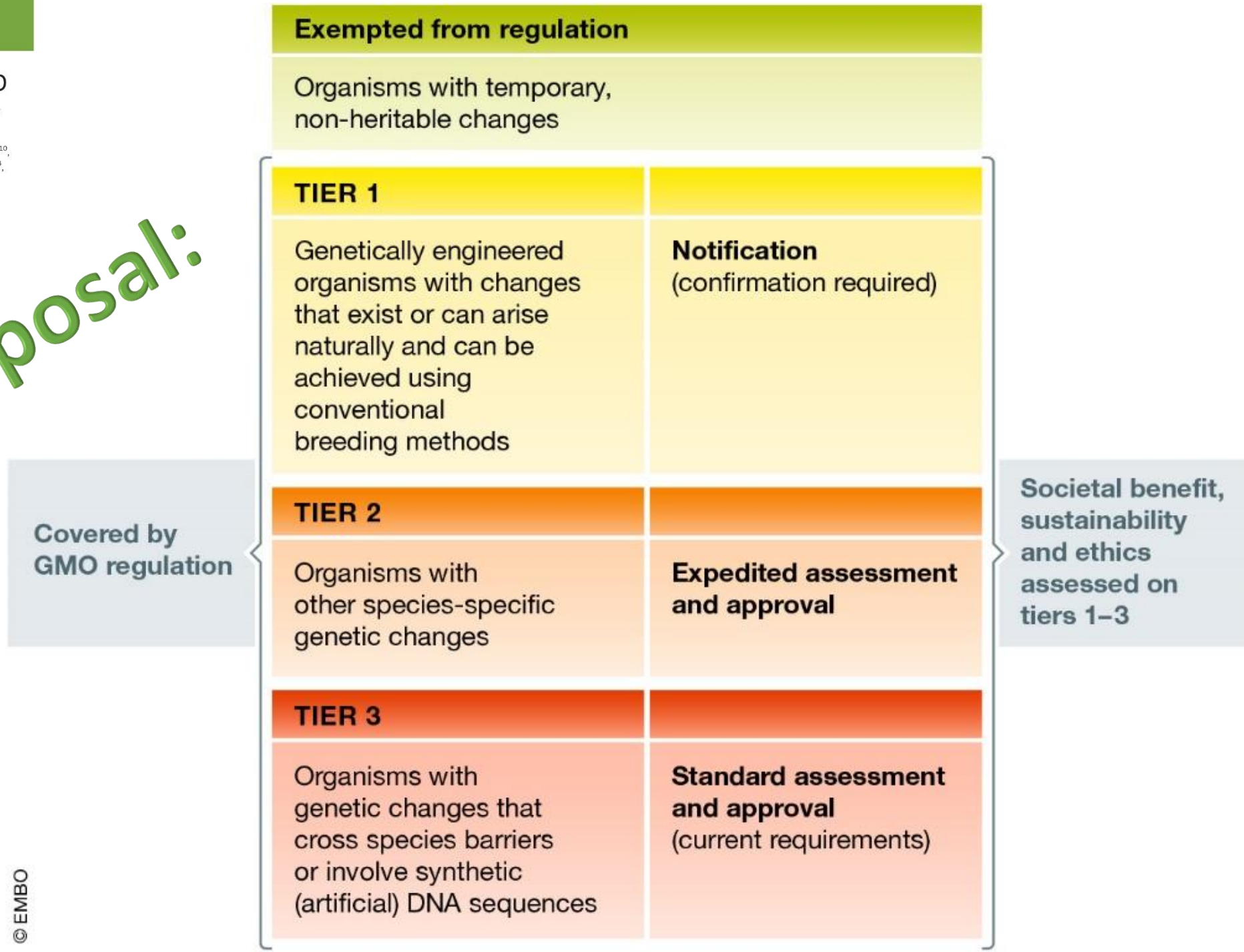
A novel governance framework for GMO

A tiered, more flexible regulation for GMOs would help to stimulate innovation and public debate

Sigrid Bratlie[1], Kristin Halvorsen[1,2], Bjørn K Myskja[1,3], Hilde Mellegård[1], Cathrine Bjorvatn[1,4], Petter Frost[1,5], Gunnar Heiene[1,6], Bjørn Hofmann[1,7,8], Arne Holst-Jensen[1,9], Torolf Holst-Larsen[1,10], Raino SE Malnes[1,11], Benedicte Paus[1,12], Bente Sandvig[1,13], Sonja Irene Sjøli[1], Birgit Skarstein[1,14], May B Thorseth[1,3], Nils Vagstad[1,15], Dag Inge Våge[1,16] & Ole J Borge[1]

Our proposal:



Controversial technologies – transparency important for trust

What to regulate under Gene Technology Act? And why?

- Definition should be clear and resilient to technology developments → predictable
  - Inheritability? Include som technologies that are currently exempt (mutagenesis, triploidisation, cell fusion)?
- Exemptions should not appear as *ad hoc* solutions → trust and transparency

Labelling: why, what and how?

- Information! Providing knowledge for informed decisions or perceived as warning of risk?
- Detectability, is it possible to identify/distinguish and at what cost?
- Everything or level based/exemptions?

Label all levels?

TIER 1 — Exempt from labelling?

TIER 2 — Label only tier 2 & 3?

TIER 3

Contribution to sustainability, societal benefits, ethics

- Justification for the use of controversial technologies

Positive contribution required for all three tiers?

TIER 1 — Neutral, (not negative) impact required for tiers 1 & 2?

TIER 2

TIER 3 — Positive contribution required only for tier 3?

Level-based regulation

Benefits:

- **Simplified regulation process**
  - lowers threshold for utilizing gene technology
  - sustainability and societal benefit not compromised
- **Acknowledge differences in risks**
  - often depends on nature of change
  - more predictable when change is more targeted
- **Compatible with a case-by-case approach**
  - Possible to move cases between levels

Challenges:

- **Scale of change and scale of phenotypic effect may not correlate**
  - Small genetic change can yield large phenotypic change, and *vice versa*
- **Definition of operational and fair distinctions between levels**
  - Feasible? Not scrutinized by the Board
- **Will the complexity of accountable factors effectively lead to current case-by-case regulatory approach?**
  - Nothing gained + failure to meet expectations from stakeholders?

Objectives with the proposed approach

- Prevent over-regulation
- Authorities will maintain product overview and access to necessary information
- Prevent excessive resource use in «simple» cases (documentation and reviews)
- Equal treatment of different technologies leading to «identical» changes
- Predictable regulation
- Bridge the process-product approaches to regulation
- Pay heed to thirty years of experience with release of GM plants
- Keep non-safety issues (ethics, sustainability and societal benefits) in regulation
- Pay heed to public concerns with issues of ‘naturalness’ within a science-based regulation
- Maintain public trust (avoid *ad hoc* exemptions from regulation)