anses

Risks and socio-economic issues related to NTG plants

Opinion of the Anses Collective expertise report

January 2024

Knowing, assessing, protecting

Opinion of the Anses
Referral no. 2021-SA-0019

The Managing Director

Maisons-Alfort, 22 January 2024

OPINION
of the French National Health and Safety Agency of Food, Environment and Labour

on methods for assessing the health and environmental risks and socio-economic issues associated with plants obtained using certain new genomic techniques (NTG)

Anses provides independent and pluralist scientific expertise.
The main role of Anses is to ensure health safety in the fields of the environment, work and food, and to assess the health risks they may entail.
It also helps to protect the health and welfare of animals and plants, and to assess the nutritional properties of foodstuffs.
It provides the competent authorities with all the information on these risks, as well as the expertise and technical scientific support needed to draw up legislative and regulatory provisions and implement risk management measures (article L.1313-1 of the Public Health Code).
Its opinions are published on its website.

On 28 January 2021, Anses was asked by the Directorate General for Risk Prevention (DGPR) and the Directorate General for Food (DGAl) to carry out the following expert appraisal: "Request for an opinion on background work on risk assessment methods related to the use of GMOs in feed and food". Following the assumption by Anses of certain missions of the High Biotechnology Council (HCB) from 1er January 2022, the expert appraisal contract between the agency and its commissioning ministries (May 2022) specifies that the scope of this referral has been extended to environmental and socio-economic aspects.

This collective expertise work is being carried out within the scope of the Anses' missions on biotechnologies, including the assessment of the risks to the environment and public health of all uses of biotechnologies in the open environment, and their socio-economic impacts. This opinion and the associated expert report are intended to enlighten applicants and stakeholders on this scope, which covers some of the issues related to the use of plants obtained by certain NTGs and their derived products. The other bodies that have taken over the HCB's remit, namely the Economic, Social and Environmental Council (CESE) and the National Consultative Ethics Committee (CCNE), have also been asked to comment on the issues associated with NTG plants, in their respective remits corresponding to societal and ethical issues. The analyses and conclusions of these expert assessments should therefore be seen in the context of the opinions of the other bodies consulted.

1. CONTEXT AND PURPOSE OF THE REFERRAL

New Genomic Techniques (*NGT*) are a heterogeneous group of genome-modification techniques involving different mechanisms (mutations, insertions/deletions, gene silencing, etc.). Some of these techniques aim to modify a genetic sequence in a precise and targeted way (directed or targeted mutagenesis), offering a very broad field of application, particularly in the field of varietal selection. Like other genetic modification techniques, these NTGs can be used in a wide range of applications beyond plants. This is the case, for example, in the field of medicines (human or veterinary), where their targeting precision can bring considerable progress to gene therapy.

These genome modification techniques, particularly those based on the CRISPR-Cas system, have developed very rapidly, and plant varieties obtained using these NTGs are already available on the market in certain countries, notably the United States and Canada. No plants obtained using these NTGs are currently authorised for the European Union market.

Following an appeal by the Confédération paysanne and other organisations to the Conseil d'État, which will in turn refer questions to the Court of Justice of the European Union (CJEU) for a preliminary ruling, the CJEU's ruling of 25 July 2018 (Case C-528/16) concludes that only organisms obtained by means of mutagenesis techniques/methods which have traditionally been used for various applications and whose safety has long been proven are excluded from the scope of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms". As a result, plants obtained by these NTGs are intended to fall within the current regulatory framework applying to genetically modified organisms (GMOs), particularly in terms of risk assessment.

The European Commission published a study on NTGs on 29 April 2021, concluding that it did not consider the current GMO regulations to be appropriate for plants obtained using certain NTGs. For other organisms (animals and micro-organisms), the Commission considers that it is necessary to continue to build up the necessary scientific knowledge and to maintain products derived from NTGs within the current GMO regulations at this stage. The European Commission's study also points to legal uncertainties, difficulties in implementing controls in particular, and the lack of flexibility in the current regulations. The study also concludes that certain plants obtained using NTGs could be of benefit to society and meet the challenges of resilience and sustainability of the food system under the "farm to table" strategy. The study also highlights a number of key issues, notably relating to intellectual property, traceability, consumer information, the competitiveness of businesses and the agricultural sector, trade and the acceptability of these products to society.

In its letter of 29 April 2021 to the Portuguese Presidency of the Council of the European Union, the Commission indicated that, in the light of the results of the study, it intended to launch a legislative initiative for plants derived from directed (or targeted) mutagenesis and cisgenesis. The aim was to adapt the current regulatory requirements in terms of risk assessment, authorisation procedures, labelling and traceability, while maintaining a high level of protection for the environment and human health and

animal feed, and taking into account the potential contribution of these plants and the products derived from them to the sustainability of the food system. This intention has taken the form of a proposal for a regulation prepared by the Commission and published on 5 July 2023.[1].

Against this backdrop, the French Directorate-General for Risk Prevention (DGPR) and the Directorate-General for Food (DGAl) have referred the matter to Anses, in order to obtain a scientific opinion within the scope of Anses' remit, in preparation for the forthcoming discussions at European level.

In line with this scope, and in accordance with the appraisal contract, the two main objectives of the appraisal were established as follows:

- to determine whether adaptations could be made to the current regulatory requirements for assessing the risks (health and environmental) of genetically modified plants when the assessment concerns plants resulting from directed (or targeted) mutagenesis;
- document and analyse the socio-economic issues associated with NTGs.

As regards aspects relating to health and environmental risks, the scope of the referral has been restricted to plants derived from site-directed mutagenesis using the CRISPR-Cas system (cf. section 3.1), which represent the type of application and tool most commonly used or envisaged.

These two objectives were broken down into six questions to be examined (questions 1 to 4 for the first objective and questions 5 and 6 for the second objective):

- *Question 1*: Establish the state of knowledge on the potential undesired effects at the genome level, at the target and off-target, in the event of directed mutagenesis using the CRISPR-Cas system;
- *Question 2*: Determine the specific requirements in terms of health and environmental risk assessment for plants derived from site-directed mutagenesis using the CRISPR-Cas system;
- *Question 3*: For plants derived from site-directed mutagenesis using the CRISPR-Cas system, determine which of the current regulatory requirements for the assessment of genetically modified plants can be waived;
- *Question 4*: Depending on the progress made on the previous questions, determine how the current GMO assessment framework could be adapted for plants derived from site-directed mutagenesis using the CRISPR-Cas system;
- *Question 5*: Draw up a description of the sector or sectors concerned by the use of plants obtained by means of NTGs and the products derived from these plants, from upstream to downstream in the value chain;
- *Question 6*: On this basis, document and analyse the associated socio-economic issues, firstly for the companies and economic operators concerned, particularly in terms of competitiveness and capacity for innovation, and secondly, depending on the data available, for consumers and the supervisory authorities.

This appraisal was initiated before the publication of the Commission's proposal for a regulation on 5 July 2023. Following this publication, as well as that of the technical note

[1] https://food.ec.europa.eu/system/files/2023-09/gmo_biotech_ngt_proposal_2023-411_fr.pdf and https://food.ec.europa.eu/system/files/2023-09/gmo_biotech_ngt_proposal_2023-411_annex_fr.pdf (consulted on 12/10/2023)

published by the European Commission in October in support of the equivalence criteria for conventional plants, Anses decided to carry out an analysis of the criteria defining category 1 NTG plants, set out in Annex 1 of the draft regulation. This analysis was carried out in parallel and published on 21 December 2023 (Anses 2023). Given the respective work schedules, the conclusions of this analysis have not been incorporated into the present expert appraisal, carried out within the scope defined above, which does not distinguish between category 1 and 2 NTG plants.

2. ORGANISATION OF EXPERTISE

The appraisal was carried out in compliance with standard NF X 50-110 "Quality in appraisal - General competence requirements for an appraisal (May 2003)".

Expertise falls within the remit of specialist expert committees (CES) "Biological risk assessment in food" (BIORISK, pilot ESC), "Socio-economic analysis" (ASE) and "Biological risks to plant health" (SANTVEG). Anses has entrusted the expertise to the "New genomic techniques" working group set up following a public call for candidates. The CES ASE is responsible for validating work relating to economic and social sciences and the CES SANTVEG for validating work relating to environmental aspects. The CES BIORISK is responsible for endorsing all the work.

The methodological and scientific aspects of the work were presented to the various ESCs between May 2022 and December 2023. It was adopted by the BIORISK ESC at its meeting on 11 December 2023.

The Anses analyses the links of interest declared by the experts before their appointment and throughout their work, in order to avoid the risk of conflicts of interest with regard to the points dealt with in the expert appraisal.

Experts' declarations of interest are published on the website: https://dpi.sante.gouv.fr/.

Finally, in order to answer the questions set out in the previous section, the WG "Following validation by CES BIORISK, NTG used the following methodology:

Question	Methodology
1	Analysis of systematic reviews available in the literature Systematic review of the literature on undesired effects on the tomato genome associated with the use of the CRISPR-Cas system Systematic literature review (years 2021-2023) on undesired effects on the plant genome associated with the use of the CRISPR-Cas system
2	Systematic review of the literature on the health and environmental risks associated with the use of the CRISPR-Cas system on plants Study of 12 representative cases of CRISPR-Cas applications on plants

3	Analysis of the current assessment framework and its suitability for the assessment of plants derived from site-directed mutagenesis.
4	Building a decision tree
5	Description of the value chain in the tomato, soft wheat, carrot and vine sectors
6	Systematic review of the literature on the socio-economic issues associated with plants and products derived from NTGs Hearings of stakeholders concerned by NTG plants and products Analysis of systematic reviews available in the literature on the impact of transgenic plants Analysis of the potential impact of regulatory changes on plants and products derived from NTGs

Part 3 of this opinion is a summary of the collective expertise report, in which the methodologies, analyses and results are detailed and developed.

3. ANALYSIS AND CONCLUSIONS OF THE GT AND CES

3.1. Identification of NTG applications most likely to lead to commercial varieties in the short term

In a report published by the European Commission's Joint Research Centre (JRC) in 2021 on the current or expected (worldwide) marketing of organisms and products derived from NTGs, 426 commercial applications on plants were identified. In 2020, 17 of these applications were at the pre-commercialisation or commercialisation stage, including 7 obtained using a CRISPR system. Furthermore, of the applications for which the genome modification tool is known (382 applications out of 426), 90.2% (305/382) involve a DNA double-strand break using a site-specific nuclease (CRISPR-Cas, Transcription activator-like effector nucleases (TALEN), meganucleases and Zinc-finger nucleases (ZFN)), with CRISPR-Cas accounting for 78.8% of cases. The JRC report indicates, without quantifying, that it is a mechanism of deletion or insertion of a few base pairs, during DNA repair by the cellular *non-homologous* end-joining (NHEJ) system, that is used in the vast majority of cases. Two other reviews (Brinegar et al. 2017; Modrzejewski et al. 2019) confirm the predominance of the use of the CRISPR-Cas system among NTGs, both in terms of the number of applications published in the literature and the number of patents filed in the United States.

In terms of the plant species concerned, the JRC report states that 38% are cereals, 17% are oil or fibre plants, 12% are vegetables and 11% are tubers and root vegetables. NTGs are thus applied to a wider variety of species than those derived from transgenesis, which are the subject of the majority of marketing authorisation applications under Regulation (EC) No 1829/2003 (maize, soya, rape, cotton and beet). Species that were little or not concerned by transgenesis, such as banana, cocoa and chickpea, are among those identified in this report. In terms of the types of traits conferred on NTG plants, the three main ones are a change in the biochemical composition of the plant, tolerance to biotic stress and a change in yield and/or plant architecture.

plants. Moreover, herbicide tolerance only concerns less than 7% of applications, whereas this type of trait is the most common among transgenic plants.

In order to identify the plants most likely to result in the short term in commercial varieties, or that have already resulted in commercial varieties, obtained using the CRISPR-Cas system (which appears to be the most widely used system), the NTG has compiled a database of applications developed in plants obtained using these techniques. The information has been extracted from publications by Brinegar et al (2017), Détain et al (2022) and Modrzejewski et al (2019), the report by the Joint Research Centre (2021), international patent databases and the databases of the World Bank and the IMF (consulted on 21/12/2022), with only plants obtained using the CRISPR-Cas system being included.

One hundred and twenty-one applications have been identified. They concern a very wide variety of species, the most common of which are rice, tomato and maize. In terms of the traits conferred on plants genetically modified using CRISPR-Cas, changes in biochemical composition are the most numerous. These are followed by modifications to plant architecture and/or yield improvement, tolerance to biotic stresses and selection tools. Herbicide tolerance accounts for only 5% of the applications obtained using the CRISPR-Cas system.

Finally, the NTG experts note that plants derived from site-directed mutagenesis are beginning to appear on the market in countries outside the European Union.

If :

- **the use of the CRISPR-Cas system appears to be dominant in NTG applications likely to lead to commercial varieties in the short term;**
- **the use of the CRISPR-Cas system concerns applications already available on the market outside the European Union;**
- **cisgenesis is still not widely used;**

the "NTG" WG has chosen to carry out its expert appraisal work on the health and environmental risks of plants derived from directed (or targeted) mutagenesis using the CRISPR-Cas system[2].

3.2. Site-directed mutagenesis using the CRISPR-Cas system

3.2.1. Description of the CRISPR-Cas system

The CRISPR-Cas system is a complex consisting of an enzyme capable of cutting DNA (endonuclease), Cas, and a strand of guide RNA with a sequence complementary to that of the DNA targeted for mutation. The CRISPR-Cas system is used to create a double-strand break in the DNA at a specific site, thereby activating intracellular DNA repair mechanisms. As these mechanisms are more or less error-prone, changes to the genome can then occur. Point mutations or insertions/deletions of DNA fragments can appear at the targeted site, as can specific modifications to the sequence of the targeted gene if a repair matrix is used.

[2] This choice was formalised by an amendment to the consultancy contract.

is added by the breeder (the person or company developing the new variety). The CRISPR-Cas system can also be modified by genetic engineering to obtain new tools, the applications of which may vary. For example, modified CRISPR-Cas systems, with or without other proteins, can be used to produce single-strand DNA breaks. These are known as nickases (or nCas9), and have applications such as *base editing* or *prime editing*, enabling a single base to be modified by enzymatic reaction or by reverse transcription of a specific guide RNA.[3].

The CRISPR-Cas directed mutagenesis stage is necessarily preceded by a stage in which the CRISPR-Cas system is delivered to the plant. Two types of modality can be used by the breeder: those leading to stable expression of the system, and those leading to transient expression of CRISPR-Cas. Stable expression of CRISPR-Cas occurs when the genetic material enabling expression of the guide RNAs and the Cas nuclease is integrated into the genome of the plant to be modified. Conversely, transient expression occurs when there is no integration of foreign genetic material into the plant genome, and the guide RNAs and nuclease are not permanently expressed in the plant. Finally, once the CRISPR-Cas system has been delivered and the targeted mutation is effective, additional excision, transgene segregation or backcrossing steps can be implemented by the breeder, enabling the CRISPR-Cas system to be eliminated from the plant genome in the case of stable expression.

3.2.2. Potential undesired effects at the level of the plant genome modified using the CRISPR-Cas system

Although the specificity of the CRISPR-Cas system for its target sequence in the genome is regulated, on the one hand, by a specific 20-nucleotide 'protospacer' sequence in the guide RNA (complementary to the target DNA sequence) and, on the other hand, by the recognition by the Cas protein of a defined *protospacer-adjacent motif sequence* (PAM), off-target cleavage by the Cas nuclease in the genome remains possible. CRISPR-Cas cuts to the target can also lead in some cases to unwanted genome modifications, such as larger deletions or insertions on large chromosomal regions. In both these cases, we talk about undesired effects, on or off target, associated with the use of CRISPR-Cas.

In order to assess the nature and frequency of undesired effects on the plant genome, both on target and off target, the WG first carried out a systematic review of the literature on undesired effects on the tomato genome over a period up to December 2022. The tomato was selected because of the many applications obtained using CRISPR-Cas on this species, and its original character compared with authorised transgenic plants, mainly cereals or oilseeds, which are not very rich in water.

This assessment was then extended to all plants, by analysing existing systematic reviews in the scientific literature, and by systematically reviewing original articles published over the 2021-2023 period, which is not covered by the systematic reviews identified.

[3] It is also possible to produce CRISPR-Cas systems that do not cause DNA cutting (*dead- Cas9*). Their use and applications have therefore not been evaluated in this report.

As part of the systematic review carried out on tomatoes, the search for undesirable effects was carried out using a "biased" approach[4] (using bioinformatics tools to predict the zones that could be modified, followed by PCR amplification and sequencing analysis of these zones) in 58/61 of the articles analysed. Off-target effects were described in four of these publications. An unbiased approach (carried out by complete sequencing of the genome, but whose effectiveness in detecting off-target effects depends in particular on the depth of sequencing) was used in four references and no off-target effects were detected.

An analysis of the literature reviews concerning all the plants published prior to this opinion and assessed as being of very good quality according to the AMSTAR-2 evaluation grid[5] (Shea et al. 2017), on the other hand, shows:

- for Modrzejewski et al (2019): the preferred use of a biased approach for identifying off-target effects (211/228 studies), and the identification of 55 off-target effects out of all the 1738 sites analysed (i.e. 3%). The authors nonetheless emphasise the great heterogeneity observed between the studies, particularly in terms of prediction and selection of off-target sites to be studied (15 different bioinformatics prediction tools used), detection method and species modified, as well as the lack of detailed information in several articles;
- for Modrzejewski et al (2020): the number of *mismatches* (minimum number of different bases between the targeted sequence and another potentially off-target sequence) appears to be the most important factor in the appearance of off-target effects, with the probability of an off-target effect decreasing as the number of mismatches increases, with an almost zero probability of obtaining off-target effects above 4 mismatches;
- for Sturme et al (2022): a biased approach was used to identify off-target effects (97/107 studies), and the analysis identified off-target effects in 28 of the 107 publications selected. In particular, it was observed that off-target effects were identified when the number of mismatches between the off-target site and the guide RNA was between 1 and 3. One study (Arndell et al. 2019) also mentions the insertion of transfer DNA which, according to the authors, is an important element to take into account in risk assessment.

Finally, as part of the systematic review of original articles published over the period 2021-2023, out of all the plants for which applications of CRISPR-Cas have been reported, 82 articles mentioning a search for unwanted effects on the plant genome were selected. Of these 82 articles, 64 (78%) mention a biased search for unwanted effects, 15 (18%) mention an unbiased search and three (4%) mention a combination of biased and unbiased searches. The WG observed a higher proportion of articles opting for unbiased research compared with the Modrzejewski et al. (2019) review (18% in the WG analysis, compared with 9/228, or 3.4%). The WG considers that this trend could be explained by the progress made in sequencing techniques (which are increasingly robust and powerful, less costly and offer higher sequencing depths). Of the 82 articles analysed, 28 (34%) described an unwanted off-target effect. Of these, 18 (64%) were identified by biased search, 8 (29%) by unbiased search and 2 (7%) by parallel use.

[4] The approach is said to be "biased" only insofar as it is based on *a priori* knowledge of the sites most likely to be modified, and not on the entire genome.
[5] AMSTAR: a measurement tool to assess the methodological quality of systematic reviews

of the two approaches. Of the 837 sequences analysed for off-target unwanted effects using a biased approach (amplification and sequencing of the amplification products), only 60 showed an off-target mutation, i.e. 7% of the sequences analysed.

Although the type of unwanted mutations observed is not often described in the articles analysed, the vast majority of cases described are short deletions or insertions (Jedličková et al. 2022; Liu et al. 2022; Narushima et al. 2022; Wang et al. 2021; You et al. 2022). Most of the unwanted effects observed are off-target effects due to rather non-specific guide RNAs, which most of the time have a number of mismatches with off-target sequences less than or equal to 3. The choice of guide RNA sequence is therefore important in limiting these off-target effects, but can prove complex in the case of sequence homologies in the genome. In addition, the choice between several guide RNAs for the targeted zone is not always possible, since it depends on the presence of a PAM site at the target. Among the undesired effects identified, off-target insertions of unidentified origin (a 35 bp insertion in grapevine (Wang et al. 2021) and a DNA insertion, from the vector used, at the target in soybean (Adachi et al. 2021)) were observed. Large deletions were also observed in tomato and rice in the studies by Li R. et al. (2022) and Zhang et al. (2022), where a large deletion of 3200 bp and 1525 bp, respectively, were reported.

In conclusion, the WG recommends, with regard to the molecular characterisation of plants resulting from site-directed mutagenesis using the CRISPR-Cas system (Figure 1), that :

- **the target zone(s) are sequenced, the modification(s) obtained are characterised and an appropriate detection method is provided by the petitioner;**
- **where possible, the breeder uses guide RNAs with more than 4 mismatches with the non-targeted zones of the genome, or justifies this impossibility;**
- **when the complete genome sequence of the species concerned is available and resequencing of the genome of the modified plant is feasible, an unbiased search for undesired effects on the genome should be carried out, combining *long read* and *short read* techniques, ensuring a minimum coverage of 20 X ;**
- **when resequencing is not feasible (for example in the case of polyploid plants or very large genomes) but a complete reference genome is available, a biased search is carried out on any genome sequence presenting 4 mismatches or less with the guide RNAs;**
- **when a complete reference genome of the species concerned is not available, a search for unwanted effects is carried out on any known homology zone;**
- **the absence of foreign DNA (including in the form of fragments) in the plant genome is demonstrated, either by resequencing the genome, or by targeted sequencing or Southern blot using probes specific to the plasmid or transfer DNA and the sequence corresponding to the CRISPR-Case system used.**

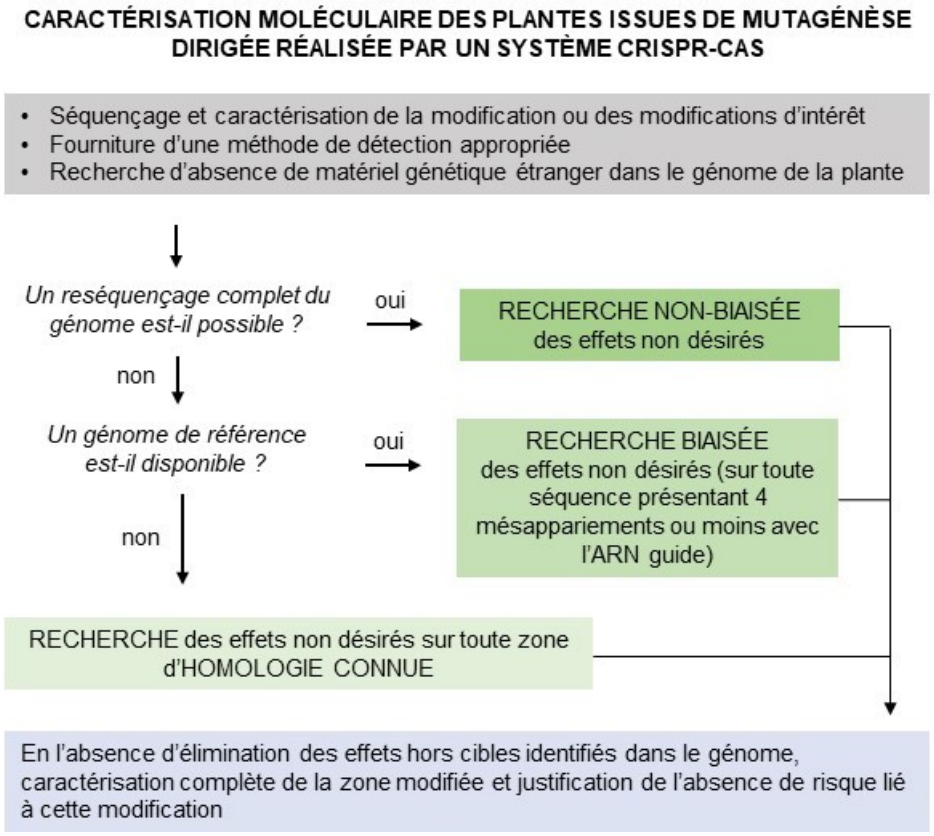


Figure 1: Recommendations for the molecular characterisation of plants resulting from site-directed mutagenesis using the CRISPR-Cas system.

3.3. Health and environmental risks associated with the use of plants derived from site-directed mutagenesis using the CRISPR-Cas system

In order to identify the health and environmental risks associated with the use of plants derived from site-directed mutagenesis using the CRISPR-Cas system, the WG successively analysed the risks covered by the current guidelines for assessing genetically modified plants, analysed a systematic review of the literature on the health and environmental risks associated with the use of plants obtained in this way, and studied 12 cases considered to be representative of applications of the CRISPR-Cas system on plants intended for food use.

3.3.1. Analysis of the current assessment framework for genetically modified plants and its suitability for the assessment of plants resulting from CRISPR-Cas directed mutagenesis

The reference system considered is defined by the various regulatory texts applicable to GMOs (Directive 2001/18/EC of the European Parliament and of the Council, Regulation (EC) No 1829/2003 of the European Parliament and of the Council, Commission implementing Regulation (EU) No 503/2013) and the EFSA guidance documents (EFSA GMO Panel 2010; EFSA GMO Panel 2011a; EFSA GMO Panel 2011b; EFSA GMO Panel 2011c; EFSA GMO Panel 2015;

EFSA GMO Panel 2017; EFSA GMO Panel 2019; EFSA GMO Panel 2023). In addition to identifying risks that are also relevant to plants derived from site-directed mutagenesis, the WG assessed the applicability of the current guidelines to plants derived from site-directed mutagenesis.

In the case of plants obtained by site-directed mutagenesis, **the WG considers that unexpected effects on the phenotype and agronomic characteristics of the modified plants are always possible, and that unexpected changes in the composition of the plants or the foods derived from them could also be observed, regardless of the modified trait**. Similarly, the WG points out that some food species may naturally contain toxic or anti-nutritional substances (EFSA 2012). These substances should be taken into account during the comparative study, and the WG considers that the 90-day toxicity study remains essential to identify a risk to human or animal health linked to the consumption of the genetically modified plant, or products derived from it. The WG also stresses that it remains possible to generate new reading frames in the genome, particularly in the case of insertions or deletions of a few base pairs in one or more exons of a gene, and that the overall allergenicity of the plant may be modified. In addition, the WG considers that a nutritional study remains relevant in the case of differences in the composition of plants obtained by site-directed mutagenesis.

With regard to environmental risks, the WG considers that the assessment of environmental risks as required by the current guidelines remains relevant for plants derived from site-directed mutagenesis. In a context where the number of species concerned, the number of modified traits and the number of applications could increase significantly in the short and medium term, the WG considers that this environmental risk assessment should take into account the potential cumulative effects on the environment in the long term associated with an increase in the area under authorised GM plant cultivation, as well as the agro-environmental characteristics of their cultivation. With regard to the transfer of genes to micro-organisms, the WG nevertheless considers that, insofar as only plant genes will be modified in the case of site-directed mutagenesis using CRISPR-Cas (without the introduction of a bacterial genome), the risk of transfer will be negligible.

Finally, the WG's conclusions for each area of risk assessment, in terms of applicability, identified limitations and recommendations, are set out in **Table 1.**

	Current requirements	Applicability according to the WG	Identified limits and WG recommendations
Comparative evaluation	1. Comparative study of the agro-phenotypic characteristics and composition between the genetically modified plant, an unmodified plant that is as close as possible genetically and six reference varieties, on at least eight sites. 2. Comparative study of the composition of processed products.	1. Yes 2. Yes	• Unavailability of OECD guide to compounds to be analysed for certain species

Toxicity	1. Oral toxicity study on rodents of newly expressed proteins at repeated doses for 28 days 2. Whole plant oral toxicity study on rodents at repeated doses for 90 days 3. Calculating exposure to newly expressed proteins	1. No (except in specific cases) 2. Yes 3. No (except in specific cases)	• Low palatability of certain plant species for rodents • Difficulty in ensuring the ingestion of controlled quantities of certain species (if high water content, for example)
Allergenicity	1. Analysis of the possible appearance of new reading frames due to genetic modification of the plant 2. Study of the allergenicity of newly expressed proteins (including resistance to digestive proteolysis and thermal denaturation) 3. Literature review on the allergenicity of whole plants	1. Yes 2. No (except in specific cases) 3. Yes	• In general, adaptations could be made to take better account of species diversity, in particular by using LC/MS-MS[6] techniques.
Nutritional assessment	1. Calculation of nutritional intake in the event of consumption of the genetically modified plant 2. Nutritional study on target animals	1. Yes 2. Yes	• Low palatability of certain plant species • Difficulty ensuring the ingestion of controlled quantities of certain species
Environmental risks	Literature-based analysis of any direct or indirect, immediate or delayed risk to the environment associated with the marketing authorisation	Yes	• Generally speaking, we need to take better account of long-term cumulative effects and agri-environmental characteristics. • Analysis of the risks of gene transfer to micro-organisms applicable but not very effective relevant

Table 1. Applicability and limitations of the current assessment framework for genetically modified plants for plants derived from site-directed mutagenesis using a CRISPR-Cas system.

[6] Liquid chromatography *tandem mass* spectrometry (*LCMS*)

The WG therefore considers that the current framework for assessing health and environmental risks is only partially adapted to plants derived from directed (or targeted) mutagenesis. In particular, the WG considers that all the requirements relating to newly expressed proteins contained in toxicity and allergenicity assessments cannot be directly transposed to the assessment of plants derived from site-directed mutagenesis, and that the analysis of the risk of gene transfer to micro-organisms is not very relevant.

3.3.2. Systematic review of the literature

The search was carried out using both original articles and reviews. However, the 13 references selected were exclusively reviews, as it was not possible to identify any original articles presenting results relating to the health or environmental risks of plants obtained by site-directed mutagenesis. In addition, only reviews containing a description and analysis of the potential risks associated with plants obtained by site-directed mutagenesis were retained.

The WG notes from this systematic review of the literature that new applications, which were not feasible using other selection techniques, could emerge as a result of the use of NTGs. These include applications involving multiplexing, or targeting protected regions of the genome (for example, heterochromatin regions and genomic regions with low recombinogenicity) and therefore not reached by conventional selection methods. The WG also points out that the CRISPR-Cas system could be applied to wild species, leading to *de novo* domesticated plants, without any history of safe use being available.

With regard to the risks associated with plants derived from CRISPR-Cas directed mutagenesis, the WG also notes that some of the known risks already associated with transgenic plants are also true in the case of plants derived from directed mutagenesis. The WG notes that the level of occurrence of these risks could be accentuated if the number of genetically modified plants appearing on the market and put into cultivation were to increase, particularly as regards risks to the environment (differential use of certain herbicides or appearance of resistance in certain target pathogens or insects, for example).

Finally, the WG agrees with the conclusions of several authors who point to a new risk associated with the potential off-target effects of NTGs and the possibility of pleiotropic effects (on several distinct traits). The WG also shares the finding that the possibility of pleiotropic effects or unintended changes in plant composition is increased in the case of multiplexing, which one article indicates is commonly used at the research and development stages (Kawall 2021).

3.3.3. Case studies

To complete its analysis, and in the absence of original articles on the health and environmental risks associated with plants derived from site-directed mutagenesis, the WG carried out a case study based on the analysis of 12 plants identified among the applications most likely to reach the market in the short term and selected to represent the diversity of applications, species and modified traits.

Based on these case studies, the WG concludes that there are potential new health and environmental risks associated with plants derived from CRISPR-Cas directed mutagenesis, mainly due to :

- obtaining new genotypes that cannot be obtained using other selection techniques;
- new species and traits that can potentially be modified by CRISPR-Cas, compared with what is classically observed for plants derived from transgenesis (modification of more invasive species, or easier modification of composition, for example);
- the potentially large increase in the area under cultivation of varieties with the same modified trait.

The WG also points out that some of the known risks associated with genetically modified plants remain true for plants derived from site-directed mutagenesis.

The main risks identified in these case studies are presented in **Table 2**.

	Risks identified	Case studies
Comparative assessment, plant composition	• Pleiotropic effects leading to a change in the plant's agro-phenotypic properties or composition • In the case of multiplexing or if a transcription factor is targeted, increased risks associated with pleiotropic effects	• Herbicide-resistant potatoes • Gluten-reduced wheat
Toxicity, allergenicity, nutritional assessment	• In the event of a change in composition, whether desired or unexpected, or a potential change in the toxicity, allergenicity or nutritional characteristics of the plant	• Tomato with high GABA (γ-aminobutyic acid) content
Environmental risks	• Risk of gene flow from edited genes to wild or cultivated populations • If a growing number of modified species are cultivated, there is an increased risk of gene transfer to weed species, including invasive species. • Modification of interactions with animals consuming plants obtained using NTGs and with insect pollinators • Changes in selection pressure could lead to an increase in the pathogenicity of certain biological hazards, particularly for long-lived crops. • In the case of multiplexing, transfer of gene combinations with unassessed epistasis	• Tomato with high GABA content • Reduced-size rice • Sage with reduced phenolic acid content • Vine resistant to grey rot • Erect switchgrass with increased tillering

Table 2. Health and environmental risks associated with plants derived from site-directed mutagenesis and identified in the case studies.

In particular, the WG notes that certain potential risks appear repeatedly in these case studies. These include, in particular, risks associated with an unexpected change in the composition of the plant, which could lead to nutritional, allergenicity or toxicity problems, or medium- and long-term environmental risks, such as the risk of gene flow from edited genes to compatible wild or cultivated populations (increased by the new diversity of potentially modified species) or risks associated with a change in interactions with animals (including insects) in the event of consumption of or visits to plants resulting from site-directed mutagenesis, which could become more frequent if the variety of modified species increases. However, the WG also concludes that in some cases, the use of CRISPR-Cas for site-directed mutagenesis only allows known phenotypes to be replicated, by acting rapidly on one or a few well-described genes, and that it does not therefore identify any new risk to health or the environment.

3.3.4. Recommendations for assessing identified risks

The WG recommends a case-by-case assessment of the health and environmental risks associated with genetically modified plants resulting from site-directed mutagenesis using the CRISPR-Cas system, taking into account the characteristics of the genetic modification carried out and of the resulting product, and analysing the consequences of the genetic modification in terms of agronomic, phenotypic and compositional characteristics, as well as immunological, toxicological and nutritional aspects.

The WG recommends that this assessment be supplemented by an analysis of the literature extended to the modified gene or the new trait. For plant species which, following authorisation, would be newly cultivated in all or part of the country, the WG also recommends that, in addition to the required tests, the literature review should highlight, if available, articles relating to the environmental risks associated with the introduction or mass cultivation of these plants.

To take account of certain potential risks associated with the technical possibilities offered by genomic modification of plants using CRISPR-Cas, the WG recommends in particular :

- **if the modification(s) carried out are intended to modify the biochemical composition of the plant, to carry out an analysis of the content of the new compounds and of the compounds potentially affected by this modification, in parallel with the comparative study of composition;**
- **if the purpose of the modification(s) is to suppress or modulate one or more transcription factors, to carry out a bioinformatics analysis to identify the target genes of the transcription factor, followed by a comparative study of the transcription levels of the target genes identified;**
- **if the modified species presents a known allergenic profile or reveals potentially allergenic substances, to carry out, in parallel with the comparative compositional study, a systematic ELISA or LC-MS/MS assay of the major allergens least susceptible to environmental variations (nsLTP, cupins, trypsin inhibitors), supplemented in the case of wheat by an assay of gliadins and glutenins;**

- **if the species on which the modification is made naturally expresses known toxic, genotoxic or anti-nutritional compounds, to carry out a systematic assay of these compounds in parallel with the comparative study of composition.**

The WG also notes that, in some cases of plant genome modification, the CRISPR-Cas system may be used to reproduce known mutations, either because they have already been obtained by other systems, or because they are intended to replicate a known allele in another variety or in a closely related species. The WG recommends that, where a history of knowledge is available, i.e. :

- **if the genetic modification(s) carried out are functionally similar at molecular level to a modification obtained by other techniques, including random mutagenesis or conventional selection, and already authorised on the market without any specific risk to health or the environment having been described OR if the genetic modification(s) carried out are naturally present in another species (homologous gene).**
- **AND that the genetic modification(s) carried out lead(s) to a known phenotype whose health and environmental safety has been demonstrated**

that the assessment procedure be simplified and limited, after molecular characterisation, to a comparative study of the composition of the plant (EFSA GMO Panel 2015), in order to rule out any unexpected pleiotropic effect on the plant.

The SANTVEG ESC recommends that the literature on environmental risks, when available for a plant with a similar trait (and obtained by other selection methods), should also be taken into account as far as possible in the assessment of plants resulting from site-directed mutagenesis.

In view of the lack of data on the medium- and long-term environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system, particularly for long-crop species (in arboriculture, for example) or in the event of intensification of cultivation of this type of NTG plant, and the potential direct and indirect cumulative effects, including on cultivation practices, the WG recommends that a post-authorisation environmental risk monitoring plan be set up by a body independent of the petitioner, regardless of the assessment framework used. This monitoring plan should take into account the cumulative impacts associated with the cultivation of different varieties derived from site-directed mutagenesis presenting the same modified trait, as well as the impact of marketing authorisations for plants derived from site-directed mutagenesis on cultivation practices. In particular, it should contain :

- **in the case of plants resistant to biotic stress, monitoring the development of bypassing in the bio-aggressors concerned;**
- **the dispersal of these plants in the environment;**
- **gene flow from these plants to compatible weeds or wild plants;**
- **an assessment of the impact of the modified characteristics, enabling an estimate to be made of the volumes of inputs used.**

In the event of a proven negative environmental impact, the WG recommends that the results of the monitoring plan should lead to a review of the marketing authorisation.

3.4. Proposed guidelines for assessing the risks associated with growing and using plants derived from site-directed mutagenesis using the CRISPR-Cas system in food and feed

On the basis of the results and conclusions presented in sections 3.1 to 3.3, the WG is proposing a comprehensive, case-by-case assessment framework, a graphic representation of which in the form of a decision tree can be seen in **Figure 2**.

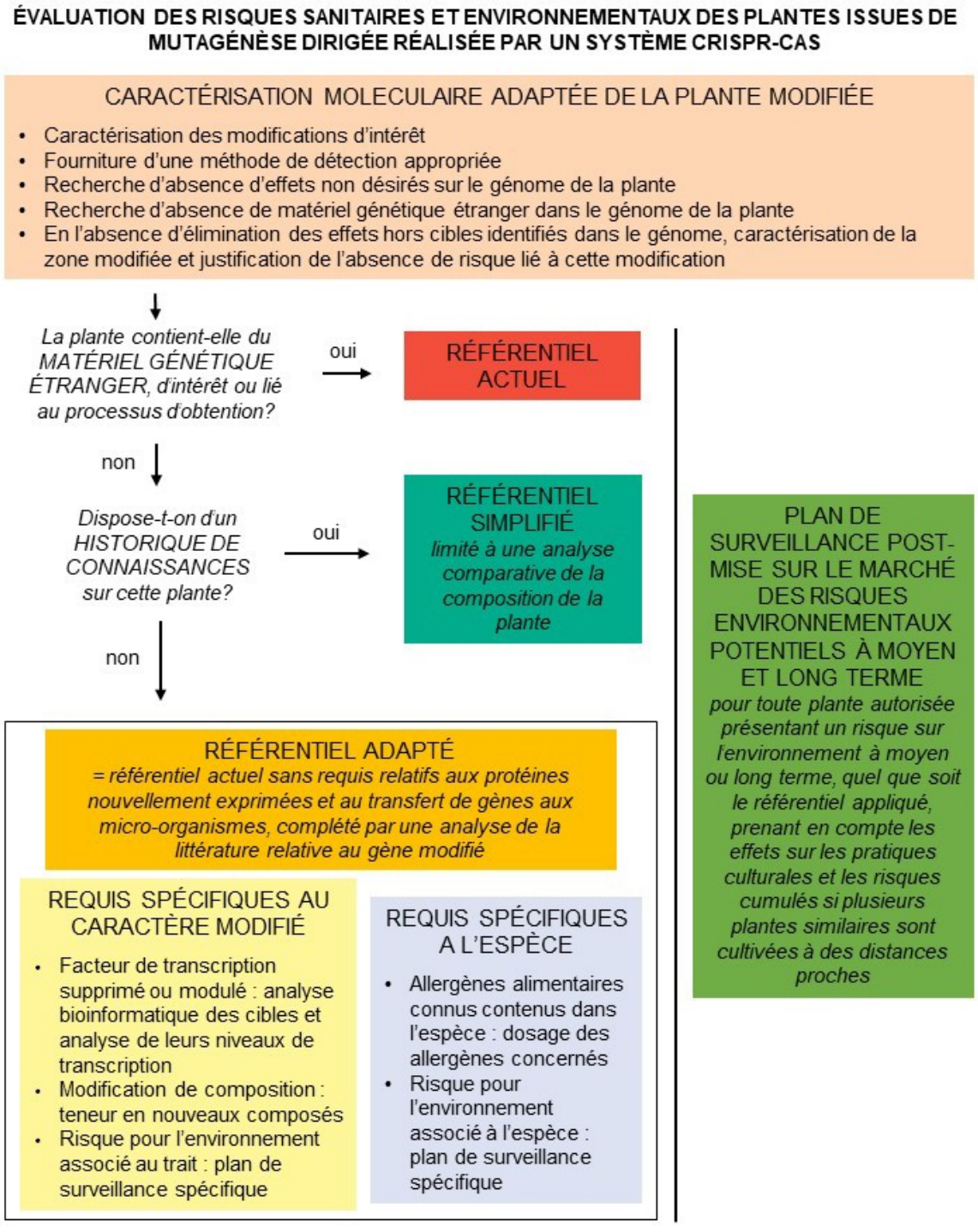


Figure 2. Decision tree for assessing the health and environmental risks of plants derived from site-directed mutagenesis using a CRISPR-Cas system.

The complete assessment reference system proposed by the WG provides, **for any new plant resulting from site-directed mutagenesis, a molecular characterisation of the modified plant**, including a characterisation of the modified site, a search for undesired effects on the plant genome and a search for the absence of any foreign genetic material introduced during the transformation stage, according to the procedures described in section 3.2.2. Furthermore, if unwanted effects on the genome are identified and their elimination is not demonstrated, the WG recommends that a characterisation of the region concerned by the unwanted effect be carried out and that the absence of risks associated with the unwanted modification be justified by the petitioner.

If the absence of foreign genetic material in the plant obtained using NTGs cannot be demonstrated, in particular following a stable expression phase of the CRISPR-Cas system in the plant in order to obtain the desired mutation, **the WG recommends that the plant be assessed according to the current assessment reference system**, i.e. according to the provisions of Directive 2001/18/EC, Regulation (EC) No 1829/2003 and Implementing Regulation (EU) No 503/2013, according to their respective fields of application.

If the absence of foreign genetic material is demonstrated and the petitioner has a proven track record (cf. section 3.3.4), the WG recommends a simplified assessment framework limited to a comparative study of the plant's composition.

If the absence of foreign genetic material is demonstrated but the petitioner cannot provide a history of knowledge, the WG recommends that an appropriate standard be established. This corresponds to the current assessment framework for genetically modified plants, with the exception of the requirements relating to the expression of a new protein and the requirements relating to the risk of gene transfer to micro-organisms (see section 3.3.1), but supplemented by specific requirements relating to the modified species or trait, in accordance with the procedures described in section 3.3.4.

Lastly, the WG recommends that a post-authorisation monitoring plan for environmental risks be put in place for the entire duration of the authorisation, taking into account the cumulative impacts of growing different varieties derived from site-directed mutagenesis with the same modified trait, as well as the impact on cultivation practices of marketing authorisations for plants derived from site-directed mutagenesis.

3.5. Socio-economic issues associated with plants and products derived from NTGs: multiple sectors and players

The introduction of plants or products obtained using NTGs could have an impact on the agricultural sectors concerned in France, from upstream to downstream in the value chain. The WG identified the various sectors of activity and players potentially concerned by NTG-derived plants and their derived products through a description of four agricultural sectors (tomato, common wheat, carrot and vine), representing various possible applications of NTGs and different technical and economic situations in terms of varietal development, production, marketing and consumption in France. The socio-economic issues associated with plants and products derived from NTGs for these different sectors and French players were then analysed through a systematic literature review. This literature review was supplemented by an analysis of the positions of the players, based on the existing literature on the controversies surrounding plants derived from NTGs.

NTGs and stakeholder hearings[7]. On this basis, the WG analysed the potential socio-economic implications of changing or not changing the regulations concerning plants obtained using NTGs according to various possible scenarios.

3.5.1. Description of the agricultural sectors potentially concerned by NTG plants and products

The description of the agricultural sectors potentially concerned by plants and products derived from NTGs has made it possible to identify the different types of players involved in these sectors and to perceive the challenges for these sectors of introducing these plants and products. However, given the current absence of NTG-derived plants or products in Europe, it has not been possible to analyse the impact of these innovations on the sectors potentially concerned.

The value chains for the varieties selected as case studies (tomato, common wheat, carrot and vine) comprise six stages: variety creation, seed and plant production, variety production, agri-food processing, variety or product distribution and consumption (**Figure 3**).

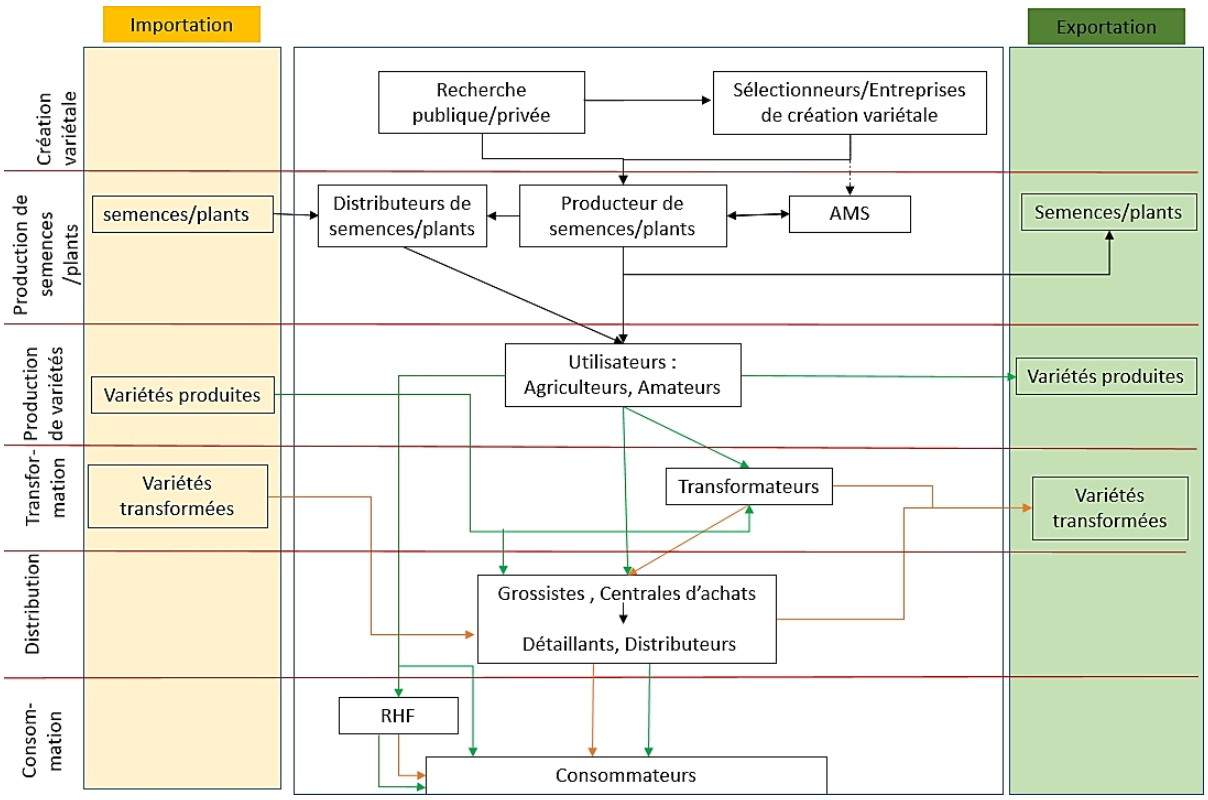


Figure 3: Conceptual diagram of the value chain for selected varieties. The abbreviations AMS and RHF stand for "Agriculteurs-Multiplicateurs de Semences" and "Restauration Hors Foyer" respectively. The arrows show the links between the different groups of players from upstream of variety production to the last link in the value chain. The black arrows represent seed transactions, the green arrows represent direct seed product transactions and the orange arrows represent processed product transactions.

[7] The list of stakeholders interviewed is presented in the collective expertise report.

Variety creation is a dynamic sector for all four sectors in France, although to a lesser extent for the carrot sector. This dynamism does not always translate into dynamic production. Over the last few years, tomato production has tended to fall, soft wheat production has remained static, grape production has fluctuated with no clear trend, and carrot production, a sector where new varieties are the least developed, has increased. These different trends are linked to the strategic choices made by producers (the choice of high quality for tomatoes), weather conditions, prices and disease (for vines).

The four sectors are not equally dependent on international trade. The tomato and carrot sectors depend on imports to meet demand. Each sector imports twice as much as it exports. The carrot sector imports almost exclusively from the European Union, while the tomato sector depends mainly on countries outside the European Union. Morocco alone accounts for 66% of tomato imports into France.

The French wine industry is differently integrated into international trade depending on whether the grapes are table or wine grapes. Imports of table grapes are significant, while those of wine grapes are non-existent, according to the various institutions that record trade. Nevertheless, the wine sector is highly integrated into international trade, exporting more than it imports, with imported wines coming primarily from Italy, a member of the European Union.

The soft wheat sector is very well integrated into international trade and plays a very favourable role in France's trade balance. Exports are 79 times greater than imports of common wheat.

Given the specific characteristics of each sector, it is likely that the introduction of plants or products from NTGs into the European Union would not affect them in the same way. The effects could be significant for industries that are highly integrated into international trade. Industries dependent on imports, such as tomatoes and carrots, could be encouraged to use NTG varieties in order to become more competitive. As for sectors with a significant weight in France's trade balance, such as soft wheat and vine, the introduction of plants or products derived from NTG could enable them to maintain their market share, or even gain market share. Finally, sectors that are highly dependent on countries outside the European Union would be affected to a greater or lesser extent depending on the regulations governing NTG-derived plants.

Despite the interest that plants obtained using NTGs can present through the various characteristics highlighted in the potential applications, the adoption of these innovations in the various sectors could require changes in the specifications, particularly for organic farming. This raises potential difficulties associated with the coexistence of the NTG, conventional and organic sectors.

3.5.2. Socio-economic issues associated with NTG plants and products

Figure 4 identifies the main points on which the economic and social impacts associated with the introduction of plants and products obtained using NTGs need to be considered (right-hand side of the figure). The socio-economic literature available is fairly limited and is largely made up of *position papers* on the issues at stake.

innovations rather than their impact. Few empirical studies have been carried out to date. A few articles are based on survey data and, to a certain extent, make it possible to specify the impacts perceived by various types of player, but there is very little work quantifying the real impacts of choices to regulate plants and products obtained using NTGs on seed prices, agricultural and food prices, costs and gains for the sectors, or the economic risks for the various types of player. Quantitative assessments are therefore very partial.

As NTG-derived plant varieties are not currently on the European market, the analyses are prospective and aim to assess the possible economic and social impacts that would result from the strategies of the players and the public regulatory choices. Assessment of these possible impacts presupposes that the NTG-derived plants in question have been granted marketing authorisation (and therefore health or environmental risk assessment if they are not considered equivalent to conventional plants). The abundant literature on GMOs derived from transgenesis can provide benchmarks and illustrate certain economic mechanisms. **However, most of the elements from the economic literature available on plants and products obtained using NTGs should be considered as hypotheses that have yet to be confirmed rather than as proven results.**

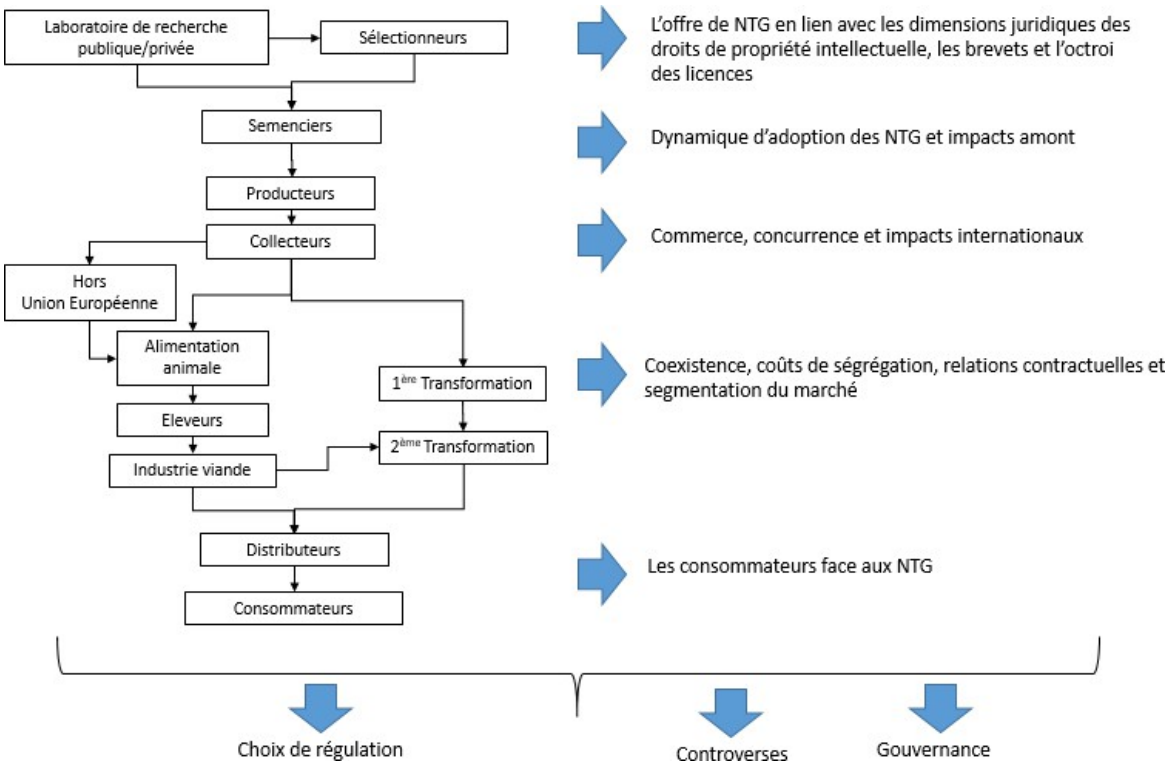


Figure 4: Conceptual diagram of the analysis of the socio-economic issues associated with NTG plants and products.

3.5.2.1. The supply of plants and products obtained using NTGs in relation to the legal aspects of intellectual property rights, patents and licensing.

Analysis of the regulatory landscape for plants shows that, even if GMO regulations (including NTGs) have no direct impact on the patentability of plants and products derived from these techniques, the supply of these plants and products may nevertheless be indirectly impacted by the regulatory situation. Changes in regulations can influence patenting decisions, depending on whether they are perceived as flexible or rigid by biotech companies.

As far as plants are concerned, there are two industrial property titles that apply in Europe. Firstly, plant variety certificates (VOCs), which confer rights only on products, enabling breeders to reproduce processes to obtain other marketable varieties. On the other hand, patents apply to products and processes, the use of which requires the negotiation of a licence with the holder. In the European context, a plant variety can only be protected by a PVC (and not by a patent), unlike in the United States, for example, where a plant variety can be protected (including simultaneously) by a PVC and by a patent. The scope of patent regulations also varies from one legal system to another. Exceptions applied in European regulations, for example, make it possible to protect the natural characteristics of plants by including a *disclaimer* in patents.

According to the literature, several solutions have been proposed to regulate the development of patents on NTGs. These range from specific forms of patent (*patent pools, clearinghouses, licensing pledges, open source)* to legislative reform of the system, with various possible options: abandonment of patents, in-depth revision or adjustments to patent law. The interest in and use of these different types of patent (in the development phase) depend on the type of players/companies (small breeders, large biotech companies, etc.) developing these technologies.

The regulation of intellectual property linked to patents on plant breeding is a major issue to be considered in connection with possible changes to GMO regulations. Assuming that the objective is to enable the dynamics of varietal innovation by limiting imbalances between players in terms of value sharing, the WG stresses the importance of adapting the current regulatory framework in terms of intellectual property rights.

3.5.2.2. NTG adoption dynamics and impacts upstream of the supply chain

Compared with other available breeding methods, most scientific publications consider that NTGs increase the precision in targeting the traits to be developed and the probability of success in the Research and Development (R&D) phases. As a result, NTGs could make it possible to develop varieties likely to reach the end market at a lower cost and in a shorter time than plants derived from transgenesis. As a result, (i) the profiles of companies involved in R&D appear, at this stage, to be more diversified in the case of NTGs than in the case of transgenic plants, with a significant involvement of small and medium-sized companies and public bodies; (ii) NTGs would make it possible to reduce the size of the market needed to ensure profitable investments for those who use them; (iii) NTGs would make it possible to

more diversified varietal innovations in terms of desired characteristics and species covered.

The plant breeding industry has undergone a strong process of concentration at international level, to which the strategies of companies developing transgenesis applications have contributed. In the case of plants obtained using NTGs, the question is to what extent their characteristics (precision in the selection of desired traits, lower development costs, ease of use, etc.) could amplify the process of concentration in the variety breeding and seed sector, or on the contrary contribute to reducing the barriers to entry into these markets. At this stage, the available literature does not allow us to answer this question. Among the consequences to be studied in particular are those relating to the effects on the market power of the players in plant breeding, on the sharing of value within the sectors and on seed prices for growers.

The literature analysed also emphasises that the economic impacts associated with plants and products obtained using NTGs will depend heavily on the regulatory choices made at European level. By affecting the economic trade-offs of the different types of players, these will have a direct influence on the incentives to develop and adopt these techniques. These regulatory choices may also influence the degree of concentration in the sector and decisions on R&D investment and location, and will have an impact on the ability of European companies to operate on export markets.

The question of the extent to which the characteristics of site-directed mutagenesis technology could amplify the process of concentration in the plant breeding and seed sector, or, on the contrary, contribute to reducing the barriers to entry into these markets and encourage the involvement of small and medium-sized biotechnology companies, or even public research players, remains an open question. It is clear, however, that the impact of the development of NTG-derived plants on the concentration of the plant breeding and seed sector is a major issue, and one that the public authorities should be vigilant about in the event of changes to GMO regulations, and be alert to any abuses of dominant market positions.

3.5.2.3. Trade, competition and international impact

Based on the body of literature analysed, publications on international trade, competition and international impacts focus mainly on the implications of differences in regulatory frameworks for NTG-derived plants and products. The threat of unpredictable and restrictive trade environments has been highlighted, in that they can lead to the establishment of trade barriers and have an impact on competition. Although there have been no documented cases of disruption to international trade in crops or products derived from genome editing, the experience of GMOs derived from transgenesis is frequently cited as an early warning of such tensions.

Scenario-based studies show that regulatory differences could affect trade and the competitiveness of EU farmers on world markets using NTGs. These studies offer insights into the future challenges and opportunities for international trade in products derived from NTG plants. **However, as these studies are few in number, the perspectives they offer should be interpreted with caution. Opportunities linked to barriers**

trade caused by differences in regulatory choices (such as protecting national or European economic activities, encouraging the development of alternative technologies, etc.) have not been studied.

3.5.2.4. Coexistence, costs of segregation, relations relations and market segmentation

The economic impact of the introduction of plants obtained using NTGs on the sectors will depend on the nature of the traits being innovated.

The first type of innovation involves varietal innovations aimed at increasing the effectiveness and/or efficiency of agricultural and agro-industrial production. The economic interests of producers and the upstream levels of the supply chain will be decisive in the development and adoption of these innovations. In the presence of GMO-type regulations, based on strict rules of coexistence and product segregation, the additional costs associated with these rules are likely to be higher than the gains for the players in the sector, due to the probable devaluation of the product by consumers (as products derived from NTGs offer nothing more to consumers than conventional products, suppliers of products derived from NTGs could only enter the market at a lower price than conventional products). As with products derived from transgenesis, this could act as a brake on the development of these varietal innovations in the human food sector.

A second type of varietal innovation is part of companies' product differentiation strategies (allergen-free products, different sensory and nutritional qualities, etc.). The aim here is to capitalise on the potential willingness of a proportion of consumers to pay for these distinctive characteristics. This type of strategy could be envisaged, even in the case of restrictive regulations on coexistence, because traceability and segregation requirements would be imposed, in any case, for reasons of commercial credibility in the eyes of consumers. However, this would require selection objectives to be defined in a coordinated way between players in the industry, based on contractual relations between seed companies, producers and final product marketers. Given the additional costs and the complexity of the co-ordination arrangements to be put in place, the first condition is that the distinctive characteristic should be significantly valued by consumers.

A third type of innovation concerns varietal innovations designed to meet environmental, health and/or social challenges, for which there is not necessarily an economic incentive to adopt them (e.g. restoring biodiversity). The private costs of these environmental or health innovations may exceed the anticipated private benefits. If net collective benefits (economic cost/benefit balance or environmental risks/benefits) are proven, this would raise the question of possible public support to encourage their adoption.

While certain characteristics of varieties derived from NTGs (increased yields, allergen-free products, different sensory and nutritional qualities, etc.) may encourage players in the sector to develop them, this is not necessarily the case for certain innovations which, although they respond to environmental and climatic issues, do not generate either productivity gains or growth in demand (additional willingness to pay on the part of consumers for these characteristics in particular). **In this context, by taking into account health, environmental and**

In view of the potential social impact of these innovations, public intervention, and in particular support for public research, would be decisive in guaranteeing the capacity to develop innovations with a view to making the European agricultural and food system more sustainable.

3.5.2.5. Consumers and NTGs

With regard to consumer behaviour, the literature consulted shows that, even if genetically engineered food products are *a priori* less well accepted and appreciated by consumers than conventional products, there is a certain heterogeneity of perceptions between different consumer profiles and between countries, even within the European Union. Although some studies show that consumers with a good knowledge of the technologies are the most averse and tend to reject them, other studies emphasise that the information available on biotechnologies and the differences between transgenesis and NTGs could change the positions of some consumers from rejection to acceptance of food products derived from them, especially as products derived from NTGs are associated with lower prices. Furthermore, the studies do not allow us to identify categorically whether consumers appreciate NTGs differently depending on the potential benefits (productivity, environment, health) they bring to food products or production processes. However, insofar as NTG-derived products are not currently available to consumers, the decisions and behaviour observed remain declarative (intention rather than action). Finally, no study has assumed that NTG products are untraceable or unlabelled. In this sense, there is still uncertainty as to how consumers would react if all or part of the foodstuffs derived from plants obtained using NTGs were not traced and labelled right through to the final product.

Generally speaking, the acceptability of and willingness to pay for NTG food products places them between GMO products and conventional farming products, which are themselves less well perceived than organic farming products. Further studies, more precise in terms of the characteristics of the products on offer and the information disseminated in particular, would be necessary in order to gain a better understanding of the mechanisms of acceptance and rejection. The question of the intensity of this information could also be raised.

One of the expectations of consumers is to be informed about the nature of the products they are offered, particularly in terms of the technologies used for varietal selection. This concern should also be taken into account with a view to increasing the overall transparency of these products. Requiring the applicant to provide a detection method when applying for marketing authorisation for a variety derived from NTGs could help to ensure the traceability of products derived from these plants.

Sectors (particularly organic) wishing to highlight the non-NTG nature of their products could develop specific labelling on a voluntary basis. However, this provision could require a strengthening of documentary traceability, which is already in place in sectors with labels, and would most certainly result in an increase in product monitoring costs for the sectors as well as for the control authorities, all the more so in the absence of methods for tracking and tracing products.

standardised detection methods. Seed labelling, mentioning the technology used, would be an essential requirement for traceability.

3.5.2.6. Choice of regulation

The publications analysed highlight four important characteristics of NTGs that need to be taken into account when discussing the issues involved in regulatory choices:
(i) the difficulty of tracing NTGs in the resulting organisms (and products) on the basis of current analytical methods, which raises the question of the conditions and procedures for controls to discriminate between products on the markets; (ii) the decentralisation of knowledge and uses made possible by easier access to the technology, which could potentially open up the market to new players, but could also increase the risks (e.g. uncontrolled off-target alterations), if these players have less experience than the traditional players on the breeding market; (iii) uncertainties relating to *off-target* alterations, which require a combination of *ex-ante* regulatory procedures (prior to the deployment of innovations), defining the framework for the application of NTGs, and *ex-post* procedures (after their deployment, where applicable), based on liability and compensation rules in the event of unexpected effects; (iv) rapid developments in knowledge and plant breeding technologies, which risk rendering certain regulations rapidly obsolete and make it necessary to put in place appropriate modes of governance.

A first trade-off discussed in numerous articles concerns the choice between process-based and product-based regulations. In the first case, it is the technologies used in the selection process that determine the procedure for authorising the marketing of the new variety. In the second case, the legislation is product-based: the specific characteristics of the new variety determine the authorisation procedure (on a case-by-case basis). The two regulatory frameworks have different properties: product-based regulation is more flexible because it can be applied to any technology, whereas process-based regulation has to be adjusted each time a new technology is introduced.

A second trade-off concerns the possibility of differentiating the rules according to the level of alteration of the initial genome associated with the technology by establishing, for example, exemptions for products obtained by SDN-1 or even SDN-2 techniques (which could be assimilated to conventional products) and retaining process-based regulations for products derived from SDN-3[8] including transgenes.

A third trade-off concerns the role of *ex ante* regulations (e.g. coexistence rules in the field) and liability rules in the event of *ex post* damage. An important point here, in the event of new varieties derived from NTGs being introduced onto the market, is the interaction between products derived from them and products complying with specifications that exclude these technologies, such as organic farming in particular. This will determine how products derived from NTG varieties are identified (detection and labelling) on the market, and how they coexist with organic products.

[8] The SDN-1 mechanism is used when the results obtained are point mutations or insertions/deletions of DNA fragments (generally a few base pairs), in the absence of a DNA sequence added to act as a repair template. When a DNA sequence is added as a repair template, the results obtained are either a modification of the sequence of one or more genes (this is known as the SDN-2 mechanism, as the template is not integrated into the genome), or the integration of this sequence into the genome (this is known as the SDN-3 mechanism).

products from non-NTG varieties (which will influence the costs of segregation, control and preservation of product identity). To date, there is no specific analysis of this point in the economic literature on NTGs, but the parallel with GMOs produced by transgenesis could provide food for thought.

3.5.2.7. Positioning of stakeholders and governance of NTG controversies

An analysis of the controversies surrounding NTGs shows that there is no unanimity on how to frame the problems to be addressed: as the debate often focuses on technical aspects, risk and efficiency, it leaves in the shade the issues associated with the systemic context, intellectual property, market dynamics, the question of justice and equity, and ethical issues. As a result, one of the visible lines of tension is that between different agricultural systems and aims: on the one hand, a vision that sees technological innovation as a guarantee of greater precision, yield and economic benefits; on the other, a vision that criticises this system, arguing that it does not respond to social and ecological issues, that it is based too much on monoculture and pesticides, and that it mobilises - as was the case at the start of the development of GMOs or synthetic biology - an entire 'economy of promise'. One of the criticisms voiced in some of the hearings (see table 10 in the report) is that NTGs can only resolve certain symptoms of climate change and ecological problems, but are not capable of resolving their root causes. Analysis of the controversies surrounding NTGs also highlights the issue of choice. Whether through traceability and/or labelling, studies show that consumers have a preference for making the issue of genetic modification visible.

The hearings held as part of the processing of this referral show the existence of many lines of tension and uncertainty. This is consistent with the results of the literature showing that different publics - whether consumers, farmers or other stakeholders - do not form homogenous groups, and that placing the
By placing the "public" in the position of a recipient of information, there is a risk of overlooking the values, criticisms, arguments, choices and political questions (particularly when they relate to systemic issues) of the public. Among the questions raised by the stakeholders interviewed, we might mention: (i) the attribution of costs associated with a possible health problem or contamination and/or downgrading of a batch of organic products due to NTG products, (ii) the implications of the profusion of new terms, such as "NTG",
"NGT", "NBT" or genome editing - and the parallel disappearance of terms like
"These include: (i) the impact of GMOs on the accessibility of the debate to different audiences, (iii) the potential consequences of the development of NTG-derived plants on market diversification or concentration, (iv) the modalities of any labelling of NTG products and those of coexistence between different agricultural systems. If the current regulations are revised, a new controversial issue is likely to emerge, relating to the indicators used to draw the line between GMOs and NTGs (and to determine an 'equivalence' between conventional products and NTG products), and this is likely to become a hotly contested issue.

The WG's analysis of these controversies has identified several points of tension. The technology of directed mutagenesis creates a new node in the controversies, namely that of the existence, or not, of a boundary between the

GMO" and "NTG" technologies, and that of the indicators used to draw this boundary and determine a possible "equivalence" between conventional products and products derived from directed mutagenesis (NTG). The debates on regulatory developments raise potential problems of "path dependence", i.e. decisions taken today could limit the scope for manoeuvre in the future. On the one hand, **today's decision not to use the technology of directed mutagenesis may be seen as limiting the scope for action in the event of difficulty in meeting future climate and environmental challenges by changing agricultural practices and production methods alone. On the other hand, the use of directed mutagenesis technology can be seen as opposing the necessary evolution of the current agricultural and food system towards a more sustainable agro-ecological model. The role of technology, and in this case genetic engineering, in establishing an agro-ecological model for European agriculture is at the heart of these debates.**

In this context, the question of how to ensure that opposing viewpoints and their foundations are expressed in public debate on a scientific basis, and how to overcome them, is crucial. While there seems to be a consensus on the need for public dialogue, it is less clear how this dialogue should be organised and conducted if it is to be fruitful and contribute to overcoming these oppositions. The study of the conditions and procedures for the governance of these controversies goes beyond the scope of this referral, and further work should be devoted to it.

3.5.2.8. Regulatory scenarios applying to plants and products obtained using certain NTGs and associated socio-economic issues

The question of possible changes to GMO regulations, and whether or not varieties derived from transgenesis and those derived from site-directed mutagenesis should be considered in the same way, can be approached from different angles. Firstly, it can be analysed from the point of view of the impact it could have on the incentives for industry players to develop and use varieties derived from site-directed mutagenesis, on the choices given to consumers, and more generally on the advantages and disadvantages, particularly economic, that the various types of player may find.

However, beyond the short-term effects of the possible options, changes in regulations also raise questions about the longer-term dynamics of the agricultural and food system, and the role, for example, that genetic engineering-based varietal innovation should play in it, in relation to changes in farming practices in an agro-ecological model for European agriculture, the need to rethink patent and licensing regulations in the light of the development of directed mutagenesis technology, and the role of public research bodies in guaranteeing varietal innovation that meets the challenges of sustainability. These are important questions, but they go beyond the scope of this referral. They nevertheless deserve to be analysed and discussed in depth in subsequent studies, especially as they lie at the root of many controversies.

The WG therefore confined itself to examining 'feasible' scenarios in the short term, focusing on an analysis of possible economic impacts. It has nevertheless attempted to link this to the

controversies identified, and in so doing to place it in relation to a number of longer-term issues.

The scenarios considered range from the status quo (current GMO regulations) to a scenario of revision of the current regulations, and therefore from a situation in which the probability of the development of varietal innovations resulting from directed mutagenesis technology is low, to a situation in which it would be significantly higher.

To sum up, with regard to the possible economic impacts of different regulatory scenarios, a change in regulations, based on the distinction between plants derived from site-directed mutagenesis, which would be subject to regulatory measures similar to those for plants derived from conventional breeding, and those which would continue to be subject to the current regulations on GMOs, could therefore lead to different impacts depending on whether the varietal innovation is in one or the other situation.

The first point concerns the criteria on which this distinction would be made. These criteria could play an important role if they are not too restrictive for biotechnology companies. They would facilitate access to the market for varietal innovations for plants covered by regulatory systems similar to those for conventionally bred plants, and would limit the development of innovations covered by current regulations. By choosing these criteria, the public decision-maker can steer the dynamics of innovation in a direction expected by the community. It should be noted that in terms of risk assessment, the WG's proposal set out in the first part of this conclusion is to maintain, for varieties similar to those of conventionally bred plants, a risk assessment, albeit a simplified one, in order to obtain a marketing authorisation. The WG recommends a case-by-case approach, without exempting either type of NTG from a risk assessment. In addition, by requiring the introduction of an environmental impact monitoring system, this proposal aims to ensure the reversibility of regulatory choices in the event of unanticipated negative effects on the environment.

A second point concerns the effects on the industry of a change in regulations aimed at considering plants derived from site-directed mutagenesis as conventional varieties. In the context of the regulation of conventional varieties, this would exempt the sectors concerned from the rules of segregation in the field, coexistence and labelling, thus creating a context favourable to their development on European soil. This regulatory approach would reinforce the effects of lower R&D costs made possible by directed mutagenesis technology. On the one hand, considering plants derived from NTGs as conventional varieties would make it possible to use this technology, in addition to other policy levers, for varietal innovations of agronomic and/or environmental interest. It would also allow a certain degree of harmonisation with regulations in place outside Europe, which would limit import tensions and enable European companies to operate on NTG export markets. On the other hand, such a change in GMO regulations could have a major impact on non-NTG sectors such as the organic sector.

3.6. WG and ESC conclusions

The WG and the ESCs[9] consider that the current framework for assessing the health and environmental risks of genetically modified plants is only partially adapted to the assessment of plants derived from site-directed mutagenesis using the CRISPR-Cas system, and recommend that a specific assessment be carried out on a case-by-case basis (Figure 2). In addition, the WG and ESCs believe that a comprehensive monitoring plan should be applied to each marketing authorisation (MA) decision.

This post-MA monitoring plan should make it possible to gather environmental and socio-economic data on the *in situ* impacts of authorised plants and products derived from NTGs. From a socio-economic point of view, it should help to monitor the effects of the development of plants derived from NTGs, particularly on the market power and degree of concentration of biotechnology companies and the plant breeding sector, while paying attention to any abuses of dominant market positions. The definition and implementation of such a global plan should involve all stakeholders in a transparent and democratic framework.

Given the uncertainties of a technical (on the detection of NTG-derived plants), economic and social nature identified in this report and the controversies raised by the development of NTG-derived plants, this monitoring plan will have to be based on a system to ensure the traceability and monitoring of NTG-derived plants and products and to inform the public about their characteristics.

The WG and the ESCs conclude by emphasising that this work has highlighted the major socio-economic issues involved in the existence of plants and products derived from NTGs. These issues show that decisions on the development and management of future varietal innovations obtained using NTGs are societal choices that cannot be based solely on scientific and socio-economic arguments. The WG and the ESCs consider that these societal choices should be subject to structured and democratic governance.

4. CONCLUSIONS AND RECOMMENDATIONS OF THE AGENCY

The National Agency for Food, Environmental and Occupational Health Safety (Anses) was asked to study the specific characteristics of plants obtained using certain new genomic techniques (NTG), in particular directed mutagenesis, and to propose an appropriate health and environmental risk assessment framework, based on the current framework for assessing GMO plants. In addition to the potential risks of these modified plants, and in line with its extended remit since January 2022, Anses has also analysed the socio-economic issues for various stakeholders associated with the development of these plants and their derived products. This work was commissioned against a backdrop of intense legislative activity at European level concerning the adaptation of the provisions applicable to GMOs since the early 2000s to regulate these new techniques as they apply to plants. While the European Commission's current work is limited to plants, the

[9] "New genomic techniques" WG, CES "Assessment of biological risks in food", "Socio-economic analysis" and "Biological risks to plant health".

emphasises that, like transgenesis, NTGs are used in a wide range of applications (therapeutic applications, vaccines, etc.).

This assessment was undertaken before the draft European regulation had been published. As a result, it does not take into account the proposed mechanism for distinguishing between two categories of NTG plants, the first of which is considered equivalent to conventional techniques, with a view to applying different requirements to them. Following the publication of the proposed regulation in July 2023, Anses conducted a self-investigation to analyse the criteria defining category 1 NTG plants within a short timeframe. This work concluded that there was a need to clarify definitions and fields of application, and identified limitations in the scientific justification for the equivalence criteria, while noting that "the equivalence criteria system effectively extends, for NTGs, the dividing line between plants subject to prior assessment and those not subject to prior assessment" that characterises GMO regulation (Anses 2023).

With regard to the assessment of the health and environmental risks of plants derived from site-directed mutagenesis using the CRISPR-Cas system, the Anses endorses the experts' conclusion that the current risk characterisation and assessment reference framework is only partially adequate, and refers to the proposals made on these subjects in the body of the opinion.

Anses also endorses the conclusions and recommendations of the WG and the ESCs in favour of a case-by-case assessment of the health and environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system. It also accepts the possibility, opened up by the experts, of a simplified assessment for genetically modified plants for which the history of knowledge justifies a lower level of risk.

The Agency points out that the current framework for GMOs under the legislation resulting from Directive 2001/18/EC draws a distinction between plants subject to and those not subject to prior assessment, which is based on the technique used and not on the nature of the plant obtained. The experts recommend an *ex-ante* risk assessment that takes into account both the technique used and the characteristics of the plant thus obtained. This choice is a matter for the political decisions to be taken in the light of all the issues covered by GMOs in general, the range of which is growing with the NTGs.

Anses agrees with the experts that some of the risks identified for plants derived from site-directed mutagenesis are similar to those already identified for plants derived from transgenesis, but that exposure to these risks could increase with the development of site-directed mutagenesis and the size of the market for these plants, especially as work is underway on widely distributed plants not currently affected by transgenesis.

The Anses therefore stresses the importance of post-market monitoring and considers that it should be given greater weight. It therefore endorses the recommendation for a global mechanism to monitor the use of plants obtained using NTGs after they have been placed on the market, both environmentally and socio-economically, for example by tracking changes in cultivation practices. Because of the nature and variety of what is expected, such a mechanism may require a combination of several different tools: risk monitoring plans, actions such as observatories of practices, and monitoring of results by health and environmental agencies. Such monitoring would make it possible both to supplement the still limited knowledge of plants and

NTG-derived products and to take corrective action if any adverse effects are identified following cultivation or marketing.

To conclude this section on risk assessment, the Anses considers that it will be important, once the European regulatory requirements have been defined, for precise risk assessment guidelines to be drawn up in order to avoid or limit disparities in assessment from one country to another. For its part, it will be working with EFSA to develop shared guidelines.

With regard to the socio-economic issues associated with plants and products derived from NTGs, the Anses also endorses the results of the work of the WG and the ESCs. It highlights the value of the value chain diagram used to carry out the corresponding analysis, and welcomes the willingness of stakeholders to participate in the hearings conducted by the experts to provide input for this section.

The Agency underlines the diversity of motivations that can lead to the development of varietal innovation, of which three main families are described in the opinion: increasing the effectiveness or efficiency of agricultural and agro-industrial production, product differentiation strategies, and responding to health, environmental or societal issues. Each innovation may fall into one or more of these families. These different motivations could be dealt with differently in future legislation and regulations. This would require consideration of the best way to achieve the objectives to be prioritised, taking into account the health, environmental and social concerns that these different types of innovation are likely to introduce, and the respective roles of public research and market mechanisms.

The Anses also mentions the importance of adapting the current regulatory framework in terms of intellectual property rights to these varietal innovations and of taking into account the concerns of the various groups of players involved, including consumers in terms of information on the nature of the products they are offered. Some of the expectations downstream in the value chain also entail major constraints for those upstream, particularly in terms of traceability and detectability.

Given the scarcity of data, with very few of these innovations currently on the market, the agency stresses the need for scientific research to better characterise the socio-economic issues associated with plants and products derived from NTGs.

Finally, work on the socio-economic aspect shows that the controversies surrounding plants and products derived from NTGs go beyond the scientific and technical issues that may be associated with them and extend to a much broader set of concerns relating to agricultural production models and the place of genomic technologies in an agro-ecological transition. These concerns go beyond health safety. Each of the possible regulatory development scenarios is based on choices that go beyond the sole issue of health risk, and which may generate potentially very different economic and social impacts for the various stakeholders concerned. The Anses therefore considers that the corresponding issues should be discussed within institutions whose role it is to do so, such as the EESC or the CCNE, and then, of course, in parliamentary bodies.

This same diversity of issues and concerns leads Anses to recommend that, in future choices, the question of health risks, including in a very global approach to health, should be considered as a necessary but not sufficient factor in the structural choices that will be made.

Professor Benoit Vallet

KEYWORDS

New genomic techniques, new breeding techniques, genetically modified organisms, plants, site-directed mutagenesis, CRISPR-Cas, risk assessment, socio-economic analysis

New genomic techniques, new breeding techniques, genetically modified organisms, plants, directed mutagenesis, CRISPR-Cas, risk assessment, socio-economic analysis

SUGGESTED QUOTE

Anses. (2023). Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à l'évaluation des risques sanitaires et environnementaux et des enjeux socio-économiques associés aux plantes obtenues au moyen de certaines nouvelles techniques génomiques (saisine 2021-SA-0019). Maisons-Alfort: Anses, 34 p.

Methods for assessing the health and environmental risks and socio-economic issues associated with plants obtained using certain new genomic techniques (NTG)

Referral no. 2021-SA-0019

REPORT
collective expertise

Specialist expert committee on "Assessment of biological risks in food".

Socio-economic analysis" expert committee

Specialist Expert Committee on Biological Risks to Plant Health Working Group

on New Genomic Techniques

December 2023

AGENCE NATIONALE DE SÉCURITÉ SANITAIRE de l'alimentation, de l'environnement et du travail
14 rue Pierre et Marie Curie 94701 Maisons-Alfort Cedex, France
Tel: +33 (0)1 49 77 13 50 - www.anses.fr

Suggested quote

Anses. (2023). Assessment of the health and environmental risks and socio-economic issues associated with plants obtained using certain new genomic techniques. (saisine 2021-SA-0019). Maisons-Alfort: Anses, 287 p.

Key words

New genomic techniques, new breeding techniques, genetically modified organisms, plants, site-directed mutagenesis, CRISPR-Cas, risk assessment, socio-economic analysis

New genomic techniques, new breeding techniques, genetically modified organisms, plants, directed mutagenesis, CRISPR-Cas, risk assessment, socio-economic analysis

Presentation of the speakers

PREAMBLE: Experts who are members of specialised expert committees, working groups or appointed as rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chairman

Michel GAUTIER - Professor (Institut Agro centre de Rennes/Angers) - Genetic engineering, microbial ecology

Members

Mr Guillaume FRIED - Research Project Manager (Anses) - Community ecology, biodiversity monitoring in agrosystems, risk assessment of invasive alien plants

Mrs Thaura GHNEIM-HERRERA - Scientific Manager, Montpellier Advanced Knowledge Institute on Transitions (MAK'IT), University of Montpellier - Genetic engineering, molecular and cellular biology, plant improvement.

Florian GUILLOU - Research Director (INRAe) - Genetic engineering, animal health

Mrs Valérie LE CORRE - Research Fellow (INRAe) - Evolution and ecology of weeds and invasive plants, agronomy

Mrs Charlotte LÉCUREUIL - Lecturer and researcher (University of Tours) - Ecotoxicology and entomology, environmental risk assessment on target and non-target insects

Mr Youenn LOHEAC - Lecturer and researcher (Rennes School of Business) - Economics of behaviour, food consumption, experimental economics

David MAKOWSKI - Research Director (INRAe) - Statistics, Meta-analysis, Agronomy

Mrs Julie MALLET - Research project manager / Head of the GMO detection team in the BVO unit, Plant Health Laboratory (Anses) - Molecular biology, detection methods

Mrs Marianne MAZIER - Research engineer (INRAe) - Plant transgenesis and new genomic techniques, molecular and cellular biology, plant improvement

Morgan MEYER - Research Director (CNRS) - Sociology of science, analysis of controversies

Mr François MOREAU-GAUDRY - PU-PH, Team Leader (University of Bordeaux) - Genome editing techniques, gene therapy

Mr Sergio OCHATT - Research Fellow (INRAe), retired project leader - Cellular and molecular biology, transgenesis, *in vitro* selection, secondary metabolites, genetics, plant improvement

Mr Pierre ROUGÉ - Professor Emeritus (Toulouse III University) - Allergology

Mr Louis-Georges SOLER - Director of Research (INRAe) - Economics of food chains and consumption

Mrs Paule VASSEUR - Emeritus Professor of Toxicology, University of Lorraine - Toxicology expertise

RAPPORTEURS EXTERNAL TO THE WG

Mrs Karine ADEL-PATIENT - Research Director (INRAe) - Allergology

Mrs Élisabeth BAÉZA-CAMPONE - Research engineer (INRAe) - Agronomy, zootechnics, poultry feed and nutrition

M. Jean DEMARQUOY - University Professor (University of Burgundy) - Metabolic physiology, food, nutrition

Luc FERRARI - University Professor (Université de Lorraine) - Toxicology, genotoxicology

Mrs Nolwenn HYMERY - Lecturer and researcher (University of Western Brittany) - Food toxicology, mycotoxins

Mr Michel LESSIRE - Retired (INRAe) - Feed composition, animal nutrition and poultry zootechnics

SPECIALISED EXPERT COMMITTEE

The work covered by this report was monitored and adopted by the following ESCs:

- CES "Assessment of biological risks in food" (2018 - 2022) - 18 May 2022

Chairman

Mr Philippe FRAVALO - Conservatoire National des Arts et Métiers, Professor. Food hygiene and microbiology, methods for detecting, quantifying and characterising micro-organisms, ecology of microbial ecosystems in the food industry.

Members

Frédéric AUVRAY - Toulouse National Veterinary School, Research Engineer. Molecular biology, microbial genetics, bacteriology.

Mr Mickaël BONI (arrived June 2021) Armed Forces Biomedical Research Institute, Chief Veterinary Officer - Head of Unit. Microbiology, hygiene, food safety and quality, food and water safety, food safety inspection, treatment and sanitary control of EDCH.

Frédéric CARLIN - INRAe, Research Director. Spore-forming bacteria, plant products, predictive microbiology.

Mrs Catherine CHUBILLEAU - Niort Hospital, Head of Department. Epidemiology, health risk assessment, hygiene, water risks.

Mrs Florence DUBOIS-BRISSONNET - AgroParisTech, University Professor. Food microbiology, biofilms, mechanisms by which microorganisms adapt to stress (preservatives, disinfectants).

Mr Steven DURET - INRAe, Research Engineer. Modelling, process engineering, heat transfer.

Mr Michel FEDERIGHI - ONIRIS, University Professor. Microbiology, food hygiene and quality, hazard analysis.

Mr Michel GAUTIER - Agrocampus Ouest, University Professor. Microbiology and food hygiene, molecular biology, bacteriophages, fermented foods.

Ms Michèle GOURMELON (arriving June 2021) - IFREMER, Research Fellow. Bacteriology, molecular biology, microbial ecology - *Campylobacter,* bacteria from the land-sea continuum and marine bacteria.

Stéphane GUYOT - AgroSup Dijon, Senior Lecturer. Processes for destroying pathogenic bacteria, mechanisms for adapting to environmental stress.

Ms Nathalie JOURDAN-DA SILVA - Santé publique France, Scientific Project Manager. Epidemiology of enteric diseases and zoonoses.

Mr Renaud LAILLER - Anses, Food Safety Laboratory, Project Manager. Surveillance, *Salmonella,* food hygiene.

Mr Bertrand LOMBARD (arrived June 2021) - Anses, Strategy and Programmes Department, Project Manager. Microbiological analysis of foodstuffs, reference activities, standardisation.

Mrs Sandra MARTIN-LATIL - Anses, Food Safety Laboratory, Scientific Project Manager. Virology, detection methods.

Ms Jeanne-Marie MEMBRÉ - INRAe, Research Engineer. Quantitative assessment of microbiological risk, applied statistics.

Mr Eric OSWALD - Toulouse University Hospital, University Professor. Clinical infectiology, microbial ecology, *E. coli*.

Pascal PIVETEAU (arrived June 2021) - INRAe, Research Fellow. Microbial ecology, Ecology of pathogenic bacteria in agroenvironments

Mrs Sabine SCHORR-GALINDO - University of Montpellier, Professor. Mycology, microbial ecology, biotechnology.

Ms Nalini RAMA RAO - INRAe, Research Director. Microbiology, host/pathogen interaction, intestinal microbiota.

Mrs Régine TALON - INRAe, Research Director. Food microbiology, microbial ecology, fermented foods of animal origin.

Mrs Muriel THOMAS - INRAe, Research Director. Intestinal microbiota and human health, physiology.

Mrs Isabelle Villena - Reims University Hospital, University Professor. Parasitology, infectiology.

- CES "Assessment of biological risks in food" (2022-2026) - 24 October 2022, 23 January 2023, 18 April 2023, 21 June 2023, 23 October 2023, 13 November 2023, 11 December 2023

Chairman

Mr Philippe FRAVALO - Conservatoire National des Arts et Métiers, Professor. Food microbiology, meat industries, bacterial hazards, *Salmonella*, *Campylobacter*, *Listeria*

monocytogenes, methods (including 16S metagenomics of digestive contents and surfaces, molecular characterisation of hazards), rearing/slaughtering.

Members

Frédéric AUVRAY - Toulouse National Veterinary School - Research engineer. Food microbiology and microbial ecology, *Escherichia coli*, *Staphylococcus aureus*, zoonotic pathogenic bacteria, microbiota, bacteriophages, microbiological diagnostics and genome sequencing.

Mickaël BONI - Armed Forces Biomedical Research Institute - Chief Veterinary Officer, Head of Unit. Microbiology, hygiene, food safety and quality, food and water safety, food safety inspection, EDCH treatment and health control, wastewater epidemiology.

Frédéric BORGES - University of Lorraine - Senior Lecturer. *Listeria*, genetic engineering, biopreservation, fermented food ecosystems, genotyping, phenotyping, HACCP.

Mr Gilles BORNERT - Rennes Army Health Service - Chief Veterinary Officer. Food and water microbiology, microbial ecology, regulations, food safety, HACCP, water and catering.

Mr Frédéric CARLIN *(until March 2023)* - INRAe - Research Director. Spore-forming bacteria, Bacillus, Clostridium, effects of processes, predictive microbiology, plant products.

Mrs Catherine CHUBILLEAU - Niort Hospital - Head of Department. Food hygiene, epidemiology, food microbiology, health management plan, EDCH.

Mrs Monika COTON - University of Brest - University Professor. Food microbiology, fermented products, mycology, microbial ecology, secondary metabolites (including mycotoxins, biogenic amines, volatile compounds), analytical methods, molecular biology.

Mr Georges DAUBE - University of Liège - University Professor. Food microbiology, quantitative assessment of microbiological risks, HACCP, Good Hygiene Practices, meat and dairy industries.

Ms Noémie DESRIAC - Université Bretagne occidentale - Senior Lecturer. Food microbiology, spore-forming bacteria, mechanisms by which microorganisms adapt to stress, predictive microbiology.

Mrs Florence DUBOIS-BRISSONNET - AgroParisTech - Professor. Food microbiology, biofilms, mechanisms of bacterial adaptation to stress (including preservatives, disinfectants, refrigeration), membrane biochemistry, *Listeria monocytogenes*.

Mr Michel FEDERIGHI - École Nationale Vétérinaire d'Alfort - Professor. Food microbiology, food hygiene and quality, hazard analysis, HACCP, food chains and technologies for meat and processed products.

Mr Michel GAUTIER - Institut Agro - Professor. Food microbiology, molecular biology, microbial GMOs, bacteriophages, fermented foods, pathogenic bacteria.

Mrs Michèle GOURMELON - IFREMER - Researcher. Bacteriology and molecular biology, microbial ecology of coastal marine environments including shellfish and shellfish farming areas and the land-sea continuum, environmental bacteria and bacteria of health interest, *Campylobacter.*

Ms Sandrine GUILLOU - ONIRIS - Research engineer. Health risk assessment, microbiology and microbial ecology of foodstuffs, modelling, *Campylobacter*, decontamination processes, detection methods, mechanisms of adaptation to environmental stress, poultry industry.

Mr Stéphane GUYOT - Institut Agro Dijon - Senior Lecturer. Food microbiology, food powders, pathogens, bacteria, viruses, decontamination processes, mechanisms of adaptation to environmental stress.

M. Didier HILAIRE - Direction générale pour l'armement - Engineer, open innovation assistant; CBRN decontamination and medical countermeasures architect. Bacterial and plant toxins, botulinum toxins, biological risks, decontamination and identification of biological agents.

Ms Nathalie JOURDAN-DA SILVA - Santé publique France - Medical epidemiologist, scientific project manager. Epidemiology of enteric and zoonotic diseases, investigations.

Ms Claire LE HENAFF-LE MARREC - Bordeaux INP, INRAe - University Professor. Food microbiology, microbial ecology, lactic bacteria, bacteriophages, malolactic fermentation.

Mrs Sandra MARTIN-LATIL - Anses, Food Safety Laboratory - Research Director. Food virology, detection methods, decontamination processes.

Ms Jeanne-Marie MEMBRÉ - INRAe - Research engineer. Quantitative assessment of microbiological risk, modelling, predictive microbiology, risk-benefit and multi-criteria assessment, applied statistics.

Mr Eric OSWALD - CHU Toulouse - University of Toulouse - University Professor - Hospital Practitioner. Bacterial pathogenicity, Toxins, *Escherichia coli*, antibiotic resistance, microbial genomics, microbiota, One health, infectiology.

Mrs Nadia OULAHAL - Université Claude-Bernard Lyon 1 - Senior Lecturer. Food microbiology, food hygiene, antimicrobial biomolecule interactions
- food, food microbial ecosystem, biofilms, Biopreservation.

Pascal PIVETEAU - INRAe - Research Director. *Listeria monocytogenes*; microbial ecology, ecology of pathogenic bacteria in agri-environments, food systems, plant industry.

Mrs Sabine SCHORR-GALINDO - University of Montpellier - Professor. Food safety, food and industrial microbiology, mycology, mycotoxins, microbial ecology, food technology, HACCP, biotechnology, fruit, coffee and cocoa sectors.

Mrs Régine TALON - INRAe - Research Director, Project Leader. Food science, microbial ecology, fermented products, ferments, pathogenic bacteria, meat and dairy industries.

Mrs Isabelle Villena - Reims University Hospital, University of Reims Champagne-Ardenne - University Professor - Hospital Practitioner, Head of Department, Reims Hospital, Director of the CNR for Toxoplasmosis. Health risk assessment, parasitology, medical mycology, clinical infectiology, epidemiology, molecular biology.

- CES "Socio-economic analysis" - 20 June 2022, 20 October 2022, 08 December 2022, 19 January 2023, 07 March 2023, 11 September 2023, 05 October 2023, 09 November 2023, 07 december 2023

Chairman

Mrs Laura MAXIM - Research Fellow (CNRS) - Socio-economics, chemical risks, uncertainty

Members

Ms Bénédicte APOUEY - Research Fellow (CNRS - Paris School of Economics) - Health economics, social inequalities in health

Luc BAUMSTARK - Senior Lecturer (Lyon 2 University) - Public economics, environmental economics, health economics, public economic calculation

Céline BONNET - Research Director (INRAe) - Industrial economics, food and environmental policy analysis

Thierry BRUNELLE - Research Fellow (CIRAD) - Modelling, land use, food security, biodiversity, climate change

Mrs France CAILLAVET - Research Director (INRAe) - Socio-economic determinants of food decisions, inequalities, food policy analysis

Mr Alain CARPENTIER - Research Director (INRAe) - Analysis of agricultural production systems, agri-environmental policy, use of chemical inputs

Mr Thomas COUTROT - retired - Labour statistics, economic evaluation, work organisation

Mrs Cécile DETANG-DESSENDRE - Deputy Scientific Director (INRAe) - Economics of rural areas, agricultural labour market

Serge GARCIA - Research Director (INRAe) - Economics of natural resources, water, forests, ecosystem services, environmental public policy

Mr Julien GAUTHEY - Research Officer (OFB) - Sociology, socio-economics, biodiversity, agroecology, circular economy, micropollutants

Mrs Emmanuelle LAVAINE - Lecturer and researcher (University of Montpellier) - Applied economics in health-environment, evaluation of environmental externalities in health

Mr Marc LEANDRI - Senior Lecturer (Université Versailles-Saint Quentin) - Risk and information economics, pollution economics, ecosystem services, sustainable development

Mrs Christine LE CLAINCHE - University Professor (University of Lille) - Health at work, social inequalities in health, prevention, equity and redistribution, behavioural economics

Mr Youenn LOHEAC - Lecturer and researcher (Rennes School of Business) - Experimental and behavioural economics, analysis of eating habits

M. Selim LOUAFI - Deputy Director (UMR AGAP- CIRAD) - Social sciences, biodiversity, biotechnologies, sustainable development, food security, public decision-making

Mr Eric PLOTTU - Scientific coordinator (Ademe) - Decision theory, assessment methodology and multi-criteria decision-making aid, participative approaches, socio-economic and environmental assessment of projects.

Ms Élodie ROUVIERE - Senior Lecturer (AgroParisTech) - Industrial organisation, applied econometrics, agri-food industries

Mrs Maïder SAINT JEAN - Lecturer and researcher (University of Bordeaux) - Economics of innovation, eco-industry, environmental economics, socio-technical transition

Mr Denis SALLES - Sociologist, retired research fellow (INRAe) - Sociology of the environment and public action, water resource management

Mr Louis-Georges SOLER - Deputy Scientific Director (INRAe) - Economics of agricultural and agrifood sectors, nutritional policies

Ms Léa TARDIEU - Research Fellow (INRAe) - Ecosystem services, environmental justice, biodiversity, spatial analyses

Mr Jean-Christophe VERGNAUD - Deputy Director (Centre d'économie de la Sorbonne - École d'Économie de Paris) - Applied public economics in health and the environment, decision theory, experimental economics, REACh

- CES "Biological Risks to Plant Health" - 14 September 2022, 22 November 2022, 31 January 2023, 28 March 2023, 23 May 2023, 4 July 2023, 29 November 2023

Chairman

Mr Thomas LE BOURGEOIS - Research Director, CIRAD, Botany and Modelling of Plant and Vegetation Architecture research unit

Members

Philippe CASTAGNONE - Research Director, INRAe, PACA Centre, Institut Sophia Agrobiotech

Thierry CANDRESSE - Research Director, INRAe, Centre Nouvelle-Aquitaine- Bordeaux

Nicolas DESNEUX - Research Director, INRAe, PACA Centre, Institut Sophia Agrobiotech

Mrs Sandrine EVEILLARD - Research Fellow, INRAe, Centre Nouvelle-Aquitaine- Bordeaux

Mrs Florence FONTAINE - University Professor, Université Reims-Champagne- Ardenne

Mr Pascal GENTIT - Head of the Bacteriology, Virology and GMO Detection Unit, Plant Health Laboratory, Anses

Mr Martin GODEFROID - Post-doctoral student, CSIC, Spain (Madrid)

Ms Lucia GUERIN - Senior Lecturer, Bordeaux Sciences Agro, Bordeaux

Mr Bruno HOSTACHY - Retired, Anses

Hervé JACTEL - Research Director, INRAe, Centre Nouvelle-Aquitaine-Bordeaux, UMR Biodiversity, Genes & Communities

Mrs Eleni KAZAKOU - Professor, SupAgro Montpellier

Mr Christophe Le MAY - Senior Lecturer, Agrocampus Ouest, Rennes

Mr Eric LOMBAERT - Research Engineer, INRAe, PACA Centre, Institut Sophia Agrobiotech

David MAKOWSKI - Research Director, INRAe, Ile-de-France-Versailles Centre, AgroParisTech, Université Paris-Saclay, UMR MIA

Mr Charles MANCEAU - Retired, INRAe

Arnaud MONTY - Lecturer and researcher, University of Liège - Biodiversity and Landscape Department

Mrs Maria NAVAJAS - Research Director, INRAe, Centre Occitanie-Montpellier, UMR CBGP Centre de biologie pour la gestion des populations (Centre of Biology for Population Management)

Mrs Cécile ROBIN - Research Director, INRAe, Centre Nouvelle-Aquitaine-Bordeaux

Aurélien SALLE - Senior Lecturer, University of Orléans

Frédéric SUFFERT - Research Engineer, INRAe, Agro Paris-Saclay Campus

Stéphan STEYER - Scientific Attaché, Centre wallon de Recherches Agronomiques, Département Sciences du Vivant, Head of Plant Virology

Mr Pierre-Yves TEYCHENEY - Research Director, CIRAD, La Réunion

Mr Éric VERDIN - Research Engineer, INRAE, Centre PACA Avignon, Plant Pathology Unit

Mr François VERHEGGEN - Lecturer and researcher, University of Liège - Functional and Evolutionary Entomology Unit

The Biotechnology WG was also informed and consulted at various stages in the progress of the work, on 16 December 2021, 20 January 2022, 21 April 2022, 22 December 2021, 22 January 2022, 22 April 2022, 22 April 2022, 22 April 2022 and 23 April 2022.
September 2022, 15 December 2022, 13 March 2023, 12 April 2023, 6 June 2023, 19 September 2023, 17 October 2023, 22 November 2023.

PARTICIPATION ANSES

Scientific coordination

Mr Dylan CHERRIER - Scientific Expertise Coordinator - DER (Risk Assessment Department) - Anses

Mr Legrand SAINT-CYR - Agro-economic project manager - DISSES (Social Sciences, Economy and Society Department) - Anses

Mrs Emmanuelle PIC - Scientific Expertise Coordinator (until August 2023) - DER (Risk Assessment Department) -Anses

Mr Alexis LAROUSSE - Socio-economic analysis officer in industrial economics - DISSES (Social Sciences, Economy and Society Department) - Anses

Mathieu BAUDRIN - Social Science Project Manager - DISSES (Social Sciences, Economy and Society Department) - Anses

Mrs Lucie EYRAUD - Scientific expertise coordinator - DER (Risk Assessment Department) - Anses

Mrs Karine FIORE - Deputy Director of DISSES (Social Sciences, Economy and Society Department) - Anses

Mr Youssef EL OUADRHIRI - Head of Mission - DER (Risk Assessment Department) - Anses

Administrative secretary

Ms Angélique LAURENT - Anses

HEARING OF EXTERNAL PERSONALITIES

The people listed below were interviewed by the working group. The working group's experts would like to thank all those consulted for the quality of their discussions. The information provided has been taken into account in the preparation of the report.

Disclaimer: the mention of individuals in the table below does not imply endorsement of the conclusions of this report.

List of people interviewed

Name	Function	Institution	Date hearing
LEMARIE Stéphane	Research Director	INRAe	24 January 2022
GIRARD Fabien	Senior Lecturer, Private Law	University Grenoble Alpes	
VASSANT Charlotte	Farmer	FNSEA	21 June 2023
BERNARD André	Farmer and Chairman of the Tomato Industry Interprofession		
GIOVINAZZO Robert	Director of SONITO		
BIZOT-ESPIARD Melchior	Head of innovation and foresight at the FNSEA		
COHAN Jean-Pierre	Head of the Crop Adaptation to Agroclimates, Genetics and Phenotyping Department ARVALIS		
BERTHEAU Yves	Scientific advisor biotechnologies FNE	FNE	28 June 2023
JACQUEMART Frédéric	Co-pilot of the Biotechnologies mission at FNE		
LE MEUR Hervé	Scientific advisor biotechnologies FNE		

MEUNIER Éric	Scientific advisor biotechnologies FNE		
DESENCÉ Lionel	Quality Director in charge of Scientific and Technical Affairs regulatory affairs, Carrefour Group	FCD	30 June 2023
TAFOURNEL Émilie	Quality Director at the FCD		
LIGNON Bernard	Director of Quality and Regulatory Development at SYNABIO	SYNABIO	30 June 2023
Guy KASTLER	Member of the Confédération paysanne's GMO and Seeds Commission	Confédération paysanne	04 July 2023
Nicolas LE BOËDEC	Coordinator at the Confédération paysanne, in charge of the GMO/seed committees		
DESPREZ François	Chairman of Semae	SEMAE	06 July 2023
GAUTIER Jacques	Chairman of the family company Semences GAUTIER		
EVAIN Daniel	Biotechnology and GMO referent at the FNAB	FNAB	6 July 2023
LEONARD Julien	Chairman of CNAFAL	CNAFAL	12 July 2023
LE MEUR Hervé	Scientific advisor CNAFAL		
BLANCHEMANCHE Sandrine	Director of the Healthy, Safe and Sustainable Food Division	ANIA	17 July 2023
DESPOUY Anne	Director of the sugar beet division at the Syndicat national des fabricants de sucre		
CONTAMINE Anne-Céline	Director of the French National Milling Association		
JACQUELIN Paul	Head of Public Affairs at Tereos		

CONTENTS

Acronyms and abbreviations

AB	:	Organic farming
ADLC	:	French Competition Authority
DNA	:	Deoxyribonucleic acid
AMM	:	Marketing authorisation
AMAP	:	Association for the preservation of peasant agriculture
AMS	:	Seed multiplication farmers
ANIA		National Association of Food Industries
Anifelt	:	Fruit and vegetable trade association
ANMF	:	French National Milling Association
Anses	:	Agence nationale de sécurité sanitaire, de l'alimentation de l'environnement et du travail (French National Agency for Food, Environmental and Occupational Health and Safety)
PDO	:	Protected designation of origin
RNA	:	Ribonucleic acid
ESA	:	Socio-economic analysis
BIORISK	:	Assessment of biological risks in food
BIOT	:	Biotechnologies
CAP	:	Consent to pay
Case	:	*CRISPR associated protein*
CE	:	European Community
CEE	:	European Economic Community
CES	:	Specialist expert committee
CJEU	:	Court of Justice of the European Union
CNAFAL	:	National Council of Secular Family Associations
VOCS	:	Variety certificate
CPVADAAA	:	Standing Committee on Plants, Animals, Food and Feed
CRISPR	:	*Clustered regularly interspaced short palindromic* repeats
CRISPRa	:	CRISPR activation
CRISPRi	:	CRISPR interference
crRNA	:	CRISPR RNA

CTPS	:	Standing Technical Committee on Selection
dCas	:	*Dead case*
DER	:	Risk Assessment Department
DGAl	:	Directorate-General for Food
DGPR	:	Risk Prevention Department
DHS	:	Distinction, homogeneity, stability
DISSES	:	Social Sciences, Economics and Society Department
DSB	:	*Double-strand break*
Efsa	:	Autorité européenne de sécurité des aliments (*European food safety authority*)
ELISA	:	*Enzyme-linked immunosorbent assay*
ERA	:	*Environmental risk assessment*
FCD	:	Federation of Commerce and Distribution
IMF	:	International Monetary Fund
FNAB	:	National Federation of Organic Agriculture
FNE	:	France Nature Environnement
FNSEA	:	National Federation of Farmers' Unions
GABA	:	Gamma-aminobutyric acid
GEVES	:	Group for the study and control of varieties and seeds
GT	:	Working group
HR	:	*Homologous* recombination
IFV	:	French Institute of Vine and Wine
GI	:	Geographical indications
PGI	:	Protected geographical indications
Indel	:	Insertion or deletion
INRAE	:	French National Research Institute for Agriculture, Food and the Environment
FSI	:	*International seed federation*
ITAB	:	Technical Institute for Organic Agriculture
IUF	:	University Institute of France
JRC	:	Joint *research centre* of the European Commission

LC-MS/MS	:	Liquid chromatography *tandem mass* spectrometry (LCMS)
PRIVATE LABEL	:	Private label
MDF	:	Brand name
nCase	:	*Nicking case*
NGT	:	*New genomic* techniques
NHEJ	:	*Non-homologous end-joining*
nsLTP	:	*Non-specific lipid transfer proteins*
NTG	:	New genomic techniques
OECD	:	Organisation for Economic Co-operation and Development
ODM	:	Oligonucleotide directed mutagenesis
EPO	:	European Patent Office
GMOS	:	Genetically modified organism
NGO	:	Non-governmental organisation
OP	:	Producer organisation
PACA	:	Provence-Alpes-Côte d'Azur
PAM	:	*Protospacer-adjacent motif sequence*
PCR	:	*Polymerase* chain reaction (*PCR*)
RdDM	:	*RNA-directed DNA* methylation
R&D	:	Research and development
RHF	:	Out-of-home catering
RP	:	Group of producers
RP 1	:	Grouping of first-degree producers
RP 2	:	Grouping of secondary producers
SANTVEG	:	Biological risks to plant health
SDN	:	*Site-directed* nuclease
SDS-PAGE	:	Electrophoresis on polyacrylamide gel in the presence of sodium dodecyl sulphate (*sodium dodecyl sulphate polyacrylamide gel electrophoresis*)
SEMAE	:	Groupement national interprofessionnel des semences et plants (National Interprofessional Group for Seeds and Plants)
sgRNA	:	*Single guide* RNA
SONITO	:	National interprofessional tomato company

Synabio	:	Union of organic food companies
TALEN	:	*Transcription activator-like effector nuclease*
tracrRNA	:	Trans-activating CRISPR RNA
EU	:	European Union
UMB	:	Mission biotechnologies
Unilet	:	Interprofession representing and developing the canned and frozen vegetable sector in France
uORF	:	*Upstream open reading* frame
UPOV	:	International Union for the Protection of New Varieties of Plants
USDA	:	*United States Department of* Agriculture
VATE	:	Agronomic, technological and environmental value
VED	:	Essentially derived variety
VMG	:	Graft nurseries
VMPG	:	Rootstock parent vines
ZFN	:	*Zinc finger* nuclease

List of tables

List of figures

Introductory remarks

From 1er January 2022, in accordance with Ordinance 2021-1325 of 13 October 2021 and Decree 2021-1905 of 30 December 2021, Anses will take over the tasks of the High Biotechnology Council (HCB) concerning the environmental risk assessment of all uses of biotechnology in the open environment, and the socio-economic impacts.

As part of these new missions, the Anses has been asked by the Directorate General for Risk Prevention (DGPR) and the Directorate General for Food (DGAl) to look into the use of new genomic techniques (NTG) on plants.

The other bodies that have taken over the HCB's remit, namely the Economic, Social and Environmental Council (CESE) and the National Consultative Ethics Committee (CCNE), have also been called upon to address this issue in their respective areas of societal and ethical concern. It should also be noted that many public institutions, professional organisations and trade unions have also produced reports on NTGs.

The collective expertise report is carried out within the scope of Anses' missions on biotechnologies, including the assessment of health and environmental risks and socio-economic impacts. It is intended to enlighten applicants on this scope, which covers only part of the issues associated with the use of NTGs in plant breeding. The questions investigated in this report are therefore limited to this perimeter and the conclusions must be taken into account only within this framework and put into perspective with the opinions of the other bodies requested.

It should be noted that this appraisal was undertaken before the Commission's proposal for a regulation of 5 July 2023.[1]. Following its publication, Anses decided to carry out an analysis of the criteria defining category 1 NTG plants, considered equivalent to conventional plants, set out in Annex 1 and justified by a technical note issued by the European Commission in October (Anses 2023). This analysis was carried out in parallel and its conclusions were therefore not taken into account in the present expert appraisal, carried out within the scope defined above, which does not distinguish between category 1 and 2 NTG plants.

[1] https://food.ec.europa.eu/system/files/2023-09/gmo_biotech_ngt_proposal_2023-411_fr.pdf and https://food.ec.europa.eu/system/files/2023-09/gmo_biotech_ngt_proposal_2023-411_annex_fr.pdf (consulted on 12/10/2023)

1 Context, purpose and procedures for carrying out the appraisal

1.1 Context

New Genomic Techniques (*NGT*) are a heterogeneous group of genome-modification techniques involving different mechanisms (mutations, insertions/deletions, gene silencing, etc.). Some of these techniques aim to modify a genetic sequence in a precise and targeted way (directed or targeted mutagenesis), offering a very wide range of applications, particularly in the field of plant breeding. These genome modification techniques, particularly those based on the CRISPR-Cas system, have developed very rapidly, and some plant varieties obtained using these NTGs are already available on the market in certain countries, notably the United States and Canada. However, no plants obtained using these NTGs have yet been authorised for the European Union market.

Following an appeal by the Confédération paysanne and other organisations to the Conseil d'État, which in turn referred the matter to the Court of Justice of the European Union (CJEU) for a preliminary ruling, the CJEU's judgment of 25 July 2018 (Case C-528/16)[2] concludes that only organisms obtained by means of mutagenesis techniques/methods which have traditionally been used for various applications and whose safety has long been proven are excluded from the scope of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms". As a result, plants obtained by these NTGs must comply with the current regulatory framework for the authorisation of genetically modified organisms (GMOs), particularly in terms of risk assessment, authorisation procedure, traceability, labelling and control. The Council of the European Union, considering that practical questions arose in order to ensure compliance with Directive 2001/18/EC, in particular insofar as current methods might not make it possible to distinguish products obtained by means of new techniques of directed mutagenesis from those born of natural mutation, asked the European Commission in November 2019 to carry out a study concerning the status of NTGs in EU law and, if appropriate, to submit a legislative proposal taking account of the results and conclusions of this study.

As part of this study, the European Commission gave Efsa a mandate to carry out work to assess the suitability of the current guidance documents for assessing the risks associated with the use of organisms obtained using NTGs. In its opinion of 14 October 2020 (EFSA GMO Panel 2020), Efsa concludes that its guidance documents on the assessment of risks associated with the use of feed and food derived from genetically modified plants and on the environmental risk assessment of genetically modified plants are adequate to cover the risks when these plants are obtained using NTGs. However, Efsa considers that

2https://curia.europa.eu/juris/document/document.jsf?text=&docid=198532&pageIndex=0&doclang=FR&mode=lst&dir=&occ=first&part=1&cid=1663321 (consulted on 12/10/2023)

its guide documents are only partially applicable, as the requirements relating to the presence of a transgene are not adapted to this type of plant.

In addition, the European Commission published its study on NTGs on 29 April 2021[3]concluding that the current regulations on GMOs did not seem appropriate for plants obtained using certain NTGs. For other organisms (animals and micro-organisms), the Commission considers that it is necessary to continue to build up the necessary scientific knowledge and to keep products derived from NTGs within the scope of current GMO regulations at this stage.

The European Commission's study also points to legal uncertainties, difficulties in implementation, particularly with regard to controls, and the lack of flexibility in the current regulations. The study also concludes that certain plants obtained using NTGs could be of benefit to society and meet the challenges of resilience and sustainability of the food system under the "farm to table" strategy. The study also highlights a number of key issues, including intellectual property, traceability and control, consumer information through labelling, the competitiveness of businesses and the farming sector, trade and the acceptability of these products to society.

In its letter of 29 April 2021 to the Portuguese Presidency of the Council of the European Union[4]the Commission states that, in the light of the results of the study, it intends to launch a legislative initiative for plants derived from directed mutagenesis and cisgenesis.[5]. The aim would be to adapt the current regulatory requirements in terms of risk assessment, authorisation procedures, labelling and traceability, while maintaining a high level of protection for the environment and human and animal health, and taking into account the potential contribution of these plants and the products derived from them to the sustainability of the food system.

Against this backdrop, the French Directorate-General for Risk Prevention (DGPR) and the Directorate-General for Food (DGAl) have referred the matter to Anses, in order to obtain a scientific opinion within the scope of Anses' remit, in preparation for the forthcoming discussions at European level.

Since this referral, on 5 July 2023 the European Commission published its proposal for a Regulation on plants obtained through certain new genomic techniques and food and feed products derived therefrom. The elements contained in this regulatory proposal have not been the subject of a detailed critical analysis within the framework of this report, but will be presented for information and analysed from the point of view of their socio-economic impact. In addition, the Anses has decided to carry out a scientific analysis of the proposed criteria for defining and classifying NTG plants into two categories (Anses 2023).

[3] https://food.ec.europa.eu/system/files/2021-04/gmo_mod-bio_ngt_eu-study.pdf (consulted on 12/10/2023)
4 https://food.ec.europa.eu/system/files/2021-04/gmo_mod-bio_ngt_letter.pdf (consulted on 12/10/2023)
[5] Cisgenesis corresponds to the introduction into the genome of a plant, by conventional transgenesis or *via* the use of site-specific nucleases (SDN3), of a transgene that comes entirely and without rearrangement from the same species or from a sexually compatible species. This may be the coding part of a gene or an entire gene, including its regulatory sequences. Expression regulatory sequences may also be contributed, voluntarily or involuntarily, by the site of insertion of the transgene into the plant genome.

1.2 Purpose of the referral

The two main objectives of the appraisal (for which the letter of referral appears in **Appendix 1**) were established as follows:

- to determine whether adaptations could be made to the current regulatory requirements for assessing the risks (health and environmental) of genetically modified plants when the assessment concerns plants resulting from directed (or targeted) mutagenesis;
- document and analyse the socio-economic issues associated with NTGs.

With regard to aspects relating to health and environmental risks, the scope of the referral has been restricted to plants resulting from directed mutagenesis obtained using the CRISPR-Cas system, as these represent the type of application and tool most commonly used.

These two objectives were broken down into six questions to be examined (questions 1 to 4 for the first objective and questions 5 and 6 for the second objective):

- *Question 1*: Establish the state of knowledge on potential undesired effects at the genome level, on target and off target, in the case of site-directed mutagenesis using the CRISPR-Cas system.[6] ;
- *Question 2*: Determine the specific requirements in terms of health and environmental risk assessment for plants derived from site-directed mutagenesis using the CRISPR-Cas system;
- *Question 3*: For plants derived from site-directed mutagenesis using the CRISPR-Cas system, determine which of the current regulatory requirements for the assessment of genetically modified plants can be waived;
- *Question 4*: Depending on the progress made on the previous questions, determine how the current GMO assessment framework could be adapted for plants derived from site-directed mutagenesis using the CRISPR-Cas system;
- *Question 5*: Draw up a description of the sector or sectors concerned by the use of plants obtained by means of NTGs and the products derived from these plants, from upstream to downstream in the value chain;
- *Question 6*: On this basis, document and analyse the associated socio-economic issues, firstly for the companies and economic operators concerned, particularly in terms of competitiveness and capacity for innovation, and secondly, depending on the data available, for consumers and the supervisory authorities.

For questions 2 and 3, the entire process of obtaining a variety through site-directed mutagenesis will be compared with that of a variety obtained by a conventional breeding method (question 2) and that of a variety obtained by transgenesis (question 3). In addition, the analysis will be limited to the applications most likely to lead to commercial varieties in the short term, which will be identified before the questions are dealt with.

[6] *Clustered regularly interspaced short palindromic repeats* (*CRISPR*)-CRISPR-associated *protein* (*Cas*). Techniques using Cas 9 or another Cas protein (e.g. Cas12) and base-editing techniques (see section 4) will be taken into account in this referral. The use of modified bases (xanthine, hypoxanthine, alkyl adenines, etc.), which is more a matter of synthetic biology, is outside the scope of this referral.

1.3 Treatment methods: resources deployed and organisation

The Anses has entrusted the *ad hoc* working group (WG), hereinafter referred to as the "NTG" WG, attached to the Specialised Expert Committee (SEC) "Assessment of biological risks associated with food" (BIORISK) with the task of examining this referral. The CES BIORISK is responsible for endorsing all the work.

Expertise work falls within the remit of the Biotechnology WG (BIOT), the Socio-Economic Analysis ESC (ASE), the Biological Risks to Plant Health ESC (SANTVEG) and the BIORISK ESC. The CES ASE is responsible for validating work relating to economic and social sciences and the CES SANTVEG for validating work relating to environmental risks.

The working group's expert assessments were regularly submitted to the GT BIOT and the various ESCs concerned (on both methodological and scientific aspects). The report produced by the NTG takes account of the comments and additional information provided by the members of the GT BIOT and the various ESCs concerned.

This work is the product of a group of experts with complementary skills.

The appraisal was carried out in compliance with standard NF X 50-110 "Quality in appraisal - general competence requirements for an appraisal (May 2003)".

1.4 Preventing the risk of conflicts of interest

The Anses analyses the links of interest declared by the experts before their appointment and throughout their work, in order to avoid the risk of conflicts of interest with regard to the points dealt with in the expert appraisal.

The experts' declarations of interest are published on the https://dpi.sante.gouv.fr/ website.

2 Introduction

2.1 GMOs and production methods

The first initiatives to regulate the use of GMOs date back to the early 1990s. At international level, the Convention on Biological Diversity, adopted on 5 June 1992, provided a framework for the development of the Cartagena Protocol on Biosafety, the first agreement to establish a regulatory framework at international level to reconcile trade objectives and environmental protection in the light of the growing use of biotechnologies.

In Europe, an initial regulatory framework was also put in place in the early 1990s, notably with Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms.

European regulations on GMOs have evolved and are now mainly based on :

- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC ;
- Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed.

At the beginning of the 2000s, there were various methods that could be used to develop new plant varieties, including three main families of techniques:

- **conventional selection** (this may involve cross-breeding or conventional hybridization techniques);
- **random mutagenesis** (mutants are generated in an organism by irradiation or the application of mutagenic chemical compounds, and then the mutants that have obtained the desired trait are selected);
- **transgenesis** (a gene of foreign origin is introduced into the organism's genome so that it expresses, for example, a new protein that will give it the desired trait).

According to Directive 2001/18/EC, a GMO is defined as "*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*". Organisms obtained by conventional breeding are therefore not considered to be GMOs.

This definition is accompanied by a list of techniques considered to result in genetic modification (Annex IA, Part 1 of Directive 2001/18/EC) and a list of techniques not considered to result in genetic modification (Annex IA, Part 2). It also specifies the exemptions, i.e. the genetically modified organisms for which the requirements, in particular with regard to

the risk assessment requirements of the directive do not apply. Mutagenesis is one of the techniques covered by this exemption (Annex IB).[7].

The techniques of genetic modification covered by Part 1 of Annex IA to Directive 2001/18/EC include :

- **transgenesis techniques**, defined as "deoxyribonucleic acid recombination techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules, produced in any way outside an organism, inside any virus, bacterial plasmid or other vector system and their incorporation into a host organism inside which they do not occur naturally, but where they can multiply continuously";
- techniques involving the direct incorporation into an organism of hereditary material prepared outside the organism, including micro-injection, macro-injection and microencapsulation;
- cell fusion or hybridisation techniques in which living cells with new combinations of hereditary genetic material are formed by the fusion of two or more cells, using methods that do not occur naturally.

Since the adoption of this directive, a range of techniques known as "new genomic techniques (NTG)" for targeted genome modification have been developed, in particular thanks to the discovery of the CRISPR-Cas system, sometimes referred to as "molecular scissors". These techniques are known as **site-directed mutagenesis,** since they allow the precise deletion, insertion or replacement of one or more base pairs at specific sites in the genome.

These NTGs can be classified into four groups (Joint Research Centre 2021):

(1) techniques that induce a change in genome sequence by creating a break in the DNA double strand using *site-directed nucleases* (SDN): meganucleases, *Zinc Finger* nucleases (ZFN), *Transcription activator-like effector nuclease* (TALE), and systems derived from CRISPR-Cas. These techniques can lead to directed mutagenesis events, as well as cisgenesis, intragenesis and transgenesis, all targeted within a given genome;

[7] This exclusion of mutagenesis techniques from the European GMO regulatory framework has given rise to two successive disputes concerning the status of these techniques, particularly insofar as the wording of Directive 2001/18/EC merely refers to "mutagenesis", without any further clarification (see also section 1.1). In 2018, following an initial dispute (*Confédération paysanne and others v./v. Prime Minister and Minister for Agriculture, Agrifood and Forestry*, C-528/16), the Court of Justice of the European Union ruled in an initial judgment (Judgment of the Court of Justice of 25 July 2018) that, since mutagenesis is not included in the exhaustive list of techniques not involving genetic modification (Annex IA, Part II of Directive 2001/18/EC), organisms obtained by mutagenesis are GMOs, and that only organisms obtained using techniques that have long been proven to be safe can be excluded from the scope of the directive, and therefore techniques that appeared after the directive was adopted cannot be excluded. This decision led to a second dispute, aimed at defining whether or not GMOs obtained by random *in vitro* mutagenesis should be excluded from the specific requirements for GMOs. On 7 February 2023, the Court of Justice of the European Union concluded in a second ruling that GMOs obtained by random *in vitro* mutagenesis are exempt from the specific requirements for GMOs in Directive 2001/18/EC.

- cisgenesis corresponds to the introduction into the genome of a plant of a transgene that comes entirely and without rearrangement from the same species or from a sexually compatible species. This may be the coding part of a gene or an entire gene, including its regulatory sequences;
- intragenesis corresponds to the introduction into the genome of a plant of a transgene constructed from a combination of different sequences from the same species or a sexually compatible species;
- transgenesis is the introduction into the genome of a plant of a transgene from another species that is not sexually compatible with the modified species.

(2) techniques inducing a modification of the genome sequence by a single-strand break or without induced DNA break, such as oligonucleotide-directed mutagenesis (ODM), *base editing* systems (inactive Cas nuclease fused to a cytidine deaminase, for example) and *prime editing* (inactive Cas nuclease fused to a reverse transcriptase)[8] ;

(3) techniques that do not modify the genome sequence but act on gene expression, including epigenetic modifications such as RNA-directed DNA methylation (RdDM), the interference principle and the use of *site-directed effectors* (inactive Cas nuclease fused to expression inhibitors or activators (CRISPRi/CRISPRa);

(4) editing techniques that act directly on RNA ("*RNA editing*").

Only techniques in groups (1) and (2) lead to the production of GMOs, as defined in Article 2 of Directive 2001/18/EC.[9].

2.2 Assessment, authorisation and use of GMOs

European regulations stipulate that a GMO may not be placed on the market or released into the environment without prior authorisation. This authorisation can only be issued by the Commission after a case-by-case assessment of the risks to health and the environment.

2.2.1 Authorisation procedure for the placing on the market of GMOs or products containing or consisting of such organisms, for import, processing and food or feed use

Authorisations for the placing on the market of GMOs or products containing or consisting of such organisms, for import, processing and use as food or feed, are issued at European level by the European Commission. They can only be issued following an assessment procedure described in the European GMO regulatory framework (Regulation (EC) No 1829/2003 of the European Parliament and of the Council) and specified in Commission Implementing Regulation (EU) No 503/2013 of 3 December 2013 on the authorisation of the placing on the market of GMOs or products containing or consisting of such organisms.

[8] *Base editing* and *prime editing* techniques allow a single base to be modified, either by enzymatic reaction or by reverse transcription of a specific guide RNA.
[9] A GMO is "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".

April 2013 on applications for authorisation to place genetically modified food and feed on the market. In particular, it details the information and studies that applicants for marketing authorisation must provide for their scientific assessment.

Each application for authorisation to place a GMO on the market under Regulation (EC) No. 1829/2003 is published on the European Commission website[10] (public consultation period of 30 days) and is assessed by EFSA, which delivers an opinion to the European Commission. This opinion is published and a vote by the Member States on the draft authorisation decision is organised in the GMO section of the Standing Committee on Plants, Animals, Food and Feed (CPVADAAA).

The authorisation decision is valid for a maximum of 10 years, after which successive renewals may be requested, also for periods of 10 years. If a Member State considers, on the basis of new information, that a GMO is likely to present a risk to human health or the environment, it may use the safeguard clause provided for in Directive 2001/18/EC to temporarily restrict or prohibit the placing on the market of the GMO. The need to maintain the national measure or to adopt a European measure is then examined at European level.

The placing on the market of a GMO intended for human or animal consumption is also subject to labelling obligations. Labelling of GMOs and GMO-derived products is compulsory, except in certain cases of adventitious presence (a threshold for exemption from labelling has been set at 0.9%).

2.2.2 Procedure for authorising the placing on the market of GMOs for non-food uses

Authorisations for non-food uses of GMOs (e.g. ornamental plants) are issued at European level following an authorisation procedure described in Directive 2001/18/EC (Part C).

An applicant planning to market such a GMO must apply for authorisation from the National Competent Authority of the Member State where the product is to be marketed for the first time. The dossier accompanying this application must contain the data required to assess the risks to human health and the environment from the release of this GMO.

The dossier is assessed by the notified Member State, which must draw up an assessment report. This report is shared with the European Commission and the other EU Member States, which may raise objections to the product being placed on the market. The application for authorisation is also made public on the European Commission website (30-day public consultation period). If there are no objections, the notified Member State grants the marketing authorisation. If there are objections, the decision is taken at European level by the Commission, following a vote on the draft decision by the CPVADAAA.

[10] https://food.ec.europa.eu/plants/genetically-modified-organisms/public-consultations_en (consulted on 20/11/2023)

The authorisation decision is valid for a maximum of 10 years. If a Member State considers, on the basis of new information, that a GMO is likely to present a risk to human health or the environment, it may use the safeguard clause provided for in Directive 2001/18/EC to temporarily restrict or prohibit the placing on the market of the GMO. The need to maintain the national measure or to adopt a European measure is then examined at European level.

2.2.3 Procedure for authorising the placing on the market of genetically modified plants for the purpose of cultivation

Authorisations for the placing on the market for cultivation of a GMO can only be granted following an authorisation procedure described in Directive 2001/18/EC (Part C) or in Regulation (EC) No 1829/2003 (if the scope of the application also covers the application for placing on the market for food and feed use). The risk assessment procedures described in sections 2.2.1 and 2.2.2 therefore apply and the authorisation periods remain unchanged, depending on the application.

Member States may request to be excluded from the geographical scope of an application for authorisation for the cultivation of a GMO, without any justification being required. This provision is set out in Article 26b of Directive 2001/18/EC.

This article provides for two hypotheses:

- **first hypothesis:** if the request is communicated to the Commission, during the authorisation procedure for a GMO or during the renewal of an authorisation, at the latest 40 days after the dissemination of the assessment report for the GMO concerned or from receipt of the opinion from Efsa, the Commission submits it to the notifier, as well as to the other Member States, and makes it available to the public by electronic means. The petitioner then has 30 days from this submission to amend or confirm the geographical scope of his initial application. In the absence of confirmation, the modification requested by the Member State is implemented in the written authorisation issued and the decision to authorise cultivation of the GMO. This is an amicable, tacit authorisation procedure. The reasons for the request must be different from those included in the EFSA report;
- **second hypothesis:** if no request has been submitted in accordance with the first hypothesis or if the petitioner has confirmed the geographical scope of his initial request, the Member State may adopt measures restricting or prohibiting, on all or part of its territory, the cultivation of a GMO or a group of GMOs defined by crop in accordance with part C of Directive 2001/18/EC or Regulation 1829/2003 (genetically modified food or feed), provided that these measures comply with Union law, are justified, proportionate and non-discriminatory. The serious grounds that may be invoked in this case are those relating to environmental policy objectives, town and country planning, land use, socio-economic impact, the desire to avoid the presence of GMOs in other products, agricultural policy objectives and public order.

2.2.4 Authorisation procedure for field trials of genetically modified plants

Authorisations for field trials of genetically modified plants, particularly for research and development purposes, are granted at national level and are subject to a procedure laid down in Directive 2001/18/EC. Cultivation is then authorised for the duration of the trial.

In France, the Ministry of Agriculture issues these authorisations, subject to a favourable environmental risk assessment by the Anses, and the agreement of the Minister for the Environment.

2.2.5 Common procedures

Whatever the application and the resulting procedure, GMOs or products derived from GMOs are subject to a health and environmental risk assessment prior to any authorisation to place them on the market or to cultivate them. European regulations also stipulate that any GMO authorised for marketing in the European Union must be accompanied by a detection method validated by the EU reference laboratory before the GMO is authorised.

In addition, before the seed of any new variety (whether genetically modified or not) can be marketed and grown in France, it must be registered in the Official Catalogue of Species and Varieties. Registration is decided by the Ministry of Agriculture on the basis of proposals made by the Permanent Technical Committee on Plant Breeding (CTPS).

A variety is registered for 10 years, then extended for 5-year periods without any further studies being required (except for forage varieties, where the extension is decided on the basis of performance).

To be registered on list A (propagation and marketing in France, and by extension in Europe), varieties must pass the DUS (distinctness, uniformity, stability) and VATE (agronomic, technological and environmental value) tests. For lists B (propagation in France for marketing outside the European Union) and C (conservation varieties traditionally grown in specific regions), DUS tests are sufficient.[11].

- **Distinctness, uniformity and stability studies are** used to check that the variety is distinct from well-known varieties and that it retains its phenotypic characteristics from generation to generation. The characteristics studied are specific to the species, its genetic structure and its mode of reproduction. These studies are harmonised at European and global level (*Community Plant Variety Office* protocol).
- **The agronomic, technological and environmental value studies** describe the variety's cultivation value in the main soil and climate conditions that it will encounter in France, as well as the use value of the harvested products derived from the variety. In order to be submitted for registration, the new variety must offer an improvement over current varieties, and is therefore compared with market reference standards. The characteristics assessed include the level of

[11] https://www.geves.fr/qui-sommes-nous/sev/etudes-dhs-vate/ (consulted on 12/10/2023)

yield, use value (protein composition, animal feed value, oil content, etc.), resistance to biotic and abiotic stresses and the earliness of the plant. To achieve this, trials covering the range of environments that the variety may encounter are carried out for at least 2 years to take account of climatic variability, under conditions that are representative of farming practices. Some trials are also carried out in controlled environments (laboratories and greenhouses).

In the European Union, there is a common catalogue of varieties[12]established on the basis of the national catalogues of the Member States (Council Directive 2002/53/EC).

2.3 Legislative proposal on plants obtained through certain new techniques of genome modification

According to the Commission's study on the status of NTGs of 29 April 2021, current EU legislation on GMOs is not adapted to the regulation of plants obtained using certain NTGs, in particular those resulting from directed mutagenesis, and products (including food and feed) derived from them. The European Commission puts forward the following problems:

- the risk assessment requirements and authorisation procedure under current GMO legislation are not adapted to the variety of potential plant products resulting from directed mutagenesis or cisgenesis and are therefore disproportionate or inadequate in some cases;
- current legislation on GMOs would be difficult to implement and enforce for certain plants derived from site-directed mutagenesis or cisgenesis, in particular those for which it is not possible to provide a precise detection method;
- the application of current GMO legislation to plants bred using NTGs would not be conducive to the development of innovative products potentially beneficial to breeders (the person or company who developed the new variety), farmers, food operators, consumers and the environment.

The Commission therefore concluded that the EU regulatory framework should be adapted to ensure that plants obtained using NTGs are subject to an appropriate level of regulatory oversight.

On 5 July 2023, the European Commission adopted a proposal for a regulation on new genomic techniques, designed to address the issues raised by the emergence of these new techniques and the inadequacy of the legislation governing them. This legislative proposal consists of a *lex specialis*[13]which creates specific procedures for applying for field trials and marketing authorisation for plants and plant products obtained using certain NTGs. Among the plants obtained by means of NTGs, the proposed regulation concerns only plants resulting from directed mutagenesis and/or cisgenesis (including intragenesis). Among these, two categories are distinguished.

[12] https://ec.europa.eu/food/plant-variety-portal/ (consulted on 12/10/2023)
[13] An Act designed not to modify the common framework but to create a specific regime applicable, in this case, to certain categories of genetically modified plants.

Category 1 of NTG plants includes plants which it is claimed could also be obtained naturally or by conventional breeding, and which meet the so-called equivalence criteria for conventional plants.

Equivalence is defined in Annex I of the proposed Regulation as a difference in the recipient/parental plant "*of up to 20 genetic modifications in any DNA sequence sharing sequence similarity with the target site*", where "*genetic modifications"* may correspond to :

- substitution or insertion of a maximum of 20 nucleotides;
- deletion of any number of nucleotides ;
- the targeted insertion of a contiguous DNA sequence existing in the breeder's gene pool, or[14] or the targeted substitution of a contiguous DNA sequence existing in the breeder's gene pool for an endogenous DNA sequence, provided that the genetic modification does not interrupt an endogenous gene;
- the targeted inversion of a sequence of any number of nucleotides or any other targeted modification of any size, provided that the resulting DNA sequences are already present in a species in the breeders' gene pool.

Recognition of category 1 status would be obtained through a single verification procedure, either with the competent authority of one of the Member States on whose territories a release for any purpose other than placing on the market is requested, or with Efsa in the case of an application for Community marketing authorisation.

Once this status is recognised, category 1 NTG plants and plant products would not be subject to the requirements of EU legislation on GMOs, but would be regulated as conventional plants (although they would be excluded from the organic sector, and seed labelling would be compulsory).

Category 2 NTG plants include plants that are not in category 1. Category 2 NTG plants and plant products would be subject to EU GMO legislation within the limits of the specific provisions and derogations set out in the Regulation. The procedures for requesting authorisation for release into the environment and for placing on the market set out in Directive 2001/18/EC and Regulation (EC) No 1829/2003 would apply in an appropriate manner. The assessment of health and environmental risks would be adapted in accordance with new principles and criteria, and the applicant could propose not to submit a post-marketing environmental monitoring plan on the grounds of irrelevance. In addition, the procedures for complying with detection requirements could be adapted if it is impossible to provide an analytical method. Finally, incentives are provided for category 2 NTG plants "with sustainability-related traits". These include a tighter deadline for examining the marketing application and the possibility of receiving advice from Efsa on the risk hypotheses identified by the petitioner. Herbicide-resistant plants are excluded from this incentive scheme.

The elements contained in this regulatory proposal have been the subject of a detailed critical analysis in a scientific and technical support note from Anses (Anses 2023).

[14] The breeder's gene pool is defined in the European Commission's legislative proposal as the total genetic information available in a species and other taxonomic species with which it can be crossed, including by means of advanced techniques such as embryo rescue, induced polyploidy and bridge crosses.

3 Identification of NTG applications most likely to lead to commercial varieties in the short term

Sections 3.1 and 3.2 are based on the analysis of three literature reviews: publications by (Brinegar et al. 2017) and (Modrzejewski et al. 2019) and the report by (Joint Research Centre 2021). They aim to provide general information on plants obtained using NTGs, taking all techniques together.

Section 3.3 is the result of the NTG's analysis of CRISPR-Cas techniques alone. As this work was not based on a systematic review of the literature and patents, there is still some uncertainty as to the completeness of the information presented below.

3.1 Techniques considered

The European Commission's Joint Research Centre[15] (JRC - *Joint Research Center*) of the European Commission has published a report on the current or expected worldwide marketing of organisms and products derived from NTGs (Joint Research Centre 2021). In this report, NTGs are defined as all techniques capable of modifying the genome of an organism that have been developed after the publication of Directive 2001/18/EC and up to the date of publication of the report. The JRC report includes epigenetic modification and RNA editing techniques on all target organisms (including animals, micro-organisms and human health applications). Its scope is broader than that of the present referral. As part of its work, the "NTG" working group has only taken into account directed mutagenesis and cisgenesis techniques applied to plants in this report.

In the JRC report, NTG applications are classified into four categories: basic research and development (R&D), advanced R&D, pre-commercialisation and commercialisation. Since the time required to move from the advanced R&D or pre-commercialisation stage to the commercialisation stage varies widely, applications at the advanced R&D stage could reach the market before applications that are currently at the pre-commercialisation stage (JRC, personal communication).

As far as NTG-derived plants are concerned, the JRC has identified 426 commercial applications. In 2020, 17 of these applications were at the pre-commercialisation or commercialisation stage, including 7 obtained using a CRISPR-Cas system. Furthermore, of the applications for which the genome modification tool is known (382 applications out of 426), 90.2% (305/382) involve a DNA double-strand break using a site-specific nuclease (CRISPR-Cas, *Transcription activator-like effector nucleases* (*TALEN)*, meganucleases and *Zinc-finger nucleases* (*ZFN)*), with CRISPR-Cas accounting for 78.8% of cases (**Figure 1**).

[15] The Joint Research Centre is a service of the European Commission responsible for producing and supplying independent scientific knowledge in support of decision-making for the European Union.

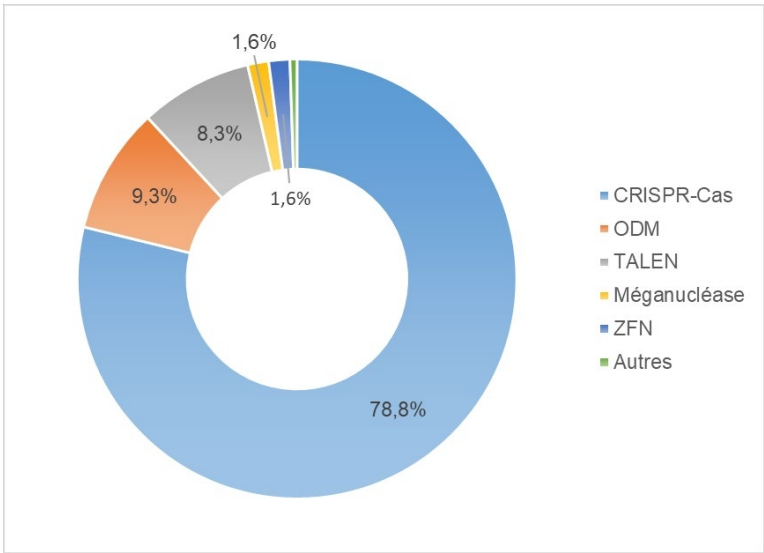


Figure 1: Proportions of different NTG techniques used for plant genome modification (adapted from Joint Research Centre (2021)) (n=382). CRISPR-Cas: *Clustered regularly interspaced short palindromic repeats - CRISPR associated protein*, ODM: *oligonucleotide-directed mutagenesis*, TALEN: *Transcription activator-like effector nuclease*, ZFN: *Zinc-finger nuclease*

The JRC report indicates, without giving figures, that it is a mechanism of deletion or insertion of a few base pairs, during DNA repair by the cellular *non-homologous* end-joining (NHEJ) system, that is used in the vast majority of cases.

The other two reviews (Brinegar et al. 2017; Modrzejewski et al. 2019) confirm the predominance of the use of the CRISPR-Cas system among NTGs, both in terms of the number of applications published in the literature and the number of patents filed in the United States (Brinegar et al. 2017).

3.2 Plant species and characteristics conferred on plants

The JRC report presents the plant species obtained using NTGs, as well as the traits conferred on plants as a result of genetic modification.

In terms of the plant species concerned, 38% are cereals, 17% are oil or fibre plants, 12% are vegetables[16] and 11% are tubers and root vegetables (**Figure 2**). If we consider only applications at the advanced R&D, pre-commercialisation and marketing stages, 28% concern cereals, 22% oil or fibre plants, 16% tubers and root vegetables, and 12% vegetables.

[16] The tomato, which is the subject of an article in this report, is included as a vegetable in the JRC report.

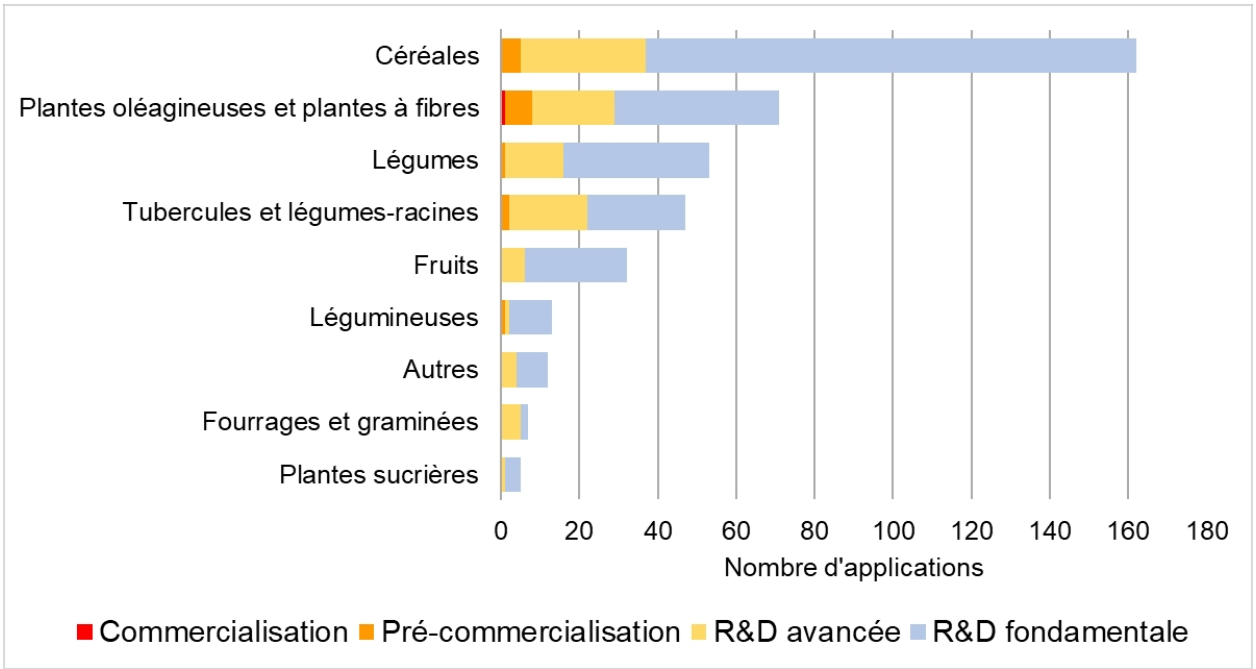


Figure 2: Groups of plants modified with NTGs (adapted from Joint Research Centre (2021))

NTGs are applied to a wider variety of species than those covered by the majority of applications for marketing authorisation under Regulation (EC) No. 1829/2003[17] and derived from transgenesis (maize, soya, oilseed rape, cotton and beet). Species that were little or not affected by transgenesis, such as banana, cocoa and chickpea, are among those identified in this report.

The range of plant species used to produce NTG varieties is therefore wide and likely to increase, in line with the accessibility and low cost of CRISPR-Cas techniques and the knowledge of plant genomes. Nevertheless, the application of CRISPR-Cas to certain species that are recalcitrant or resistant to transgenesis (legumes or peas, for example) remains difficult, as a step involving insertion of the CRISPR-Cas system into the plant genome before elimination is commonly used to obtain NTG plants.

The diversity of the countries behind the development of these varieties (African, Asian, etc.) could also be greater than that of the countries producing transgenic varieties. The arrival on the market, including in Europe, of these new varieties and the products derived from them is conceivable in the short to medium term, depending on the regulations that are adopted.

In terms of the types of traits conferred on NTG-derived plants, the three main ones are a change in the biochemical composition of the plant, tolerance to biotic stress and a change in plant yield and/or architecture (**Figure 3**). These three categories remain in the majority if we consider only those applications that are at the advanced R&D, pre-commercialisation or marketing stages.

It is also interesting to note that herbicide tolerance is found in less than 7% of applications, whereas this type of trait is more common in transgenic plants.

[17] https://webgate.ec.europa.eu/dyna2/gm-register/ (consulted on 12/10/2023)

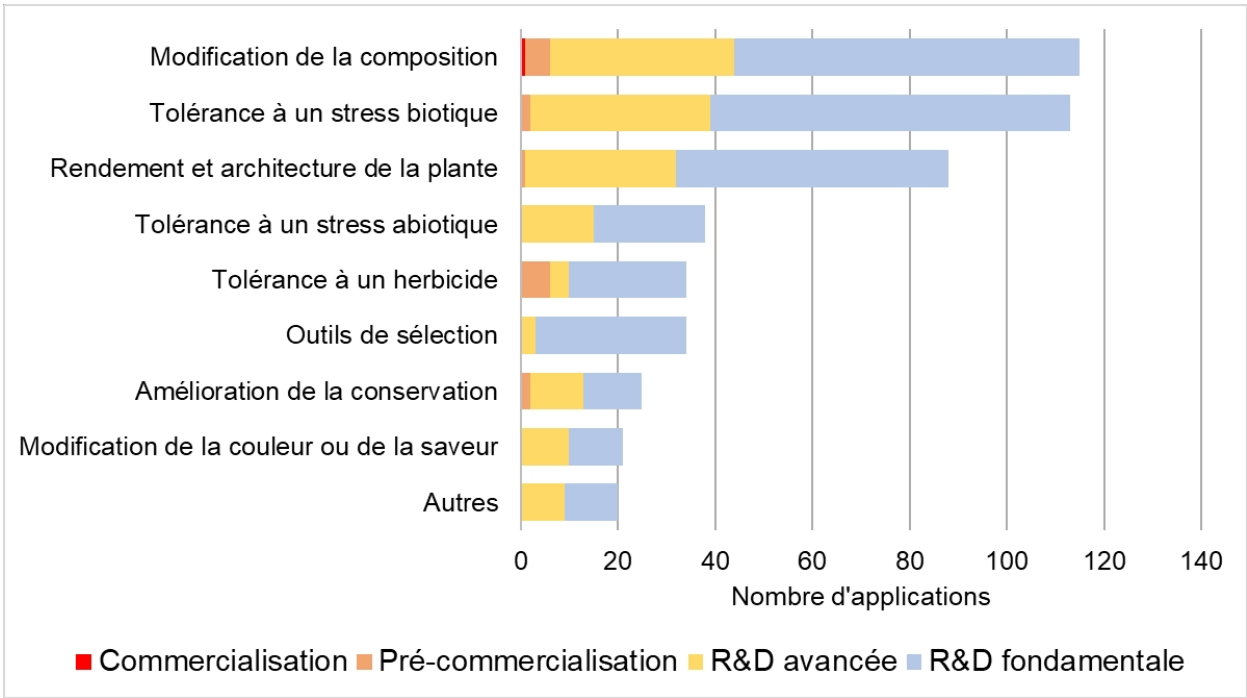


Figure 3: Characteristics conferred on plants obtained using NTG (adapted from Joint Research Centre (2021))

3.3 Plants obtained using the CRISPR-Cas system under development or available on the market

In order to identify the plants most likely to result in commercial varieties in the short term or which have already resulted in commercial varieties obtained using the CRISPR-Cas system (which appears to be the most widely used system, see section 3.1), the NTG has compiled a database of applications developed in plants obtained using these techniques (**Appendix 2**).

The information was extracted from publications by Brinegar et al (2017), Détain et al (2022), Modrzejewski et al (2019), the Joint Research Centre report (2021), international patent databases and the World Bank and IMF databases (consulted on 21/12/2022), using only plants obtained using CRISPR.

One hundred and twenty-one applications have been identified. They concern a very wide variety of species, the most represented being rice, tomato and maize (**Figure 4**).

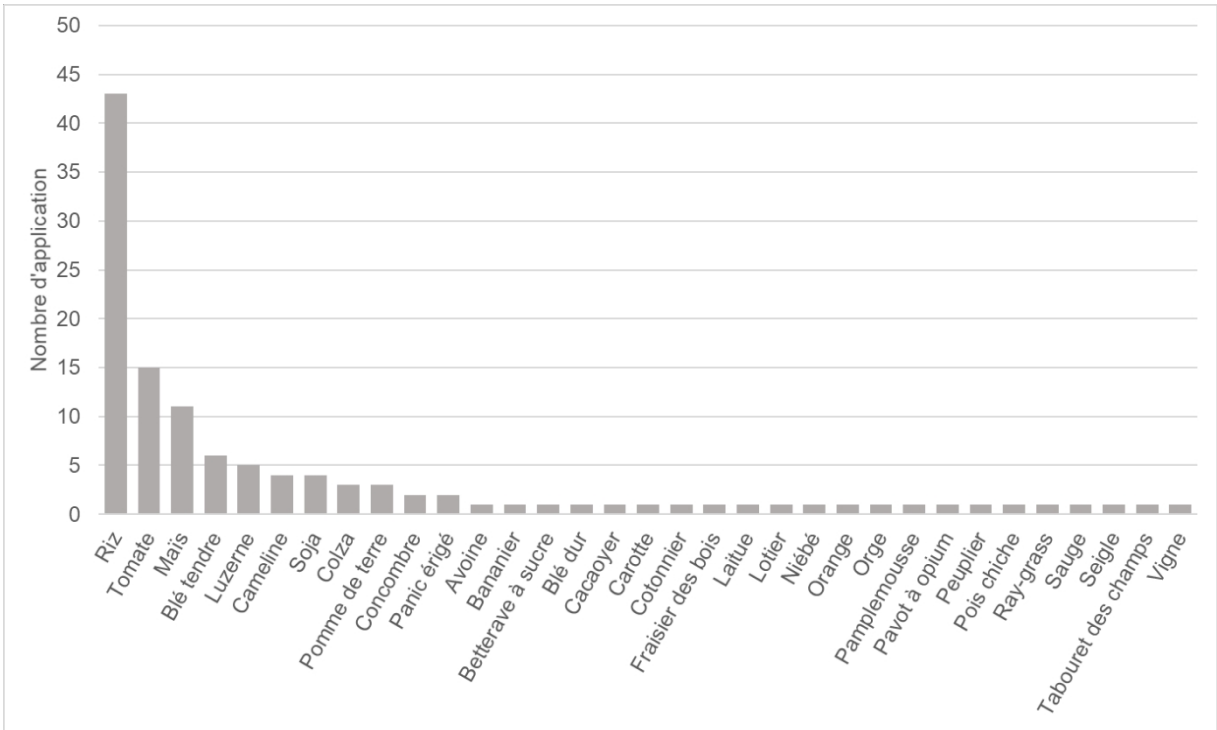


Figure 4: Plant species concerned by applications using a CRISPR-Cas system (analysis up to 21/12/2022).

In terms of the traits conferred on plants genetically modified using CRISPR-Cas (**Figure 5)**, changes in biochemical composition are the most numerous. These are followed by modifications to plant architecture and/or yield improvement, tolerance to biotic stresses and selection tools (e.g. male sterility favouring the production of hybrids). Herbicide tolerance accounts for only 5% of applications obtained using CRISPR, whereas this type of trait is more common in transgenic plants.

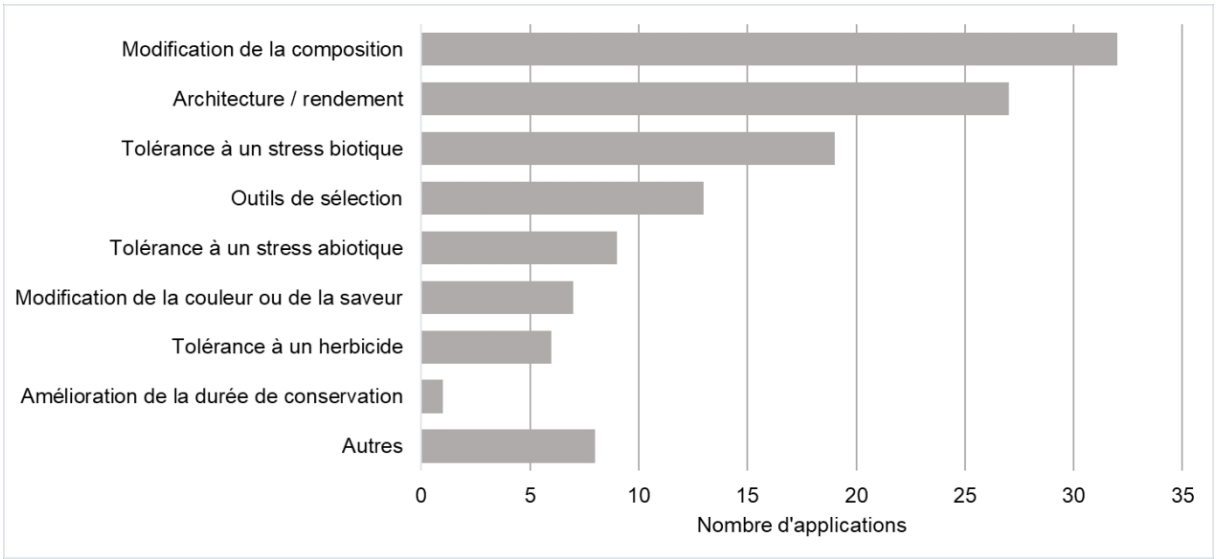


Figure 5: Characteristics conferred on plants by the CRISPR-Cas system.

3.4 Plants obtained using NTGs on the market

There is no database listing marketed products obtained using NTGs. On the basis of their knowledge, the NTG experts identified four plants derived from site-directed mutagenesis available on the market in countries outside the European Union:

- a soya developed by the company Calyxt, under the trade name Calyno™, is authorised in the United States[18]. This soybean has been genetically modified to give it a high oleic acid content with deletions in the genes for three desaturases (FAD2-1A, FAD2-1B and FAD3A), altering the function of these proteins. The oil obtained from this soya is intended for human consumption, with a health benefit claim. This soya was obtained using a TALEN system;
- a tomato, genetically modified using CRISPR-Cas9 to confer a high gamma-aminobutyric acid content (Nonaka et al. 2017; **Appendix 2**), has been available on the Japanese market since 2021. The genetic modification consists of deleting the autoinhibitory domains of 2 proteins (SlGAD2 and SlGAD3) involved in gamma-aminobutyric acid synthesis. Intended for human consumption with a health benefit claim, this tomato is marketed under the name *Sicilian Rouge High GABA* (γ-aminobutyric acid) by Sanatech Seed ;
- carrots genetically modified using CRISPR-Cas or TALEN to give them a high carotenoid content (lycopene and lutein in particular) have been developed jointly by OTERRA and the USDA in Madison (**Appendix 2**). These genetically modified carrots are intended for the production of food colourings, used mainly in meat preparations (sausages, burgers, etc.). Products containing carotenoids derived from these genetically modified carrots have been marketed in several countries (Americas, Australia, Israel, Japan) since 2018;
- a genetically modified cotton plant with improved root growth in nitrogen-limited conditions is marketed in China[19].

For genetically modified carrots and cotton, it has not been possible to access detailed information on the nature of the mutations made.

If :

- **the use of the CRISPR-Cas system appears to be dominant in NTG applications likely to lead to commercial varieties in the short term, probably because this technique is less expensive, easier to implement, faster and more effective than other site-specific nucleases (Gaj, Gersbach, and Barbas 2013);**
- **the use of the CRISPR-Cas system concerns applications already available on the market outside the European Union;**

[18] https://www.fda.gov/media/120707/download
https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/brs_response_cellectis_air_fad2k0_soy_cbidel.pdf [19] See the OPECST report (2021) on "New plant breeding techniques in 2021: advantages, limits, acceptability", page 105. https://www.senat.fr/rap/r20-671/r20-6711.pdf

- **cisgenesis is still not widely used, and the vast majority of applications observed are based on insertion or deletion mechanisms involving a few base pairs;**

The "NTG" WG has decided to focus its expert appraisal work on health and environmental risks (sections 4 to 6) on plants derived from site-directed mutagenesis using the CRISPR-Cas system.

4 Site-directed mutagenesis using the CRISPR-Cas system

4.1 Description of the CRISPR-Cas system

The CRISPR-Cas system is a complex consisting of an enzyme capable of cutting DNA (endonuclease), Cas, and a strand of guide RNA with a sequence complementary to that of the DNA targeted for mutation. The CRISPR-Cas system is used to create a double-strand break in the DNA at a specific site, thereby activating intracellular DNA repair mechanisms. As these mechanisms are more or less error-prone, changes to the genome can then occur.

CRISPR-Cas9 (**Figure 6**) is the best described and best known tool. This system is based on a defence mechanism that exists naturally in bacteria.

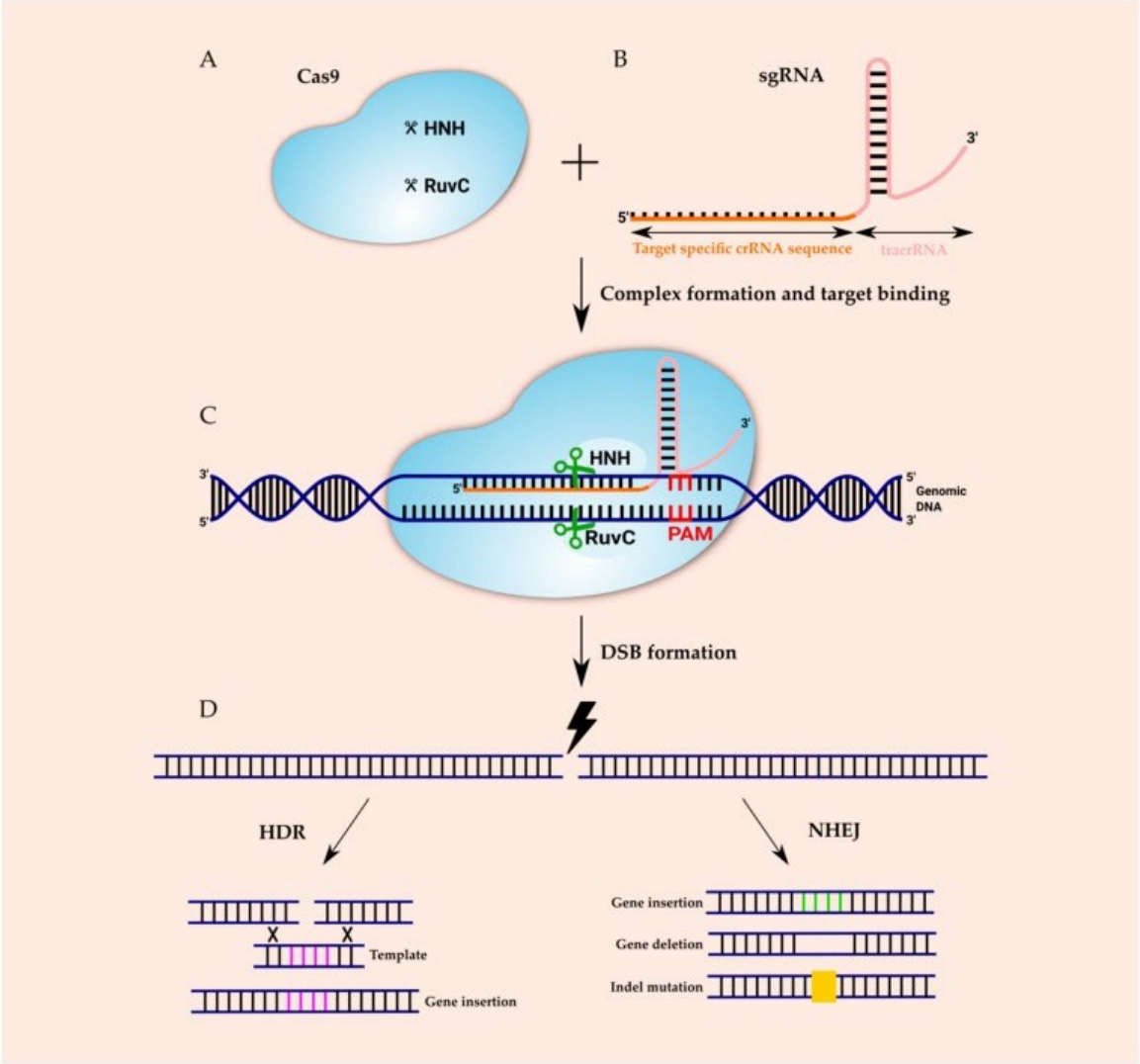


Figure 6. Schematic representation of the molecular mechanism of the CRISPR-Cas9 system (from Janik et al. (2020)). PAM: *Protospacer-adjacent motif sequence*; DSB: double-strand *break*; HDR: homology *directed repair*; NHEJ: non-homologous *end joining.*

The Cas9 endonuclease consists of two catalytic domains: the RuvC domain, which cleaves the DNA strand complementary to the sequence to which the guide RNA binds, and the HNH domain, which cleaves the DNA strands complementary to the guide RNA (A). The guide RNA (sgRNA) consists of two regions: the trans-activating CRISPR RNA (tracrRNA), which forms a hairpin structure, and the CRISPR RNA (crRNA), composed of a
A 20-nucleotide "protospacer" whose sequence is specific and complementary to the target sequence (B).

The guide RNA associates with the Cas9 protein, forming the Cas9/sgRNA complex. This complex unwinds the double-stranded DNA of the targeted genome and the crRNA anchors itself in a complementary fashion to one of the DNA strands. During this anchoring, the endonuclease domains of Cas9 cleave the two DNA strands, 3 bases upstream of a *protospacer-adjacent motif* sequence (PAM) (C). The Cas9 protein recognises guanine-rich PAM sequences (5'-NGG- 3') (Janik et al. 2020).

Following this *double-strand break* (DSB), intracellular repair mechanisms are activated and several pathways are possible (**Figure 7**).

- In the absence of a DNA sequence added to serve as a repair matrix, the repair pathway involved is known as non-homologous repair (NHEJ). The results obtained are point mutations or insertions/deletions of DNA fragments (SDN-1 mechanism); these mutations will generally lead to gene inactivation. The site of the mutation is predetermined, but the types of modification obtained are not. In addition, several guide RNAs can be used together to target several regions of the genome and thus obtain as many modifications simultaneously. This is known as multiplexing.
- When a DNA sequence is added as a repair template, the repair pathway involved is said to be "homology-based" (HR). The results obtained are either a change in the sequence of one or more genes (SDN-2 mechanism, the template is not integrated into the genome), or the integration of this sequence into the genome (SDN-3 mechanism). The site and nature of the mutation are predetermined. The "repair" DNA template has identical ends at the two adjacent regions of the chosen cut site. Even in the presence of this template, like any DNA double-strand break, the cut may also be repaired by NHEJ and therefore not result in the desired modification.

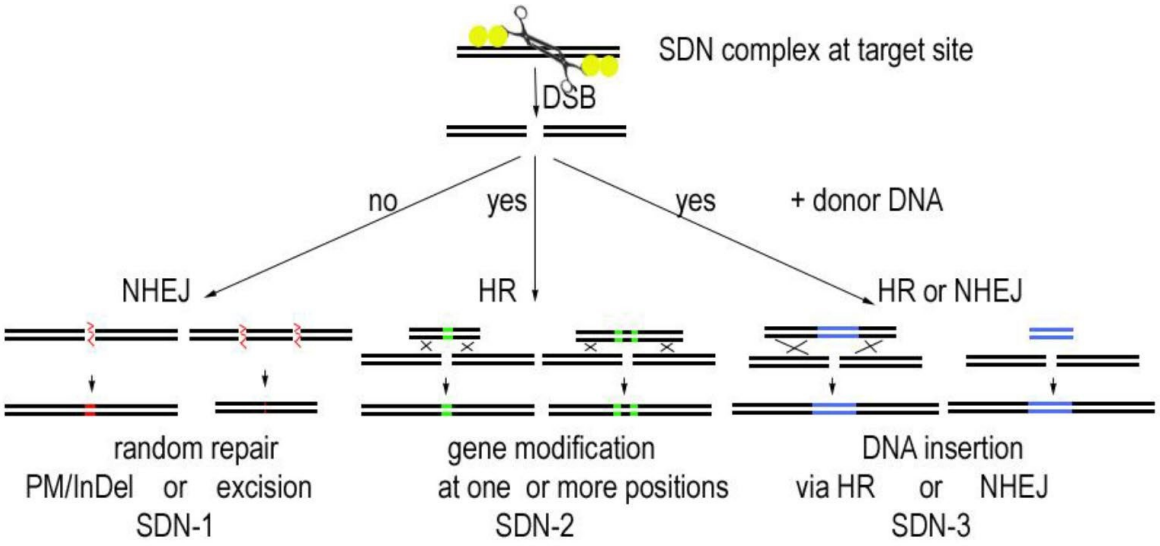


Figure 7. Schematic representation of the SDN-1, SDN-2 and SDN-3 mechanisms (from EFSA GMO Panel (2012)). *PM*: *point mutation*, *InDel*: insertions/deletions.

The SDN-3 mechanism does not correspond to site-directed mutagenesis but to transgenesis, cisgenesis or intragenesis. It was therefore excluded from the analysis.

More recently described, the CRISPR-Cas12 system can also be used for site-directed mutagenesis. The Cas12 protein is made up of several domains, including the RuvC and NUC domains that enable endonuclease cleavage activity. As with Cas9, Cas12 cleaves the DNA strand next to a PAM sequence. It recognises 5'-YTN-3' PAM sequences (NTN or TTN). Unlike Cas9, the Cas12 protein generates staggered double-strand breaks (cohesive ends), which favours the homology repair (HR) mechanism (Castagné et al. 2018; Hillary and Caesar 2022).

Lastly, the CRISPR-Cas system can be modified by genetic engineering to produce new tools with a variety of applications. For example, modified CRISPR-Cas systems, with or without other proteins, can be used to produce single-strand DNA breaks. These are known as nickases (or nCas9), with applications such as *base editing* or *prime editing*.

It is also possible to produce CRISPR-Cas systems that do not cut DNA. These are known as "*dead-Cas9*" (dCas9), and can be used to block the expression of targeted genes (CRISPR-interference) or to generate epigenetic modifications (histone modification, DNA methylation, etc.). Since no cuts are made in the genome, dCas cannot be used for site-directed mutagenesis. Their use and applications will therefore not be assessed in this report.

4.2 Steps to obtain of a variety by mutagenesis using the CRISPR-Cas system

The CRISPR-Cas-directed mutagenesis step is necessarily preceded by a CRISPR-Cas system delivery and expression step, the details of which can be widely varied.

vary. This may also be followed by *in vitro* regeneration, transgene segregation, backcrossing or excision.

With regard to the delivery and expression of the CRISPR-Cas system, two types of modality can be distinguished: those leading to stable expression of the system, and those leading to transient expression of CRISPR-Cas. Stable expression of CRISPR-Cas occurs when the genetic material enabling expression of the guide RNAs and the Cas nuclease is integrated into the genome of the plant to be modified. Conversely, transient expression occurs when there is no integration of foreign genetic material into the plant genome, and the guide RNAs and nuclease are not permanently expressed in the plant.

Different techniques can be used for each of these two methods.

- Stable expression of the CRISPR-Cas system is obtained by transgenesis. All known transgenesis techniques can therefore be applied here, in particular biolistics[20] or transformation methods using *Agrobacterium tumefaciens*[21].
- Transient expression can be achieved by delivery of genetic material that does not integrate into the genome, or by delivery of ribonucleoparticles directly containing the nuclease in protein form as well as the guide RNAs. Ribonucleoparticles can be delivered using a variety of physical techniques or *via* synthetic vectors (virus-like particles, extracellular vesicles, lipid vectors, etc.). In arboriculture or horticulture, the use of a rootstock (Zaman et al. 2023) with stable expression of the CRISPR-Cas system has also been described. This system enables the CRISPR-Cas system to be delivered to the non-genetically modified graft, in order to carry out directed mutagenesis without integrating external genetic material into the graft genome.

In vitro regeneration methods by organogenesis or embryogenesis[22] are necessary in the case of stable expression of the CRISPR-Cas system by transgenesis. For certain species that are recalcitrant or resistant to transgenesis or the regeneration of transformed plants, of which legumes are an example and peas the archetype, the use of CRISPR-Cas with stable expression of the system is not easy.

Once the CRISPR-Cas system has been delivered and the targeted mutation is effective, the breeder can carry out additional excision, transgene segregation or backcrossing steps. In the case of stable expression of the CRISPR-Cas system following its integration at a specific Cre/lox-type site, excision involves deleting this genetic sequence from the genome. Backcrossing involves crossing the newly-obtained genetically modified plant with a non-genetically modified parent plant. In the case of stable expression of CRISPR-Cas, segregation of the transgene or backcrossing can also eliminate the associated genetic material, in proportions of

[20] Transformation method consisting of projecting DNA-coated metal microbeads at very high speed onto the cells to be transformed.

[21] During transformation by *Agrobacterium tumefaciens*, a gene of interest is inserted into a plasmid of Agrobacterium, a soil bacterium capable of naturally infecting plants and transferring genetic material to them. The modified bacterium is brought into contact with a plant. Plant cells are then cultured until callus (cell clusters) form. The transformed calluses are used to regenerate the entire plant.

[22] Embryogenesis consists of all the stages involved in the transition from an egg cell to an organism. autonomous. Organogenesis, a stage in embryogenesis, consists of the formation of the embryo's tissues and organs.

Mendelian. Whether the expression of CRISPR-Cas is stable or transient, backcrossing can nevertheless also make it possible to eliminate any undesired effects on the plant genome (see section 4.3) or to introduce the modification into an elite variety of the modified species if the modification has been carried out in another variety (more suitable for transgenesis, for example).

4.3 Potential undesired effects on the genome of plants modified using CRISPR-Cas

Although the specificity of the CRISPR-Cas system for its target sequence in the genome is regulated, on the one hand, by the specific 20-nucleotide 'protospacer' sequence of the guide RNA (complementary to the target DNA sequence) and, on the other hand, by the recognition by the Cas protein of a defined PAM sequence, off-target cleavage by the Cas nuclease in the genome remains possible. Indeed, with regard to the guide RNA, while the hybridisation of the nucleotides closest to the PAM sequence is strict, that of the nucleotides located 5' to the RNA does not need to be perfect for there to be cleavage by the Cas nuclease (Trembley, 2015). This can lead to the association of guide RNAs with regions of the genome other than the intended target. The resulting off-target cuts can then be associated with mutations, through the activation of intracellular repair mechanisms (section 4.1).

CRISPR-Cas cuts to the target can also lead in some cases to unwanted genome modifications, such as larger deletions or insertions on large chromosomal regions, chromosomal rearrangements (translocations, inversions, aneuploidy), or the conversion of genes on one chromosome to match the sequence on the other chromosome (loss of heterozygosity), as already observed in animals (Lackner et al. 2023).

In both these cases, we are talking about undesired effects, on or off target, associated with the use of CRISPR-Cas.

In order to assess the nature and frequency of undesired effects on the plant genome, on or off target, the WG initially chose to focus on a plant species for which varieties obtained using CRISPR-Cas could appear on the European market in the short term. The WG chose the tomato because of the large proportion of applications obtained using CRISPR-Cas identified in the literature concerning this species, its original character compared with the transgenic species authorised in the European Union (mainly cereals or oilseeds, which are not very rich in water) and the fact that a modified tomato obtained using the CRISPR-Cas system is already present on the market outside the European Union, particularly in Japan (Waltz 2021). This analysis was then extended to all plants, by analysing systematic reviews that already existed in the scientific literature, and by systematically reviewing original articles published over the 2021-2023 period, which was not covered by the systematic reviews identified.

4.3.1 Systematic review of the literature on the undesired effects of using the CRISPR-Cas system on the genome of a plant of interest: tomato

The potential undesired effects of the CRISPR-Cas system on tomatoes, both at the target and elsewhere in the genome (off-target), were analysed by means of a literature review, carried out using the method described in the Anses guide to bibliographic research over a period up to December 2022 (**Appendix 3**).

The elements relating to the PICO[23] structure used in this systematic review are shown in **Table 1**.

Themes	Keywords from thesaurus
Population (or subjects studied)	Tomato
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Tomato not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. *Ex*: mortality, health effects, psychosocial effects, perceptions, economic results)	Unintended effects on and off target
Temporality (Research periods)	∞ - 15/12/2022

Table 1. PICO structure of the research relating to the systematic literature review on the undesired effects associated with the use of CRISPR-Cas on the tomato genome.

A search of 3 bibliographic databases (Scopus, Pubmed, CAB Abstracts) identified 904 references, including 409 duplicates which were eliminated. Of the remaining 495 original references, 294 were retained after sorting by title and abstract, for full-text analysis. Articles that did not provide information on the undesired effects of CRISPR-Cas at genome level, on target or off target, or for which the presence or absence of these effects had not been validated experimentally, were then excluded. A total of 61 references were selected for in-depth analysis and used to produce a summary. The table analysing the articles included is available in **Appendix 4**.

[23] The PICO method is designed to clearly formulate literature search questions, and consists of defining the main key elements of the search: population, intervention, comparator, outcome.

In the publications analysed, off-target undesirable effects are sought in two ways:

- by prediction, using bioinformatics tools, of the zones that could be modified in addition to the sequence(s) initially targeted (essentially zones presenting a certain sequence homology with the guide RNAs), followed by PCR amplification and sequencing analysis of these zones;
- by sequencing the entire genome and comparing it with a reference genome.

These two approaches correspond respectively to so-called biased and unbiased approaches.

The search for undesired effects was carried out using the first approach (bioinformatics) in 58/61 (95%) of the articles analysed. Off-target effects were described in four of these publications. The second approach (complete genome sequencing) was used in four references and no unwanted effects were detected.

In addition, systematic sequencing (generally after PCR) of the area targeted by mutagenesis ensures that the desired modification has been obtained and that there are no undesired effects on the target.

The use of high-performance bioinformatics tools for the design of guide RNAs, based on a high-quality reference genome sequence, probably explains the reduced number of off-target undesirable effects observed in this literature review.

Concerning the four publications in which off-target effects were described :

- (2017), these off-target effects can be explained by the simultaneous use of 165 guide RNAs, and the insufficient quality of the tomato genomic sequence available at the time;
- in the work of Shimatani et al (2017), which corresponds to the first use of the cytidine deaminase tool ("*base editing*") in tomato, a deep sequencing analysis estimated that the frequency of mutations due to the use of CRISPR-Cas at the most likely off-target sites is between 0.14% and 0.38%, which is considered low by the authors of this article;
- In the publications by Tran et al (2021) and Veillet et al (2019), the design of the guide RNAs was highly constrained, as the aim was to obtain precise deletions of certain protein domains or the mutation of a given amino acid. The guide RNAs used were not sufficiently specific to avoid any off-target effects. However, the work of Veillet et al (2019) shows that it is possible to reduce the occurrence of off-target modifications from 88% to 16% by limiting the time CRISPR-Cas9 is active in cells.

Although these results cannot be generalized to all plants, particularly in the case of incomplete genome sequencing, the WG concludes from this literature review that in the case of tomato, provided (i) good control of this technique (design of guide RNAs or activity time of the CRISPR-Cas system in the cells, for example), (ii) sequencing of the zone targeted by mutagenesis and (iii)

***a posteriori* control of potential unwanted effects, at the target and off-target (by bioinformatic prediction followed by sequencing of the identified zones or by complete sequencing of the genome), it is possible to produce genetically modified tomato plants containing only the desired modification at the target site (or containing a limited number of undetected off-target effects). The WG also believes that, in the case of tomatoes, if off-target effects are detected, segregation steps could be implemented to eliminate them in subsequent generations.**

4.3.2 Systematic review of the literature on the undesired effects associated with the use of the CRISPR-Cas system on the genome of all plants for which applications have been documented

4.3.2.1 Methodology

In order to extend the characterisation of undesired effects on the genome due to the use of the CRISPR-Cas system to all plants for which applications are described in the literature, the WG carried out a new systematic review of the literature, using the method described in the Anses guide to literature searches (**Appendix 5**).

The elements relating to the PICO structure used in this systematic review are shown in **Table 2**.

Themes	Keywords from thesaurus
Population (or subjects studied)	Plants
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Plant not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. *Ex*: mortality, health effects, psychosocial effects, perceptions, economic results)	Unintended effects on and off target
Temporality (Research periods)	∞ - 01/06/2023

Table 2. PICO structure of the research relating to the systematic literature review on the undesired effects associated with the use of CRISPR-Cas on the genome of plants for which applications have been documented.

In order to specifically target publications of interest in this analysis, mention of the terms "off-target" and/or "on-target" in the title, abstract or keywords has been added to the search equation. The WG considers this to be a minor limitation on the completeness of

the research, and believes that the research equation as formulated provides sufficient, unbiased coverage of the references on this subject.

A search of 3 bibliographic databases (Scopus, Pubmed, CAB Abstracts) identified 1861 unique references, of which 426 were retained after sorting by title and abstract and sorting by full text. It should be noted that this search was initially carried out on both original articles and journals. During the full-text sorting stage, four systematic reviews of the literature on unwanted effects, covering a broad period and a large number of applications, were identified (Chu and Agapito-Tenfen 2022; Modrzejewski et al. 2019; Modrzejewski et al. 2020; Sturme et al. 2022).

To assess their quality, the WG used the latest version of the AMSTAR grid for assessing the methodological quality of systematic reviews.[24]-2. This grid is based on criteria relating to the sound methodological construction of studies (Shea et al. 2017). The AMSTAR-2 quality assessment reports for these reviews are available in **Appendix 6**. Of the four reviews identified, three (Modrzejewski et al. 2019; Modrzejewski et al. 2020; Sturme et al. 2022) obtained a score of more than 9/12, and were therefore selected for the analysis of unwanted effects on the plant genome (section 4.3.2.2).

It should be noted, however, that these reviews cover an analysis period up to 2020. In order to cover the most recent period possible, the WG decided to supplement this analysis of the three systematic reviews with an analysis of original articles published between 2021 and June 2023 resulting from the same search equation (section 4.3.2.3). 82 articles were selected for analysis and extraction of data relating to unwanted effects on the plant genome. The analysis table for these articles is available in **Appendix 7**.

4.3.2.2 Analysis of pre-existing systematic reviews

This section is based on an analysis of the literature reviews (Modrzejewski et al. 2019; Modrzejewski et al. 2020; Sturme et al. 2022), which were judged to be of very high quality so as to be representative of the state of the art over the period covered. The aim is therefore to establish the state of the art in terms of the undesired effects observed in connection with the use of the CRISPR-Cas system on the plant genome.

4.3.2.2.1 Analysis by Modrzejewski et al (2019)

In a review published in 2019, Modrzejewski and colleagues searched for all studies conducted between January 1996 and May 2018 on potential off-target effects, based on the different NTGs. This review analyses a total of 161 scientific articles, reporting 252 separate studies (plant species or genome modification tool). Of the 252 studies referenced, 228 (90%) concern the CRISPR-Cas system.

Only the results concerning the CRISPR-Cas system have been taken into account by the WG in detail in the following paragraphs.

[24] AMSTAR: a measurement tool to assess the methodological quality of systematic reviews

Although there was considerable diversification in the species used, in line with the CRISPR-Cas system, with 32 different plant species listed in the review, 13 of these species were used in only one study and eight other species were used in no more than three studies. More than half of the studies (130/228) focused on three species, led by rice (82 studies), tomato (25 studies) and lady's cress, a model species in plant biology (23 studies).

To study off-target effects, two types of detection strategy were considered.

The first type is so-called biased detection, based on *a priori* knowledge of the sites most likely to be modified, either through knowledge of sequence homologies (in the case of multi-gene families, for example), or through bioinformatics predictions. This is the vast majority of studies (211/228). In these cases, off-target effects are generally sought by PCR amplification of regions homologous to the target and, after sequencing, by searching for variations in relation to a reference sequence. Taking into account all the studies on the CRISPR-Cas system, 1,738 potential off-target sites were analysed and off-target effects were identified at 55 of these sites, i.e. 3% of the sites analysed.

The other type of so-called unbiased detection involves analysis of systematic sequencing of the entire genome. Nine of the 228 studies analysed (3.9%) opted for this strategy, and none demonstrated off-target effects.

In conclusion, the authors nonetheless highlight the great heterogeneity found between the studies, particularly in terms of prediction and selection of off-target sites to be studied (15 different bioinformatics prediction tools used), detection method and species modified, as well as the lack of detailed information in several articles, and indicate that these two aspects may potentially influence the results of this review.

4.3.2.2.2 Analysis by Modrzejewsk et al (2020)

In another review by the same author published in 2020, Modrzejewski and colleagues have extended their bibliographic search of works mentioning the search for off-target effects up to March 2019. This review analyses a total of 468 articles covering the period between January 1996 and March 2019 and focuses solely on the CRISPR-Cas system.

The aim of this review is not, as in the first, to study the existence of possible off-target effects and assess their frequency, but to seek to determine, on the basis of a systematic analysis of the literature, the factors likely to influence their occurrence. Details of the meta-analysis and the different variables examined will not be given here.

Of the factors examined, the number of *mismatches* (minimum number of different bases between the targeted sequence and another potentially off-target sequence) appears to be the most decisive (**Figure 8**). The probability of an off-target effect decreases as the number of mismatches increases, with an almost zero probability of obtaining off-target effects above 4 mismatches. The location of these mismatches relative to the PAM site also has an effect, with a greater risk of off-target effects if the mismatches are located at a distance (17 to 21 nucleotides) from the PAM site.

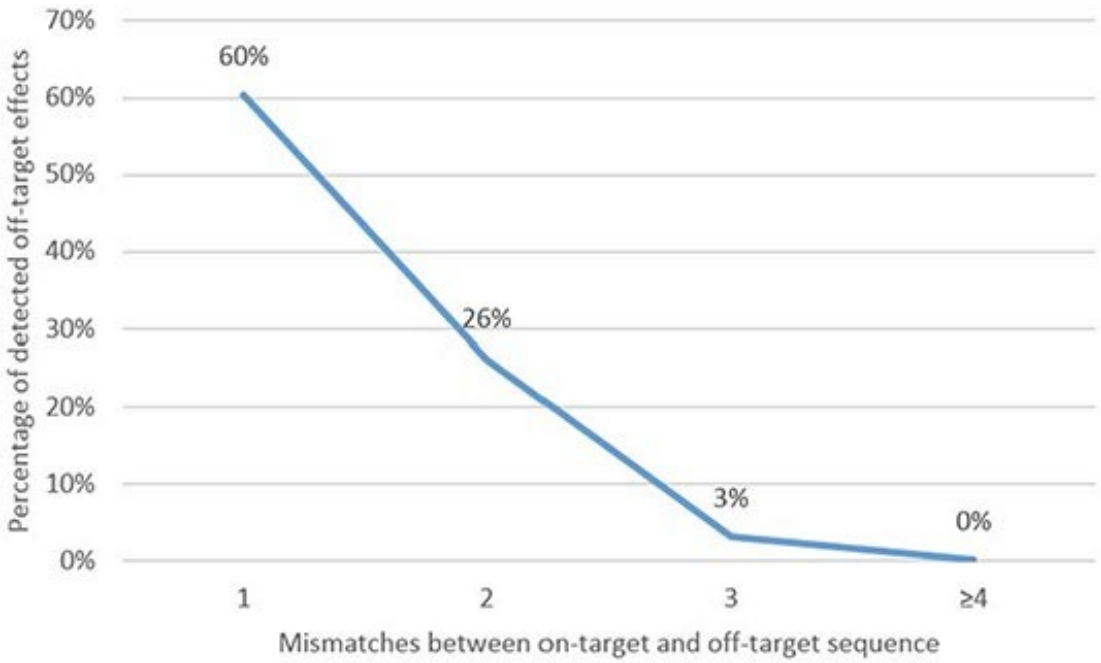


Figure 8. Percentage of off-target effects observed as a function of the number of mismatches between the guide RNA and the sequence on which the effect is sought (from Modrzejewski et al. (2020)).

4.3.2.2.3 Analysis by Sturme et al (2022)

The aim of this review, published in 2022 by Sturme and colleagues, is to bring together the information obtained concerning the off-target effects observed due to the use of the CRISPR-Cas system. It is based on an analysis of 107 selected publications. The majority of these publications report a search for off-target effects using a biased approach (97/107). A small number of articles (7/107) reported an unbiased approach. Of the 107 publications selected, 28 reported at least one observed off-target effect. The main off-target effects observed were small insertions or deletions (1-22 base pairs (bp)) or a nucleotide substitution at the double-strand break site.

In particular, it was observed, as in the studies by Modrzejewski and colleagues (Modrzejewski et al. 2019; Modrzejewski et al. 2020), that off-target effects were revealed when the number of mismatches between the off-target site and the guide RNA was between 1 and 3. Similarly, off-target sequences are generally located in coding regions and in genes homologous to the gene under study. One study (Arndell et al. 2019) also mentions the insertion of transfer DNA, which according to the authors is an important factor to take into account in risk assessment.

The authors of this review also report that most of the studies mentioning searches for off-target unwanted effects do not propose further molecular characterisation afterwards, and in particular do not specify the nature of the modification observed. They also note that their results are in agreement with those observed in the analysis carried out by Modrzejewski et al. (2019). The authors mention that there is a large number of publications opting for a biased approach to the search for off-target effects. However, they conclude that an unbiased whole genome sequencing approach would be preferable to detect off-target mutations not predicted *in silico*.

4.3.2.3 Systematic analysis of undesired effects linked to the use of the CRISPR-Cas system on the plant genome (years 2021 to 2023)

As the three systematic reviews previously analysed by the WG (section 4.3.2.2) covered the analysis of unwanted effects observed in the literature up to 2020, the WG completed this analysis of the literature for the period from 2021 to June 2023. For this analysis, 82 articles mentioning a search for unwanted effects on the plant genome were selected.

In these 82 articles, a number of plant species are mentioned (**Figure 9**). The WG notes that the crop species cited are the same as those presented in the review by Modrzejewski et al. (2019), including first and foremost: rice and tomato. This shows a continued interest in these species over time.

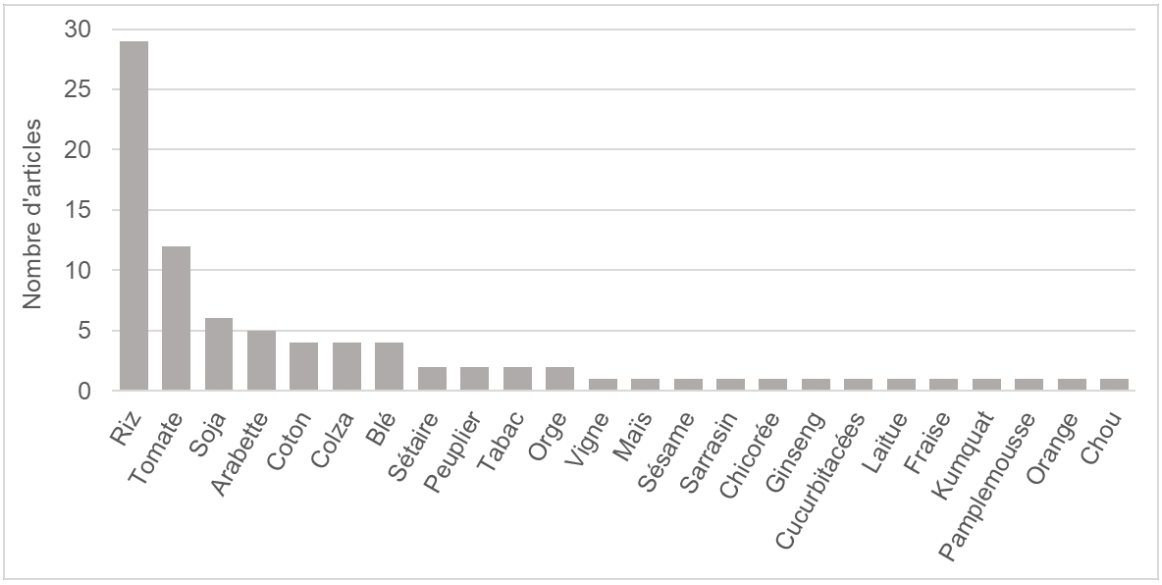


Figure 9. Plant species covered by the systematic literature review (2021 - June 2023) on the undesired effects of using the CRISPR-Cas system on the plant genome.

Of these 82 articles, 64 (78%) articles reported biased research for unintended effects, 15 (18%) articles reported unbiased research, and three (4%) articles reported a combination of biased and unbiased research. The WG notes the increased use of unbiased research compared with the Modrzejewski et al. (2019) review (18% in the WG analysis, compared with 9/228, or 3.4%). The WG considers that this trend could be explained by the progress made in sequencing techniques (which are increasingly robust and powerful, less costly and offer higher sequencing depths) and by the reduction in the cost of these analyses. Furthermore, while no biased search study identified off-target unintended effects in the review by Modrzejewski et al (2019), 8 publications out of the 15 reporting the use of an unbiased search identified off-target effects in the present literature review covering the period from 2021 to June 2023. This difference can probably be explained by

by the increase in this use combined with better availability and control of sequencing techniques in recent years.

In total, of the 82 articles analysed, 28 (34%) described an unwanted off-target effect. Of these, 18 (64%) were identified by biased search, 8 (29%) by unbiased search and 2 (7%) by using both approaches in parallel.

Of the 837 sequences that were analysed for off-target unwanted effects using a biased approach (amplification and sequencing of the amplification products), only 60 showed an off-target mutation, i.e. 7% of the sequences analysed. This represents an increase compared with the study by Modrzejewski et al. (2019) (3
of the sequences analysed showed a proven off-target effect), but the percentage of off-target effects reported remains low.

Although the type of unwanted mutations observed is not often described in the articles analysed, the vast majority of cases described are short deletions or insertions (Jedličková et al. 2022; Liu et al. 2022; Narushima et al. 2022; Wang et al. 2021; You et al. 2022).

Most of the unwanted effects observed are off-target effects due to relatively non-specific guide RNAs, which most of the time have a number of mismatches with the off-target sequence less than or equal to 3. Off-target effects are also often observed on sequences homologous to the targeted gene (Acha et al. 2021; Aesaert et al. 2022; Jedličková et al. 2022; Shin et al. 2022; Shin and Park 2023). The design of guide RNAs is therefore important to limit these off-target effects, although it can prove complex in the case of sequence homologies in the genome. Furthermore, the choice between several guide RNAs for the targeted zone is not always possible, since it depends on the presence of a PAM site at the target.

Among the publications mentioning the demonstration of off-target effects, in particular by unbiased research, or by the parallel use of the two approaches, several consist of the development of new tools derived from CRISPR-Cas and their testing, both in terms of efficacy and the occurrence of off-target effects. These include the development of *base editing* systems and other nucleases (Li S. et al. 2022; Ren et al. 2021; Wu et al. 2022; Zhang et al. 2022). This work reflects the great dynamic underway in the development of innovative genome modification tools. However, there is considerable variability between the tools tested, in terms of the precision of modifications, efficacy and reduction of off-target effects. Potential for improvement is emerging, and new modification tools could continue to appear. These options for improvement have also been highlighted by biased research, demonstrating the presence of off-target effects at low frequencies (Tan et al. 2022; Yan et al. 2021; Zong et al. 2022).

Among the undesired effects identified, off-target insertions of unidentified origin (a 35 bp insertion in grapevine (Wang et al. 2021)) and a DNA insertion from the vector used for the target in soybean (Adachi et al. 2021) were observed.

The authors consider that these insertions could be due to the natural repair systems of plant cells, known to be a source of error, which intervene after the

double-stranded DNA breaks produced by the CRISPR-Cas system. Large deletions were also observed in tomato and rice in the studies by Li R. et al. (2022) and Zhang et al. (2022), where a large deletion of 3200 bp and 1525 bp was reported, respectively.

As observed in the review by Sturme et al, 2022, at least 5 publications mention the use of the Cas12 nuclease. The interest in this nuclease is linked to its greater efficacy, associated with a reduced frequency of off-target effects. However, although this is a rare event, an unwanted deletion of 1525 bp has been observed in rice after using this nuclease (Zhang et al. 2022).

The increase in the number of studies using high-depth NGS sequencing also reveals, in addition to off-target effects that can be attributed to certain homologies with the sequence of the guide RNAs, other sequence differences between the reference genomes and the genomes studied. Some authors refer to this as 'private variation' (Wang et al. 2021), particularly in the case of nucleotide polymorphisms and insertions or deletions found mainly in intergenic regions of edited plants (Cheng et al. 2021). The multiplication of judicious controls, such as the use of plants that have undergone a regeneration cycle in *in vitro* culture similar to the edited plants, could make it possible to differentiate modifications due to the CRISPR-Cas system from those due to somaclonal variation.

Following the analysis of three systematic reviews covering a period up to 2021 and the analysis of original articles covering the period from 2021 to June 2023, the WG considers that the frequency of unwanted effects observed is very low, if not zero if the guide RNA sequence is defined with great precision, in particular to maintain more than 4 mismatches with other regions of the plant genome.

4.3.3 WG recommendations on the molecular characterisation of plants resulting from site-directed mutagenesis using the CRISPR-Cas system

In conclusion of the systematic review of the literature on the undesired effects on the plant genome associated with the use of the CRISPR-Cas system, the WG recommends, with regard to the molecular characterisation of plants resulting from site-directed mutagenesis using the CRISPR-Cas system (Figure 10), that :

- **the target zone(s) are sequenced, the modification(s) obtained are characterised and an appropriate detection method is provided by the petitioner[25] ;**
- **where possible, the breeder uses guide RNAs with more than 4 mismatches with the non-targeted zones of the genome, or justifies this impossibility;**

[25] For plants derived from transgenesis, information on detection methods can be found at https://gmo-crl.jrc.ec.europa.eu/guidance-documents.

- **when the complete genome sequence of the species concerned is available and resequencing of the genome of the modified plant is feasible, an unbiased search for undesired effects on the genome should be carried out, combining *long read* and *short read* techniques, ensuring a minimum coverage of 20 X ;**
- **when resequencing is not feasible (for example in the case of polyploid plants or very large genomes) but a complete reference genome is available, a biased search is carried out on any genome sequence presenting 4 mismatches or less with the guide RNAs;**
- **when a complete reference genome of the species concerned is not available, a search for unwanted effects is carried out on any known homology zone;**
- **the absence of foreign DNA (including in the form of fragments) in the plant genome is demonstrated, either by resequencing the genome, or by targeted sequencing or Southern blot using probes specific to the plasmid or transfer DNA and the sequence corresponding to the CRISPR-Case system used.**

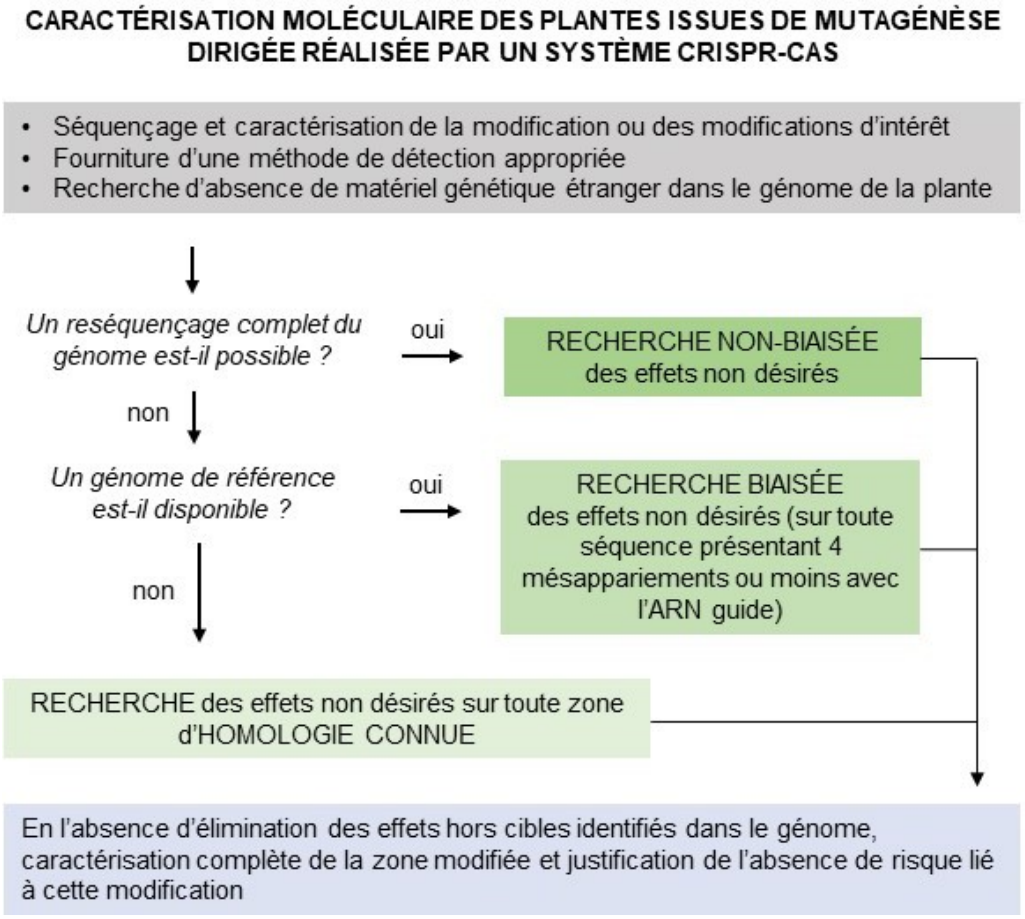


Figure 10. WG recommendations for the molecular characterisation of plants derived from site-directed mutagenesis using the CRISPR-Cas system.

5 Health and environmental risks associated with the use of plants derived from site-directed mutagenesis using the CRISPR-Cas system

5.1 Current benchmark for the assessment of genetically modified plants and suitability for the assessment of plants derived from CRISPR-Cas directed mutagenesis

The purpose of this section is to set out the current regulatory framework for assessing the health and environmental risks of genetically modified plants. The framework considered is defined by the various applicable regulations (see section 2.2) and the Efsa guidance documents (EFSA GMO Panel 2010; EFSA GMO Panel 2011a; EFSA GMO Panel 2011b; EFSA GMO Panel 2011c; EFSA GMO Panel 2015; EFSA GMO Panel 2017; EFSA GMO Panel 2017).
GMO Panel 2019; EFSA GMO Panel 2023). The possibility of adapting this benchmark to plants derived from CRISPR-Cas directed mutagenesis is also analysed below.

5.1.1 Comparative evaluation

The purpose of the comparative assessment of genetically modified plants is to draw up an inventory of any agro-phenotypic and compositional differences between the genetically modified plant and its non-genetically modified equivalent. In summary, the experimental design, described in detail in an EFSA guideline document (EFSA GMO Panel 2015), provides for a comparison of the characteristics of the genetically modified plant with those of an equivalent non-genetically modified plant, genetically as close as possible, and with those of six non-genetically modified reference varieties, selected to represent the natural phenotypic variability of the species.

The compositional characteristics are defined by species, according to reference documents published by the OECD[26]. In particular, this analysis aims to assess the absence of unexpected effects of the genetic modification on the biology of the plant, which may be due, for example, to the extinction of genes or the expression of silent sequences specific to the genome of the original plant and/or to metabolic interactions, discrete or otherwise, leading to the appearance of unexpected metabolites. The identification of any changes in the agronomic and phenotypic characteristics of the modified plant also makes it easier to detect a possible selective advantage in the event of the plant being disseminated.

Where appropriate, the comparative analysis may also aim to assess the differences in composition between the processed food (oil or cake for soya, for example) obtained from the genetically modified plant and that obtained from the non-transgenic equivalent, in order to ensure that there are no unexpected effects of the genetic modification.

[26] https://www.oecd.org/science/biotrack/consensus-document-for-work-on-safety-novel-and-foods-feeds-plants.htm (consulted on 12/10/2023)

In the case of plants obtained by site-directed mutagenesis, the WG believes that unexpected effects on the phenotype and agronomic characteristics of the modified plants are always possible, and that unexpected changes in the composition of the plants or foods derived from them could also be observed, regardless of the modified trait. Indeed, compensation phenomena or regulatory loops may be activated (El-Brolosy and Stainier 2017; Kaufmann, Pajoro and Angenent 2010) in the modified plant and certain interactions of the protein derived from the modified gene may not be known.

Furthermore, although a comparative assessment is *a priori* applicable to plants resulting from site-directed mutagenesis, the choice of comparator raises questions, particularly in the case of plants obtained by multiplexing, in which several genes have been modified simultaneously. The complexity of the genetic change would then be greater, and the equivalent comparison line could turn out to be genetically distant from the modified plant. In addition, the new diversity of species resulting from CRISPR-Cas applications (see section 3) raises practical questions about how to carry out comparative assessments. In particular, there are species for which, to the best of the WG's knowledge, no OECD guidelines for the compounds to be analysed are available (such as cocoa), and the development of such guidelines and making them available would therefore be a prerequisite for assessing the health risks associated with the use of these plants.

Similarly, the WG points out that some food species may naturally contain toxic or anti-nutritional substances (EFSA 2012). These substances should be taken into account in the comparative study.

More generally, the WG notes that the use of guidance documents presenting a finite list of compounds to be analysed, such as those of the OECD, may prove insufficient to identify certain changes in composition. However, analyses of all the proteins or metabolites of these genetically modified plants, using techniques known as proteomics or metabolomics respectively (Drapal et al. 2023), could provide a solution to the shortcomings of the OECD composition lists and their absence for certain species. However, as these techniques are not required as part of the current assessment framework, they would need to be developed and adapted for comparative studies under real field conditions before they could be applied.

5.1.2 Toxicological evaluation

Under the current guidelines for assessing genetically modified plants, toxicity studies aim to identify and assess the potential adverse effects of the newly expressed proteins on the one hand, and to demonstrate that the intended or unintended effects of the genetic modification have no deleterious effects on human or animal health if the genetically modified plant or its products are consumed on the other.

In order to assess the potential adverse effects of the new constituents, an oral toxicity study of the newly expressed protein at repeated doses for 28 days in rodents (OECD 2008) is required. This study is complemented by an analysis of the sequence homology between the newly expressed protein and known toxins, as well as an assessment of its thermal stability and resistance to digestion. Calculations of dietary exposure to these proteins in humans and animals are also required.

With regard to the demonstration of the absence of adverse effects of the whole plant on human or animal health of the effects sought or not from the genetic modification, the assessment is mainly based on the oral toxicity study of the whole plant at repeated doses for 90 days on rodents (OECD 2018).

For plants obtained by site-directed mutagenesis, insofar as no new exogenous protein is expressed, only the 90-day toxicity study is directly applicable. **The WG also considers that this study remains essential to identify any risk to human or animal health linked to the consumption of the genetically modified plant or products derived from it.** The 28-day toxicity study does not appear to be directly transposable for plants derived from site-directed mutagenesis, insofar as it applies to the newly expressed exogenous protein in the current reference framework. Adaptation of the 28-day toxicity study is nevertheless possible on a case-by-case basis, particularly if the modification obtained by site-directed mutagenesis leads to the expression of a protein in a form that does not exist naturally, and could therefore be considered as new.

However, genetic modification using CRISPR-Cas of new species, different from those traditionally the subject of marketing authorisation applications under Regulation (EC) No. 1829/2003 and resulting from transgenesis, could also lead to technical difficulties in carrying out toxicology studies. Some plants could be less palatable or cause nutritional problems in rodents. Similarly, plants with a high water content, such as tomatoes, could be difficult to ingest in sufficient, controlled quantities. In these two cases at least, technical considerations or adaptation of the studies, to species other than rodents or by transforming the food in order to increase its palatability for example, will have to be developed so that the toxicity of the genetically modified plant can be assessed.

5.1.3 Assessment of allergenicity

The study of the allergenicity of genetically modified plants, as currently required, aims to ensure that the molecular construction does not lead to the appearance of new allergenic peptides and that the newly expressed protein is not itself potentially allergenic, immunotoxic or adjuvant in nature, and that any intrinsic allergenicity of the plant is not altered.

Assessment of the allergenicity of the new proteins expressed in the modified plant is based primarily on the safety of the sources (i.e. the organisms in which the gene transferred to the plant is naturally present) of these proteins, the absence of sequence identity of these proteins with known allergens or toxins and their resistance to digestive proteolysis and thermal denaturation. The assessment of adjuvant properties is based on a literature review, and the possibility of generating peptides implicated in celiac disease is based on a bioinformatics analysis. Assessment of the allergenicity of the whole GM plant is usually based on a literature review. However, when analysis of the allergenicity of newly expressed proteins reveals significant identities with major allergens, experimental approaches using specific antibodies or sera from patients allergic to the allergens concerned must be carried out.

In the context of the assessment of plants derived from site-directed mutagenesis, the WG considers that the set of requirements relating exclusively to newly expressed proteins is not sufficient.

directly transposable in the case of plants resulting from directed mutagenesis. However, the WG considers that it remains possible for mutagenesis to have generated new reading frames in the genome, particularly in the case of insertions or deletions of a few base pairs in one or more exons of a gene, and that it remains possible to modify the overall allergenicity of the plant. The WG therefore considers that the current requirements relating to these two elements remain applicable, on a case-by-case basis, for plants derived from site-directed mutagenesis.

More generally, the WG notes that although the assessment of allergenicity within the current regulatory framework provides an overall understanding of the risks associated with genetically modified plants, it could be adapted to provide a better understanding of the diversity of plant species that can be modified by site-directed mutagenesis. In particular, the use of quantitative LC-MS/MS techniques involving the assay of major allergens has made its appearance for species such as soya and is more precise in providing information on possible variations in the major allergens of genetically modified plants, such as nsLTPs (*non-specific lipid transfer proteins*) or cupins in particular (Dramburg et al. 2023). In parallel, for plants known to be allergenic, SDS-PAGE and Western blot analysis using sera from allergic patients or ELISA assays for major allergens using specific antibodies could also be envisaged.

5.1.4 Nutritional assessment

When differences in composition are observed as part of the comparative assessment carried out for the genetically modified plant, the current assessment guidelines require a nutritional study to be carried out. This study must ensure that the genetic modification will not have an undesirable effect on the nutritional composition of the food or feed derived from the genetically modified plant. In this context, a feeding study on target animals is required to demonstrate that there is no nutritional disadvantage if the genetically modified plant is consumed.

The WG considers that such a study remains applicable and relevant in the case of compositional differences (as defined in EFSA (2009)) in plants obtained by site-directed mutagenesis, but stresses once again that genetic modification using CRISPR-Cas of new species, different from those traditionally the subject of marketing authorisation applications under Regulation (EC) No 1829/2003 and resulting from transgenesis, could give rise to technical difficulties, as some plants are not very palatable to the animals used in these studies or it is difficult to control the quantities ingested (cf. section 5.1.1).

5.1.5 Environmental risk assessment

Under the current framework, environmental risk assessment aims to analyse any risk, whether direct (such as an effect on a non-target species, a risk of gene transfer or the development of resistance in a target organism) or indirect (due to interactions with other organisms or changes in the use of the plant and in agricultural practices), immediate (during release) or delayed, that the deliberate release or placing on the market of a genetically modified plant may entail.

In accordance with Directive 2001/18/EC, seven specific areas of risk must be taken into account when assessing the environmental risks associated with genetically modified higher plants:

- the persistence properties[27] and invasiveness of the genetically modified plant;
- gene transfer from plant to micro-organism ;
- interaction between the plant and target organisms ;
- interaction between the plant and non-target organisms ;
- impact on cropping systems ;
- the effects of growing genetically modified plants on biogeochemical processes ;
- effects on human and animal health.

The environmental risk analysis is based primarily on a comparative assessment of the plant's agro-phenotypic characteristics and on existing literature. Particular attention is paid to the selective advantages or disadvantages conferred on modified plants, the possibility of gene transfer between plant species and/or with micro-organisms, and the potential effects on target and non-target animal species. *Ultimately,* the aim of the environmental risk assessment is to determine the management measures to be put in place for the release of genetically modified plants.

With regard to the transfer of genes to micro-organisms, the WG considers that insofar as only plant genes will be modified in the case of directed mutagenesis carried out by CRISPR-Cas, the risk of transfer will be negligible. Thus, although this requirement remains applicable in the case of site-directed mutagenesis, the WG considers that it is not relevant.

With the exception of this point, the WG considers that environmental risk assessment as currently requested remains applicable and relevant for plants derived from site-directed mutagenesis. In a context where the number of species concerned, the number of modified traits and the number of applications could increase significantly in the short and medium term, the WG considers that the environmental risk assessment should also take into account potential cumulative effects on the environment in the long term, linked to the accumulation of authorisations (for example if several plants tolerant to the same herbicide or resistant to the same pathogen are authorised and cultivated on nearby land).

The WG also notes that, in practice, the current assessment focuses mainly on the novel character conferred by the newly expressed protein within the GM plant. The WG considers that better account should be taken of long-term cumulative effects and agro-environmental characteristics in the development of an increasing number of plants derived from site-directed mutagenesis.

5.1.6 Summary of the analysis of the current assessment framework

The WG's conclusions by area of assessment are shown in **Table 3**.

[27] Persistence is the plant's ability to maintain itself in its environment.

	Current requirements	Applicability according to the WG	Identified limits and WG recommendations
Comparative evaluation	1. Comparative study of the agro-phenotypic characteristics and composition between the genetically modified plant, an unmodified plant that is as close as possible genetically and six reference varieties, on at least eight sites. 2. Comparative study of the composition of processed products.	1. Yes 2. Yes	• Unavailability of OECD guide to compounds to be analysed for certain species
Toxicity	1. Oral toxicity study on rodents of newly expressed proteins at repeated doses for 28 days 2. Whole plant oral toxicity study on rodents at repeated doses for 90 days 3. Calculating exposure to newly expressed proteins	1. No (except in specific cases) 2. Yes 3. No (except in specific cases)	• Low palatability of certain plant species for rodents • Difficulty in ensuring the ingestion of controlled quantities of certain species (if high water content, for example)
Allergenicity	1. Analysis of the possible appearance of new reading frames due to genetic modification of the plant 2. Study of the allergenicity of newly expressed proteins (including resistance to digestive proteolysis and thermal denaturation) 3. Literature review on the allergenicity of whole plants	1. Yes 2. No (except in specific cases) 3. Yes	• In general, adaptations could be made to take better account of the diversity of species, in particular by using LC/MS-MS techniques.
Nutritional assessment	1. Calculation of nutritional intake in the event of consumption of the genetically modified plant 2. Nutritional study on target animals	1. Yes 2. Yes	• Low palatability of certain plant species • Difficulty ensuring the ingestion of controlled quantities of certain species

Environmental risks	Literature-based analysis of any direct or indirect, immediate or delayed risk to the environment associated with the marketing authorisation	Yes	• Generally speaking, we need to take better account of long-term cumulative effects and agri-environmental characteristics. • Analysis of the risks of gene transfer to micro-organisms applicable but not very effective relevant

Table 3. Applicability and limitations of the current assessment framework for genetically modified plants for plants derived from site-directed mutagenesis using a CRISPR-Cas system.

In conclusion, the WG considers that the current framework for assessing health and environmental risks is only partially adapted to the assessment of plants derived from site-directed mutagenesis.

In particular, the WG considers that all the requirements relating to newly expressed proteins contained in the toxicity and allergenicity assessments cannot be directly transposed to the assessment of plants resulting from site-directed mutagenesis, and that the analysis of the risk of gene transfer to micro-organisms is not very relevant.

In addition, the WG considers that genetic modification using CRISPR-Cas of new species, different from those traditionally the subject of marketing authorisation applications under Regulation (EC) No 1829/2003 and resulting from transgenesis, could lead to technical difficulties in implementing certain studies. These difficulties relate in particular to the evaluation of toxicity, nutritional evaluation or the comparative evaluation of agronomic and phenotypic characteristics and composition. Finally, as part of the risk assessment of plants derived from directed mutagenesis, the WG recommends :

- **the development and adaptation of proteomic and metabolomic techniques for comparative composition studies under real conditions, after field cultivation;**
- **the determination of the main known allergens of the plants in question using quantitative LC-MS/MS techniques;**
- **depending on the species, the measurement of levels of toxic, genotoxic or anti-nutritional compounds known to be expressed (EFSA 2012);**
- **better account taken of the cumulative long-term effects and agri-environmental cultivation characteristics of NTG plants in environmental risk assessments.**

The WG also notes that these recommendations could also apply to the assessment of transgenic plants.

5.2 Health and environmental risks associated with plants derived from site-directed mutagenesis using CRISPR-Cas and proposals for appropriate assessment methods

5.2.1 Systematic review of the literature

In order to identify the health and environmental risks associated with plants derived from site-directed mutagenesis, the WG first carried out a systematic review of the literature, using the method described in the Anses guide to literature searches (**Appendix 8**).

The elements relating to the PICO structure used in this systematic review are shown in **Table 4**.

Themes	Keywords from thesaurus
Population (or subjects studied)	Plants
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Plant not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. *Ex*: mortality, health effects, psychosocial effects, perceptions, economic results)	Effect on health or the environment
Temporality (Research periods)	∞ - 01/06/2023

Table 4. PICO structure of the research relating to the systematic literature review on the health or environmental risks associated with plants derived from site-directed mutagenesis using CRISPR-Cas.

A search of 3 bibliographic databases (Scopus, Pubmed, CAB Abstracts) identified 455 references, including 159 duplicates which were eliminated. Of the 296 unique references identified, 13 were retained after sorting on title and abstract and sorting on full text. It should be noted here that this search was carried out on both original articles and reviews, and that the 13 references selected were exclusively reviews (based on theoretical reflections or case studies), as it was not possible to identify any original articles presenting results relating to the health or environmental risks of plants obtained by site-directed mutagenesis. Finally, only reviews containing a description and analysis of the potential risks associated with plants obtained by site-directed mutagenesis were included. Thus, reviews which, without further justification, simply considered that there was no overall risk for any plant obtained by site-directed mutagenesis, due to the nature of the mutation obtained, were not retained (insofar as they did not provide information on a potential risk that could be analysed by the WG).

5.2.1.1 Analysis by Agapito-Tenfen et al (2018)

In this review, the authors point out that NTGs make it possible to obtain complex modifications. Two aspects are taken into account when considering the potential risks associated with plants derived from site-directed mutagenesis: all changes at the target site (i.e. changes in nucleotides at the target sequence), and all sites that have actually been modified (including off-target sites).

According to the authors, the diversity of modifications that can occur at the targeted site (repair mechanisms following a double-strand break not being controlled), and the possibility of off-target effects can lead to the appearance of unexpected effects on the composition, toxicity or allergenicity of the NTG-derived plant.

The authors call for the whole plant and not just the modified trait to be considered when assessing health and environmental risks. The authors recommend going beyond *in silico* predictions of off-target sites and using whole genome sequencing techniques to identify potential unintended variants for examination in gene expression monitoring studies and phenotypic analysis. More generally, the authors also recommend the development and appropriate use of '-omics' technologies in the evaluation of NTG-derived plants.

5.2.1.2 Analysis by Duensing et al (2018)[28]

In this opinion article, the authors report on the results of a panel discussion held during a session entitled "*Plant genome editing-any novel features to consider for ERA and regulation? The* specific features of NTGs are listed, such as the ability of CRISPR-Cas9 to target all the genes in the same family or all the homologous genes in a polyploid species, or the ability of CRISPR-Cas9 to modify genes present in regions that are not very or not at all recombinant (and which may escape conventional selection methods). Nevertheless, the participants in the round table did not identify any new risks specific to plants derived from site-directed mutagenesis and felt that the modified character of the NTG-derived plant was more important to take into account than the method of production when assessing environmental risks.

According to the authors, existing environmental risk assessment frameworks adequately cover all genetically modified organisms, including NTG plants. They recommend that the safe use history be applied to the assessment of NTG plants.

5.2.1.3 Analysis by Eckerstorfer et al (2019)

In this 2019 review, the authors look at the diversity of modified traits in plants obtained using NTGs, and consider the potential environmental risks in four cases: herbicide resistance, disease resistance, compositional modification and improved ability to withstand environmental stresses, or a change in the morphological or reproductive characteristics of plants.

- Herbicide-resistant plants derived from NTGs: the authors do not identify any new risks compared with those already known for plants derived from NTGs.

[28] The WG notes for the record that one of the authors is affiliated with Corteva.

genetically modified, which remain true (gene flow with wild varieties, pleiotropic effects in the case of high expression of the protein conferring resistance, pesticide residues in a cocktail in the case of multiple resistances, etc.).[29] in the case of high expression of the protein conferring resistance, pesticide residues in cocktails in the case of multiple resistances, etc.), but they suggest cumulative effects if a large number of plants derived from NTGs of this type were to be cultivated.

- The case of disease-resistant plants derived from NTGs: similarly, no new risks are identified by the authors, who nevertheless stress that the possibility of pleiotropic effects and the risk of the appearance of new pathogenic microbial strains also remain applicable.
- Plants derived from NTGs whose biochemical composition is modified: for these plants, the authors indicate that particular attention should be paid to the risks of toxicity, allergenicity and the production of anti-nutritional substances. In addition, environmental effects could be observed in the event of altered interactions with the animals that normally consume these plants.
- In the case of NTG-derived plants with increased adaptive value in relation to environmental stresses or alterations in morphology or characteristics linked to reproduction: in this case, the authors stress that a selective advantage would be conferred on the plants, which should be taken into account, as is already the case for plants obtained by transgenesis. The authors also point to the possibility of *de novo* domestication, which would enable the rapid development of lines from wild forms for which there is no history of safe use.

For these reasons, the authors recommend a case-by-case assessment of plants obtained using NTGs before they are placed on the market, based in particular on the novelty of the modified trait. The authors also recommend that potential off-target effects on the genome of the NTG-derived plant be taken into account.

5.2.1.4 Analysis by Eckerstorfer et al (2021)

In this 2021 opinion piece, the authors discuss the relevance of general risk or safety denominators (i.e. criteria that would make it possible to define homogeneous groups of plants in terms of the level of risk associated with them) and address the characteristics of genetically modified plants that require specific assessment approaches. One of the authors' objectives is to identify whether there are homogeneous categories of plants in terms of the health and environmental risks associated with them. In particular, the authors discuss :

- The type of method used (SDN-1 or SDN-2): the authors indicate that the criterion concerning the method used does not take into account the number of mutated genes (in the case of multiplexing, for example) and the location of the mutations introduced, which may be different from the mutations that appear spontaneously during the conventional selection process.
- The size of the genetic changes introduced: according to the authors, the size of the modification cannot be considered a reliable denominator of the risk or safety of the specific modifications present in the various genetically modified plants, since even small changes in the DNA sequence can have a significant impact on the function and effects of the modified genes.

[29] A gene or protein is said to be pleiotropic when it acts on several distinct characteristics.

- The precision of the editing process: according to the authors, any genome editing method induces off-target modifications, and there is still room for improvement in prediction tools. The authors also point to the risk of introducing foreign DNA at DNA breakpoints such as off-target cleavage sites.
- The complexity of the changes introduced (or depth of intervention): according to the authors, "a high level of intervention and/or complexity of the changes introduced may serve as a general non-specific indicator of the need for a robust and comprehensive environmental risk assessment".
- Novelty of the traits developed: the authors state that in the case of novel traits that have never before been introduced by conventional varietal selection or in authorised genetically modified plants, the novelty of the trait implies the need for new data to assess the risks associated with the modified plant in question. The authors therefore recommend that the level of knowledge available and the history of safe use should be taken into account when assessing plants obtained by NTG with regard to the trait modified therein.
- Speed of development: in the authors' view, as fewer generations of backcrossing are needed to develop elite varieties from genetically modified plants, the possibility of unintentional modifications being eliminated during subsequent crossing stages is reduced. The authors point to an increased risk of unwanted effects on the NTG plant genome not being eliminated, particularly for species that are mainly vegetatively propagated and for long-lived perennials such as trees.

The authors conclude that, given the wide range of plant species and modified traits that need to be taken into account, it is difficult to guarantee safety for entire groups of applications, and argue in favour of a case-by-case risk assessment, taking into account both the considerations linked to the modified traits and those relating to the assessment of unintended effects linked to the method used.

5.2.1.5 Analysis by Eckerstorfer et al (2023)

In this review, the authors offer a critical analysis of the Efsa opinions on plants obtained using NTGs and the conclusions drawn by the European Commission. In particular, they outline four critical cases in terms of environmental risk assessment.

- Herbicide-resistant plants derived from NTGs: as with herbicide-resistant plants derived from transgenesis, the main risks associated with plants derived from NTGs are the indirect effects on biodiversity and the environmental and health effects resulting from the change in agricultural practices towards increased use of broad-spectrum herbicides. In addition, the propagation of NTG-derived plants, the transfer of genes to related species through hybridisation and the development of resistant weeds in the event of regular long-term use of the herbicides concerned are major concerns. Finally, like the European Commission, the authors stress that the use of plants genetically modified to be resistant to a herbicide does not contribute to the objective of moving towards more sustainable conventional agricultural practices in the European Union.

- Case of disease-resistant NTG-derived plants: in this case the authors focus on assessing the environmental risks of an apple genetically modified to be resistant to a pathogenic bacterium, *Erwinia amylovora*. The risks identified are the accidental dispersal of genetically modified apple trees through the transfer of pollen, seeds or suckers, and cross-breeding with other apple trees (in particular with wild apple species of conservation value). The authors also consider the possible effects on the target organism (*E. amylovora*) to be important factors to take into account. On the one hand, the emergence of strains of *E. amylovora* capable of bypassing the resistant character of NTG-derived apples is mentioned, based on the example of scab, where the exposure of pathogens to a resistant apple line led to the development of more aggressive pathogenic strains within seven to eight years. On the other hand, different pathogens could occupy the niche left vacant by the elimination of *E. amylovora*, leading to a change in pathogen populations and in the infestation status of apple trees, necessitating pest control by other means, notably chemical.
- The case of wheat derived from NTGs with a low gluten content: as the plant obtained is the result of a complex and highly multiplexed approach, the authors consider that the main risks in this case are linked to the molecular characterisation of the plant. The authors indicate that the absence of off-target effects should be carefully checked, and that all the modified targets should be characterised in order to identify which proteins are still expressed and which are not. The authors add that the genetic stability of these modifications should also be assessed.
- *De novo* domesticated plants: the authors point out that in this case, no history of safe use is available, and recommend a full and robust risk assessment.

Finally, with regard to potential off-target effects, the authors consider that the evidence generally gathered from simple targeted assessments (PCR and bio-IT tools) is biased and cannot be considered sufficiently conclusive to assess the risks associated with these unintentional modifications.

5.2.1.6 EFSA analysis (2021)

In this scientific report, prepared in response to a mandate from the European Commission, EFSA provides an overview of the opinions of the national bodies of the Member States and of its own previous opinions on the risk assessment of plants developed using NTGs. As opinions may differ between the various opinions compiled, and as the mandate was limited to an inventory exercise, no conclusions are presented by the authors.

5.2.1.7 Analysis of EFSA GMO Panel (2020)

In this opinion paper, the Efsa GMO Panel did not identify any risks specifically linked to the genomic modification produced by SDN-1, SDN-2 or ODM (see sections 3.1 and 4.1) compared to plants obtained by SDN-3 or conventional breeding. The Efsa GMO Panel therefore considers that the guidance documents for the risk assessment of food and feed produced from genetically modified plants and for the risk assessment of GMOs produced from genetically modified plants should be updated.

The environmental risks associated with genetically modified plants are sufficient, although they only partially apply to plants produced by SDN-1, SDN-2 or ODM.

5.2.1.8 Analysis of EFSA GMO Panel (2021)

The European Commission has asked Efsa to evaluate developments in synthetic biology[30] in the agri-food industry with the aim of identifying the suitability of existing guidelines for risk assessment and determining whether an update is necessary. This opinion deals solely with the molecular characterisation and environmental risk assessment of genetically modified plants. On the basis of the four cases selected (sweet maize producing vitamin B12, gluten-reduced wheat, fungus-resistant oilseed rape and de novo domesticated tomato), the Efsa GMO Panel concludes that the current guidelines are adequate for the risk assessment of these products, although specific requirements may not apply in some cases.

5.2.1.9 Analysis by Kawall, Cotter and Then (2020)

In this review, the authors consider that the risks associated with plants obtained using NTGs are of three types, namely (i) the risks associated with the editing process, and in particular the risk of off-target modifications, (ii) the risks associated with the transient insertion of foreign genes into the plant genome, and (iii) the risks associated with the modified trait.

The authors point out that the search for genomic irregularities is not systematic in studies using CRISPR-Cas and consider that the assessment of plants obtained using NTGs should take into account all the potential genomic irregularities resulting from genome editing. They propose additional tools to facilitate the risk assessment of genetically modified plants, and in particular that DNA analysis should be extended to include epigenetic modifications and modifications to the transcriptome, proteome and metabolome of the modified plant.

5.2.1.10 Analysis by Kawall (2021)

This review focuses on the safety and regulation of crops grown using SDN-1 techniques. Taking the 'market-oriented' SDN-1 applications from the compilation by Modrzejewski et al. (2019), the author shows that 98 studies used SDN-1 for single gene silencing (55%) in diploid plant species and 49 studies induced alterations in multiple gene variants (27.5%), including multiple alleles of a gene in a polyploid crop, multiple members of a gene family and multiple copies of a gene. Finally, 31 studies used multiplexing (17.5%) to modify several different target sites simultaneously or successively.

The author therefore states that in almost half the cases, SDN-1-type applications are used to carry out complex modifications to the genome, and therefore recommends that plants modified by SDN-1-type applications should not be considered as a homogeneous category from the point of view of assessment. The author also points out that CRISPR-Cas has the potential to induce unwanted modifications on non-targeted sites of the genome located in "protected" genomic regions.

[30] A field of biotechnology that applies engineering to the field of biology, some of whose applications can be seen in agriculture.

"These are mostly inaccessible to conventional selection techniques (for example, heterochromatin regions and genomic regions with low recombinogenicity).

5.2.1.11 Analysis by Touzdjian Pinheiro Kohlrausch Távora et al (2022)

This review presents an overview of recent technologies for genome modification (CRISPR-Cas) and plant protection (interfering RNA), as well as a series of perspectives on the risks, challenges, public perception and associated regulatory aspects.

With regard to the health and environmental risks associated with possible off-target modifications, the authors recommend carrying out an analysis of the entire genome. However, the authors admit that this is not feasible in most cases (Hahn and Nekrasov 2019; Shillito et al. 2021), particularly for polyploid crops (e.g. potato, soya, cotton, wheat, oilseed rape). In the absence of genome-wide analysis, this could lead to an underestimation of off-target mutation rates. The authors also point out that the undesired effects on the genome caused by the use of CRISPR technology, beyond off-target mutations, such as epigenetic consequences, are still little explored.

The authors also present a development on the targeting of regulatory elements, such as polyadenylation signals, alternative transcription initiation sites and upstream open reading frames (uORFs). Usually responsible for reducing translation, uORFs are located in the 5' untranslated regions of messenger RNAs. When modified, uORFs can promote the upregulation of gene expression. According to the authors, the CRISPR-Cas technique adopted and the target chosen can therefore lead to the appearance of significant pleiotropic effects.

Furthermore, the authors indicate that plant toxicity associated with the application of CRISPR-Cas could be observed depending on the CRISPR-Cas delivery methods employed and the exposure period. In particular, regarding nanoparticle-based delivery approaches for transfection of CRISPR reagents, systemic toxicity studies suggest that the physical and chemical properties of nanomaterials need to be taken into account. In addition, the authors indicate that the generation of data on the life cycle of nanomaterials in CRISPR-Cas-edited plants and their progeny, their fate and potential impact on the environment and health could enable better evaluation of plants obtained by this technique.

5.2.1.12 Analysis by Troadec, Pagès and the Scientific Committee of the High Council for biotechnology (2019)

In this opinion piece, written on behalf of the French High Council for Biotechnology, the authors point out that potential unexpected effects could occur at different levels: at the genome level (risks inherent in the genome-editing technique itself), at the phenotypic level, and at the level of the field and agricultural practices.

In terms of phenotypic traits, the authors note no specific and exclusive unexpected effects associated with NTGs compared with other plant improvement techniques. In fact, the authors indicate that certain traits currently obtained using NTGs can also be obtained using other varietal selection methods, which are exempt from assessment under GMO regulations. On the other hand, the authors state that gene modification by multiplexing is an exclusive feature of

NTG, and point out that the phenotype obtained after modification by multiplexing does not necessarily correspond to the sum of each individual phenotype. Certain modifications could therefore favour epistasis phenomena[31]This calls for verification of pleiotropic effects at an early stage of genome editing.

Finally, at the level of the plot and associated practices, the authors envisage that the use of plants obtained using NTGs could lead to an acceleration of the selection and improvement processes, with, for example, the direct modification of elite varieties or the generalisation of the same trait of interest to a large number of varieties (and therefore uniformity).

With regard to off-target effects, the authors indicate that the risk is limited and that these effects can be identified and eliminated. The authors nevertheless point out that, on the one hand, the size and diversity of sequence repeats in certain genomes, and the fact that the reference sequences used do not necessarily correspond to the sequence of the variety under consideration, may limit the identification of off-target cuts. On the other hand, eliminating these effects by crossing can be technically difficult for perennial plants such as fruit trees or for plants that reproduce mainly by vegetative propagation.

5.2.1.13 Analysis by Zhao and Wolt (2017)

In this review, the authors emphasise the need for research into the uncertainties surrounding unintended changes to the plant genome, particularly in view of the descriptions of more frequent off-target effects than initially envisaged at genome level in the case of mammalian cells modified by CRISPR-Cas9.

5.2.1.14 Conclusion of the literature review

In conclusion to this systematic review of the literature, the WG notes a relative diversity of scientific opinion between the various references selected. Nevertheless, the WG notes that new applications could emerge as a result of the use of NTGs, which could not be achieved using other selection techniques. These include applications involving multiplexing, or targeting protected regions (e.g. heterochromatin regions and genomic regions with low recombinogenicity) of the genome and therefore not reached by conventional selection methods. The WG also points out that the CRISPR-Cas system could be applied to wild species, leading to *de novo* domesticated plants, without any history of safe use being available.

With regard to the risks associated with plants derived from CRISPR-Cas directed mutagenesis, the WG notes that some of the known risks already associated with transgenic plants are also true in the case of plants derived from directed mutagenesis, and notes that the level of occurrence of these risks could be accentuated if the number of genetically modified plants appearing on the market and put into cultivation were to increase, particularly with regard to environmental risks (differential use of certain herbicides or appearance of resistance in certain target pathogens or insects, for example).

Finally, the WG agrees with the conclusions of several authors who point to a new risk associated with the potential off-target effects of NTGs (cf. sections 4.3.2 and 4.3.3), as well as with the

[31] Interaction between two or more genes

the possibility of pleiotropic effects. The WG also agrees that the possibility of pleiotropic effects or unintended changes in plant composition is increased in the case of multiplexing, which one paper indicates is commonly used in the research and development stages (Kawall 2021).

5.2.2 Case studies

In order to complete its analysis, and in the absence of original articles on the health and environmental risks associated with plants derived from site-directed mutagenesis, the WG wished to carry out a case study, based on the analysis of 12 plants identified among the applications most likely to reach the market in the short term (see section 3). These 12 cases, some of which have also been analysed by the EFSA GMO Panel (EFSA GMO Panel 2021) or by Eckerstorfer et al (2023), were selected by the WG in order to represent the diversity of applications, species and traits modified.

5.2.2.1 Case 1 - Vine resistant to grey rot

Case study 1 (Wang et al. 2018)
Characteristics of the plant Common name: Vigne Scientific name: *Vitis vinifera* Family: Vitaceae Type of reproduction : Perennial species with vegetative propagation and sexual reproduction, annual flowering Other relevant characteristics: Presence of a wild form (lambrusque)
Characteristics of the modification Characteristic conferred : Tolerance to biotic stress / Resistance to grey rot Nature of modification: SDN-1 Number of mutated genes: 1 Number of nucleotides modified: Insertion of 1 nucleotide or deletion of 1 to 57 nucleotides depending on the lines analysed.

In the case of this vine genetically modified using CRISPR-Cas, the gene targeted is a transcription factor, *VvWRKY52*, involved in the response to biotic stresses. A variety of knock-out modifications (invalidating the target gene) were obtained. The modifications can be mono- or bi-allelic.

The WG noted that a similar mutation could be obtained by other methods or naturally, but that invalidation of a transcription factor could lead to changes in transcription elsewhere in the genome, with transcription factors generally acting on many genes. The WG also noted that the absence of a transcription factor can also modify transcription complexes and change the interactions of coactivators and corepressors.

With regard to the risks to the environment, the WG considers that the main risks are associated with the lifespan of the plant, the resistance mechanism, and the presence of other interfertile plant species in Europe. In addition, widespread deployment of tolerance

is likely to cause the fungus to overcome its resistance, leading to greater pathogenicity.

Finally, the WG notes that wild grapevines (*Vitis vinifera* subsp. *sylvestris* or lambrusque), an endangered and nationally protected plant in France, can be found in the natural environment (scree and riparian vegetation), and that many naturalized and sometimes invasive American rootstocks (*Vitis riparia*, *Vitis rupestris*) can be observed in riparian vegetation. As all taxa of the *Vitis* subgenus (to which the taxa mentioned above belong) are interfertile, a risk of transmission of modified material should be taken into account. However, this risk is low, as molecular studies (with a view to the conservation biology of *Vitis vinifera* subsp. *sylvestris*) seem to indicate a very low level of hybridisation.

5.2.2.2 Case 2 - Tomato with a high GABA content

Case study 2 (Nonaka et al. 2017)
Characteristics of the plant Common name: Tomato Scientific name: *Solanum lycopersicum* Family: Solanaceae Type of reproduction: Annual plant with mainly autogamous reproduction Other relevant characteristics: Seeds can survive winter and new germination can be observed. Commercial cultivation in greenhouses or in open fields. for private customers.
Characteristics of the modification Characteristic: Change in composition / High γ-aminobutyric acid content Nature of modification: SDN-1 Number of mutated genes: 1 Number of nucleotides modified: Insertion of 1 nucleotide and/or deletion of 1 to 200 nucleotides depending on the lines analysed.

In the case of this genetically modified tomato, the introduction of a stop codon just before the auto-inhibitory domain of SIGAD-3 led to the suppression of expression of the C-terminal region of the *SIGAD-3* gene and induced an increase in the plant's GABA production by a factor of 7 to 15 (the *SIGAD-2* gene was also targeted, but the results obtained were less marked).

The WG notes that obtaining this genetic modification, resulting in the introduction of a stop codon at a precise point in the SIGAD-3 protein sequence, would be highly unlikely using other selection methods.

As GABA is a compound at the centre of various metabolic pathways in plants, it is likely that a change in the synthesis or conversion of GABA will lead to changes in the levels of GABA precursors or products (such as α-ketoglutarate). Furthermore, as GABA is involved in numerous mechanisms in both plants and humans (interaction with pesticide metabolism in plants, involvement in diabetes in humans, etc.), the WG considers that in this case the assessment should take into account the consequences of its overexpression for plants and consumers.

In addition, if the biochemical composition of the genetically modified tomato were to change significantly, a variation in its adjuvant potential could also be observed. With regard to the allergenicity of the plant, the properties of the truncated SIGAD-3 protein could also be modified, in particular its resistance to heat and digestion. In addition, given that the prevalence of tomato allergy is around 5% in Europe, the WG believes that an analysis of the levels of its main allergens and their evaluation would be relevant.

With regard to risks to the environment, the WG notes that numerous pleiotropic effects have been observed during the development of this tomato, and considers that if such effects on reproductive traits have been observed, they should be taken into account when assessing the capacity for dispersal and maintenance in the environment.

The WG also considers that the cultivation of a genetically modified tomato with a high GABA content could lead to a change in interactions with herbivorous animals consuming the plant, which would need to be assessed. Secondly, since tomatoes eaten contain viable seeds, the WG believes that consumers could deliberately or unintentionally disperse them in the environment. Tomatoes are in fact regularly found on riverbanks as occasional plants originating from germinated seeds from wastewater or picnic leftovers; in particular, fruit-forming plants are increasingly being observed (Schmitz 2004). As the seeds can survive light frosts (Schmitz 2004), it is likely that as the climate warms, the tomato will become more widely naturalised.

The WG also points out that if this genetically modified tomato with a high GABA content were to be marketed in the European Union in the same way as in Japan, it would logically also have to be subject to other regulations governing any associated nutritional and health claims.

Although this tomato is already marketed in Japan, the WG is not currently aware of any post-marketing data (in terms of volume consumed or detection of adverse reactions).

5.2.2.3 Case 3 - Reduced-size rice

Presentation of case 3 (Lu and Zhu 2017)
Characteristics of the plant Common name: Rice Scientific name: *Oryza sativa* Family: Poaceae Reproduction type: Annual plant with sexual reproduction, mainly autogamous Other relevant characteristics: Seeds can survive the winter and new germination can be observed. Wild weed species are present in France, Italy and Spain.
Characteristics of the modification Characteristic conferred : Plant yield and architecture / Semi-dwarf phenotype Type of modification: Base-editing Number of mutated genes: 1 Number of nucleotides modified: Substitution of 1 nucleotide

In the case of this genetically modified rice, a single nucleotide in the *SLR1* gene encodes the DELLA protein, a repressor of gibberellin signalling pathways.

The WG notes that a similar mutation can be obtained by other methods or naturally, and does not identify any new risk linked to the modified trait.

However, the WG recalls that in the general case of rice, there is a high risk of gene flow to adventitious forms ('crodo' rice in the Camargue, for example), as well as a risk of the appearance of new adventitious forms through de-domestication (Qiu et al. 2017). Thus, if the use of NTGs is associated with multiplexing (simultaneous introduction of modifications to several genes) or the acceleration of the introduction of various modifications, a specific new environmental risk would result from the transfer to weed populations of a diversity of gene combinations, the epistasis effects of which are not known. Similarly, if a rice resulting from site-directed mutagenesis contains genes likely to confer a selective advantage, a risk could arise if it were transferred to weed populations in regions where weeds are already abundant.

5.2.2.4 Case 4 - Herbicide-tolerant potato

Case study 4 (Butler et al. 2016)
Characteristics of the plant Common name: Potato Scientific name: *Solanum tuberosum* Family: Solanaceae Type of reproduction: Mainly vegetative reproduction but sexual reproduction is possible, self-compatible species Other relevant characteristics: Tubers can survive the winter and regrowth can be observed. Viable tubers are marketed.
Characteristics of the modification Characteristic conferred : Tolerance to a herbicide / Resistant to ALS inhibitors Nature of modification: SDN-2 Number of mutated genes: 1 Number of nucleotides modified: Substitution of 2 nucleotides

In the case of this genetically modified potato, the CRISPR-Cas system is combined with a geminivirus carrying a repair sequence designed to modify the acetolactate synthase 1 (*ALS1)* gene in two distinct locations, in order to change two amino acids in the protein sequence.

The WG notes that obtaining this genetic modification, resulting in the simultaneous introduction of two mutations in the same gene, would be highly unlikely using other selection methods. A single mutation may nevertheless be sufficient to induce resistance to certain herbicides. On the other hand, several mutations can confer this trait, which can be obtained by other methods or naturally.

However, it points out that a genetic modification linked to the ALS gene could lead to changes in the levels of branched-chain amino acids such as valine, leucine and isoleucine, which are taken into account in the OECD reference lists (see section 5.1.1).

In this particular case study, the WG also notes that following this genetic modification, a gene for resistance to an antibiotic, kanamycin, is also present in the genetically modified plant. Although it is common for this gene to be eliminated by cross-breeding during the selection stages before marketing, the WG considers that the presence of an antibiotic resistance gene, used as a selection marker, induces a risk to human and animal health that needs to be specifically assessed.

Finally, given that pleiotropic effects have already been reported in the case of herbicide resistance, and that viable tubers are marketed, the WG believes that new uses and routes of deliberate or unintentional dissemination should be taken into account in the assessment of these NTG plants, before they are placed on the market.

5.2.2.5 Case 5 - Wheat with reduced gluten content

Presentation of case 5 (Sánchez-León et al. 2018)
Characteristics of the plant Common name: Common wheat and durum wheat Scientific name: *Triticum aestivum* and *Triticum turgidum* Family: Poaceae Type of reproduction : Annual species with sexual reproduction, autogamous Other relevant characteristics: Allohexaploid (*T. aestivum*) and allotetraploid (*T. turgidum)* species. Seeds can survive winter and new germination can be observed, but the development of feral populations is not described. Spontaneous hybridisation is possible, but at a very low rate, between *T. aestivum* and species of the genus *Aegilops*.
Characteristics of the modification Characteristic granted: Change in composition / Reduced gluten content Nature of modification: SDN-1 Number of mutated genes: Up to 35 mutated genes Number of modified nucleotides: Insertions of 1 to 158 nucleotides or deletions of 1 to 126 nucleotides depending on the lines analysed.

In all types of wheat, gluten content is mainly controlled by genes in the α-gliadin family. In common wheat, this family comprises more than 100 genes or pseudogenes located at a locus on chromosome 6.

In the case of this genetically modified wheat, the authors sought to introduce knock-out mutations into a large number of genes in this family, and succeeded in simultaneously targeting 35 genes in some of the lines observed.

The WG notes that obtaining this genetic modification would be extremely unlikely using other selection methods.

With regard to the risks associated with wheat consumption, the WG points out that coeliac disease, the most serious form of intolerance to gluten proteins, gliadins and glutenins (known as glutenins in wheat), results from the toxic effects that the peptides released by digestive proteolysis of gliadins and glutenins exert on the intestinal epithelium. This disease requires the total eradication of gluten proteins (present in gluten-containing grasses such as wheat, barley and rye, and to a lesser extent in oats) from the diet of coeliac patients, and their replacement by substitutes free of gluten.

gluten. The incidence of this disease is high, estimated at around 1% in Europe and the United States.

In this case study, the analyses carried out revealed a clear decrease in α-gliadins but also in γ- and ω-gliadins in most of the mutants. The authors nevertheless indicate a compensatory effect in glutenins.

The WG considers that such compensation mechanisms could induce changes in the composition of the genetically modified wheat grain and modify the immunotoxic and allergenic profile of the plant.

The WG also considers that a change in the composition profile of gliadins and glutenins could very likely have an impact on the processing properties of wheat, particularly in bread-making, and generate a change in the bio-accessibility of allergens and immunotoxic peptides, and therefore the risk of allergenicity and toxicity for the consumer after processing.

Finally, with regard to environmental risks, the WG believes that interactions with herbivorous animals consuming wheat could be altered, and that there is a risk of transfer of genetic material to wild grasses closely related to the *Aegilops* genus (Mediterranean grasses, spreading in the south of France), with one study in particular showing transfers between *Triticum aestivum* (AABBDD genome) and *Aegilops cylindrica* (CCDD genome) at a higher level than expected (Rehman et al. 2017).

5.2.2.6 Case n° 6 - Rapeseed with an increased number of grains

Case study 6 (Yang et al. 2018)
Characteristics of the plant Common name: Rapeseed Scientific name: *Brassica napus* Family: Brassicaceae Reproduction type: Annual plant with a mixed reproductive system, 70% autogamy Other relevant characteristics: Allotetraploid species. Seeds can survive the winter and new germination is frequently observed. Several wild relatives are present in Europe, with the risk of gene flow being the most likely. with *Brassica rapa*.
Characteristics of the modification Characteristic conferred : Plant yield and architecture / Multilocular siliques containing a higher number of grains Type of modification: SDN-1 Number of genes mutated: 1 Number of nucleotides modified: Insertion of 1 nucleotide and/or deletion from 1 to 91 nucleotides according to the lines analysed

In the case of this genetically modified oilseed rape, the mutations induce a knock-out of both copies of the CLAVATA3 (*CLV3*) gene. The trait resulting from this modification is new in *Brassica napus* but has already been observed in *Brassica rapa* and *Brassica juncea*.

B. napus is allotetraploid with high redundancy between homeologous chromosomes (*B. napus* has two copies of an ancestral A genome and two copies of an ancestral B genome). C). The WG notes that obtaining this genetic modification, resulting in the simultaneous introduction of a mutation in both copies of the same gene, would be highly unlikely using other selection methods.

The WG has not identified any new health risks associated with the modified character.

With regard to environmental risks, the comparative phenotypic analysis presented in the article shows not only an increase in the number of seeds per silique, but also an increase in the number of leaves. The existence of pleiotropic effects on the phenotype must therefore be taken into account to fully assess the capacity for dispersal and maintenance in the environment.

More generally, with regard to oilseed rape, the WG points out that there is a high risk of gene flow towards populations of regrowth, feral populations or related wild species. It has also been shown that oilseed rape can naturalise on roadsides. (Schafer et al. 2011) documents the presence in the United States of two escaped transgenic genotypes, as well as naturalized non-GM oilseed rape. Different types of oilseed rape resistant to glyphosate or glufosinate have been found in the port of Basel in Switzerland, and in the port of Rouen in France, testifying to the ease with which this species can escape into the environment (Schulze et al. 2014; Anses 2022).

5.2.2.7 Case 7 - Maize with male sterility

Case study 7 (Li et al. 2017)
Characteristics of the plant Common name: Maize Scientific name: *Zea mays* subsp. *mays* Family: Poaceae Reproduction type: Annual species with sexual reproduction, mainly allogamous Other relevant characteristics: New germination possible, but does not produce independent feral populations. Presence of a weedy wild form in France and Spain, teosinte.
Characteristics of the modification Characteristic conferred: Selection tools / Temperature-sensitive male sterility Nature of modification: SDN-1 Number of mutated genes: 1 Number of nucleotides modified: Insertion of 1 nucleotide or deletion of 1 to 27 nucleotides depending on the lines analysed.

In the case of this genetically modified maize, the modification concerns the *ZmTMS5* gene (homologous to a known rice gene), a knockout having been obtained by deletion of a base pair.

The WG pointed out that temperature-dependent male sterility exists spontaneously in other plant species such as rice, where it is used in conventional breeding. In this case study, homozygous offspring from self-fertilisation are male.

sterile at a temperature of 32°C. The trait is recessive and will not be expressed in hybrid varieties grown.

The WG has not identified any new health and environmental risks associated with the modified character.

However, the WG points out that in the general case of maize, there is a risk of gene flow towards the teosinte (*Zea mays* subsp. *mexicana*) weed populations currently present in France and Spain (Le Corre et al. 2020; Trtikova et al. 2017). In addition, if the use of NTGs is associated with multiplexing (simultaneous introduction of modifications to several genes) or the acceleration of the introduction of various modifications, a specific new risk would be the risk of transferring a diversity of combinations of variations, the interaction effects of which are not known, to weed populations.

5.2.2.8 Case n° 8 - Drought-resistant chickpea

Case study 8 (Badhan, Ball and Mantri 2021)
Characteristics of the plant Common name: Chickpea Scientific name: *Cicer arietinum* Family: Fabaceae Type of reproduction : Annual plant with sexual reproduction, autogamous Other relevant characteristics: Viable whole seeds are marketed
Characteristics of the modification Characteristic conferred : Tolerance to abiotic stress / Drought resistance Nature of modification: SDN-1 Number of mutated genes: 2 Number of nucleotides modified: Insertion of 1 nucleotide or deletion of 4 nucleotides

As a preamble to this case study, the WG points out that the reference article is limited to obtaining protoplasts with knock-out mutations, without whole plant regeneration.

In the case of this genetically modified chickpea, the genes targeted are a gene involved in lignin biosynthesis, encoding 4-coumarate ligase (4CL) and a transcription factor regulating the circadian rhythm REVEILLE7 (RVE7). The modifications obtained were of the knock-out type.

The WG notes that obtaining this genetic modification, resulting in the simultaneous introduction of two genes, would be unlikely using other selection methods. In this case, the authors invalidate a transcription factor. As in the case of grapevine (section 5.2.2.1), the WG notes that invalidation of a transcription factor could lead to wider modifications of genome transcription.

The WG also points out that chickpea is a species with emerging allergenicity, and that chickpea allergy, although rare overall, is more common in Spain and Turkey where chickpea is widely consumed, but also and above all in Asian countries where it is used in the composition of an emulsifier (aquafaba). As most chickpea allergens have significant sequence similarities with allergens from other edible seeds (pea, peanut, lentil, soya), cross-reactivity with these allergens is possible, calling for vigilance when assessing this species, particularly in

in the event of a change in composition or any other change that could lead to a change in the risk of allergenicity.

As no data on the whole plant are presented in the reference article, the WG does not comment on the emergence of new risks concerning the environmental safety of such a chickpea.

5.2.2.9 Case 9 - Apple resistant to fire blight

Case study 9 (Pompili et al. 2020)
Characteristics of the plant Common name: Pommier Zoological Name: *Malus domestica* Family: Rosaceae Type of reproduction: Perennial species with allogamous sexual reproduction. Crosses are used for varietal creation, and cultivated varieties are multiplied by vegetative reproduction. Other relevant characteristics: The plant can survive winter, germinate and produce other plants. Sexually compatible wild forms are present in Europe. The fruits, containing viable seeds, are marketed.
Characteristics of the modification Characteristic conferred : Tolerance to biotic stress / Tolerance to infection by *Erwinia amylovora* Type of modification: SDN-1 Number of genes mutated: 1 Number of nucleotides modified: Insertion of 1 nucleotide or deletion of 1 to 27 nucleotides according to the lines analysed

In the case of this genetically modified apple, the gene targeted and for which a knock-out is obtained, *MdDIPM4*, is a known *Erwinia amylovora* susceptibility gene.

The WG recalled that resistance to *Erwinia* is known in certain varieties, but is difficult to use in conventional breeding because it is associated with poorer fruit quality. The WG therefore noted that a similar mutation can be obtained by other methods or naturally, and that in this case NTGs facilitate and accelerate varietal improvement.

The WG did not identify any new health risk relating to this characteristic, but pointed out that apple allergy is common, and that particular attention should be paid to it in the assessment.

With regard to the risks for the environment, the WG considers that widespread deployment of the resistance obtained would result in strong selection pressure on the pathogen, which could lead to a niche vacancy or the appearance of a more pathogenic variant. Eckerstorfer et al (2023) have also mentioned the risk of bacteria evolving to circumvent resistance. In addition, although lesser, the WG considers that there is a risk of deliberate or involuntary dissemination into the environment through fruit containing viable seeds. It would then be possible for modified genetic material to be transmitted to wild forms of apple trees, with a variable associated risk depending on whether or not such resistance already exists in the wild species.

5.2.2.10 Case 10 - Sage with reduced phenolic acid content

Presentation of case 10 (Zhou et al. 2018)
Characteristics of the plant Common name: Sage Scientific name: *Salvia miltiorrhiza* Family: Lamiaceae Type of reproduction : Perennial plant with sexual or vegetative reproduction Other relevant characteristics: A medicinal plant, particularly in Asian countries, it is wild but can be cultivated.
Characteristics of the modification Characteristic: Change in composition / Decrease in phenolic acid content Type of modification: SDN-1 Number of genes mutated: 1 Number of nucleotides modified: Insertion of 1 nucleotide and/or deletion from 1 to 20 nucleotides according to the lines analysed

In the case of this genetically modified sage, a knock-out was obtained on a rosmarinic acid synthase (RAS) gene, a member of a family of 11 genes.

The WG notes that a similar mutation can be obtained by other methods or naturally. Nevertheless, the WG notes that in the paper concerned by this case (Zhou et al. 2018), in the absence of a reference genome for *S. miltiorrhiza*, the *Arabidopsis thaliana* genome was used for the design of the guide RNAs, a species that is nevertheless very distant taxonomically, and refers to section 4 of this report for considerations related to the molecular characterisation of NTG-derived plants.

In this article, the level of the rosmarinic acid precursor, 3,4- dihydroxyphenyllactic acid, and the content of salvianic acid A sodium (SAAS) are clearly increased in the modified roots, logically demonstrating that several components of the metabolic chain are affected by the modification. The WG therefore considers that a risk assessment of the potential toxicity of metabolites whose levels are increased would be relevant.

Furthermore, the WG considers that modifying the composition of the plant could also present a risk of toxicity for animals (pollinating and herbivorous species). As phenolic compounds play a role in plant defence mechanisms, the WG considers that a change in their content could have an impact on the plant's tolerance to biotic and abiotic stresses. Finally, as this is a plant that occurs mainly in the wild, the WG considers that the risk of dispersal of the trait in wild populations should be carefully taken into account in the assessment.

5.2.2.11 Case 11 - Switchgrass with increased tillering

Case study 11 (Liu et al. 2018)
Characteristics of the plant Common name: Panic érigé

Scientific name: *Panicum virgatum* Family: Poaceae Type of reproduction : Perennial species growing in clumps and allogamous sexual reproduction Other relevant characteristics: Polyploid species (tetraploid or octoploid). Wild plant from North America, cultivated in particular for fodder or the production of biomass for biofuel
Characteristics of the modification Characteristic conferred : Plant yield and architecture / Increased tillering Nature of modification: SDN-1 Number of mutated genes: 3 Number of nucleotides modified: Deletions of 1 to 128 nucleotides depending on the lines analysed

In the case of this genetically modified switchgrass, knockouts were obtained for three separate genes, encoding teosinte-branched 1 a and b (tb1-a and tb1-b) and phosphoglycerate mutase (PGM).

The WG notes that obtaining this genetic modification, resulting in the simultaneous introduction of mutations in three genes, would be highly unlikely using other selection methods.

As switchgrass is not consumed as human food, any potential new risks will be solely a matter of animal health and the environment. The WG points out that switchgrass is a self-compatible high-yielding perennial species (Martinez-Reyna and Vogel 2002) and that it is mainly tetraploid or octoploid.

Furthermore, switchgrass is considered a potentially invasive species and there is a risk of increased invasiveness in the case of improved cultivars for biomass production (Flint, Shaw and Jordan 2021). The species is also known to allow the development of marginal land, which may impact biodiversity through increased land grabbing for biomass production (Hartman et al. 2011). Finally, the WG considers that there is a risk of dispersal of the trait in wild populations of the species.

5.2.2.12 Case n° 12 - Pink-fruited tomato

Presentation of case 12 (Deng et al. 2018)
Characteristics of the plant Common name: Tomato Scientific name: *Solanum lycopersicum* Family: Solanaceae Type of reproduction: Annual plant with mainly autogamous reproduction Other relevant characteristics: Seeds can survive winter and new germination can be observed. Commercial cultivation in greenhouses or in open fields. for private customers.
Characteristics of the modification Characteristic conferred: Change in colour or flavour / Pink fruit

Type of modification: SDN-1 Number of genes mutated: 1 Number of nucleotides modified: Insertion of 1 nucleotide or deletion of 1 to 87 nucleotides according to the lines analysed

In the case of this genetically modified tomato, a knock-out of the *SlMYB12* gene is obtained directly in elite lines.

The WG notes that a similar mutation can be obtained by other methods or naturally, and points out that this tomato has equivalent characteristics to certain conventionally bred varieties.

The WG has not identified any new health or environmental risks associated with this case.

5.2.2.13 Conclusions from the case studies

Based on these case studies, the WG concludes that new health and environmental risks are associated with plants derived from CRISPR-Cas directed mutagenesis, mainly due to :

- obtaining new genotypes that cannot be obtained using other selection techniques;
- new species and traits that can be modified by CRISPR-Cas, compared with what is classically observed for plants derived from transgenesis (modification of more invasive species, or easier modification of composition, for example);
- the potentially large increase in the area under cultivation of varieties with the same modified trait.

The WG also points out that some of the known risks associated with genetically modified plants remain true for plants derived from site-directed mutagenesis.

The main risks identified in these case studies are listed in **Table 5**.

	Risks identified	Case studies
Comparative assessment, plant composition	• Pleiotropic effects leading to a change in the plant's agro-phenotypic properties or composition • In the case of multiplexing or if a transcription factor is targeted, increased risks associated with pleiotropic effects	• Herbicide-resistant potatoes • Gluten-reduced wheat
Toxicity, allergenicity, nutritional assessment	• In the event of a change in composition, whether desired or unexpected, or a potential change in the toxicity, allergenicity or nutritional characteristics of the plant	• Tomato with high GABA (γ-aminobutyic acid) content

Environmental risks	• Risk of gene flow from edited genes to wild or cultivated populations • If a growing number of modified species are cultivated, there is an increased risk of gene transfer to weed species, including invasive species. • Modification of interactions with animals consuming plants obtained using NTGs and with insect pollinators • Changes in selection pressure could lead to an increase in the pathogenicity of certain pathogens, particularly for long-lived crops. • In the case of multiplexing, transfer of gene combinations with unassessed epistasis	• Tomato with high GABA content • Reduced-size rice • Sage with reduced phenolic acid content • Erect switchgrass with increased tillering

Table 5. Health and environmental risks associated with plants derived from site-directed mutagenesis and identified in the case studies.

In particular, the WG notes that certain potential risks appear repeatedly in these case studies. These include, in particular, risks associated with an unexpected change in the composition of the plant that could lead to nutritional, allergenicity or toxicity problems, or medium- and long-term environmental risks, such as the risk of gene flow from edited genes to compatible wild or cultivated populations (increased by the new diversity of potentially modified species) or risks associated with a change in interactions with animals (including insects) in the event of consumption of or visits to plants resulting from site-directed mutagenesis, potentially more frequent if the variety of modified species increases.

However, the WG also concludes that in some cases, the use of CRISPR-Cas for site-directed mutagenesis only makes it possible to replicate known phenotypes, by acting rapidly on one or a few well-described genes, and that it does not identify any new risk to health or the environment. The WG nevertheless notes for information that under the legislative proposal put forward by the European Commission, all the plants that were the subject of these case studies, with the exception of gluten-reduced wheat (case 5), would probably be considered as category 1 plants and would therefore not be subject to an in-depth assessment.

The WG recommends a differentiated assessment of plants resulting from directed mutagenesis using CRISPR-Cas, on a case-by-case basis, according to the methods developed in the following sections.

5.2.3 Recommendations for assessing identified risks

On the basis of the systematic literature review (section 5.2.1) and the case studies (section 5.2.2), the WG concludes that plants derived from site-directed mutagenesis using

Depending on the mutation introduced, the plant species concerned and the modified trait, CRISPR-Cas techniques may present potential risks to health and the environment:

- similar to those already taken into account by the current regulations on genetically modified plants and concerning the whole plant;
- or resulting from the technical possibilities offered by the CRISPR-Cas system, particularly with regard to the diversity of potentially modified species, the speed and ease of development of modified plants, or the possibility of multiplexing.

The WG therefore recommends a case-by-case assessment of the health and environmental risks associated with these genetically modified plants, taking into account the characteristics of the genetic modification carried out and of the product obtained, and analysing the consequences of the genetic modification in terms of agronomic, phenotypic and compositional characteristics, as well as immunological, toxicological and nutritional aspects. The WG recommends that this assessment be supplemented by a literature review covering the modified gene or novel trait. In the case of plant species which, following authorisation, are newly cultivated in all or part of France, the WG also recommends that, in addition to the required tests, the literature review should highlight any articles relating to the environmental risks associated with the introduction or mass cultivation of these plants.

To take account of certain potential risks associated with the technical possibilities offered by genomic modification of plants using CRISPR-Cas, the WG recommends in particular :

- **if the modification(s) carried out are intended to modify the biochemical composition of the plant, to carry out an analysis of the content of the new compounds and of the compounds potentially affected by this modification, in parallel with the comparative study of composition;**
- **if the purpose of the modification(s) is to suppress or modulate one or more transcription factors, to carry out a bioinformatics analysis to identify the target genes of the transcription factor, followed by a comparative study of the transcription levels of the target genes identified;**
- **if the modified species presents a known allergenic profile or reveals potentially allergenic substances, to carry out, in parallel with the comparative compositional study, a systematic ELISA or LC-MS/MS assay of the major allergens least susceptible to environmental variations (nsLTP, cupins, trypsin inhibitors), supplemented in the case of wheat by an assay of gliadins and glutenins;**
- **if the species on which the modification is made naturally expresses known toxic, genotoxic or anti-nutritional compounds, to carry out a systematic assay of these compounds in parallel with the comparative study of composition.**

The WG also notes that in some cases of plant genome modification, the CRISPR-Cas system may be used to reproduce known mutations, either because they have already been obtained by other systems, or because they are intended to replicate a known allele in another variety or in a closely related species. The WG recommends that, where a history of knowledge is available, i.e. :

- **if the genetic modification(s) carried out are functionally similar at molecular level to a modification obtained by other techniques, including random mutagenesis or conventional selection, and already authorised on the market without any specific risk to health or the environment having been described OR if the genetic modification(s) carried out are naturally present in another species (homologous gene).**
- **AND that the genetic modification(s) carried out lead(s) to a known phenotype whose health and environmental safety has been demonstrated**

that the assessment procedure be simplified and limited, after molecular characterisation, to a comparative study of the composition of the plant (EFSA GMO Panel 2015), in order to rule out any unexpected pleiotropic effect on the plant.

In view of the lack of data on the medium- and long-term environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system, particularly for long-crop species (in arboriculture, for example) or in the event of intensification of cultivation of this type of NTG plant, and the potential direct and indirect cumulative effects, including on cultivation practices, the WG recommends that a post-authorisation environmental risk monitoring plan be set up by a body independent of the petitioner, regardless of the assessment reference system used. This monitoring plan should take into account the cumulative impacts associated with the cultivation of different varieties derived from site-directed mutagenesis presenting the same modified trait, as well as the impact of marketing authorisations for plants derived from site-directed mutagenesis on cultivation practices. In particular, it should contain :

- **in the case of plants resistant to biotic stress, monitoring the development of bypassing in the bio-aggressors concerned;**
- **the dispersal of these plants in the environment;**
- **gene flow from these plants to compatible weeds or wild plants;**
- **an assessment of the impact of the modified characteristics, enabling an estimate to be made of the volumes of inputs used.**

In the event of a proven negative environmental impact, the WG recommends that the results of the monitoring plan should lead to a review of the marketing authorisation.

Finally, the WG believes that the case-by-case assessments of applications for authorisation of NTG plants will make it possible to develop a common policy that could lead to the development and regular revision of guidelines adapted to this type of application.

6 Proposed guidelines for assessing the risks associated with growing and using plants derived from site-directed mutagenesis using the CRISPR-Cas system in food and feed

On the basis of the results and conclusions presented in sections 3 to 5, the WG is proposing a comprehensive, case-by-case assessment framework, a graphic representation of which in the form of a decision tree can be seen in **Figure 11**.

The complete assessment reference system proposed by the WG provides, **for any new plant obtained using NTGs, for a molecular characterisation of the modified plant**, including a characterisation of the modified site, a search for undesired effects on the plant genome and a search for the absence of any foreign genetic material introduced during the transformation stage, in accordance with the procedures described in section 4.3.3. Furthermore, if unwanted effects on the genome are identified (according to the procedures also described in section 4.3.3) and their elimination is not demonstrated, the WG recommends that a characterisation of the region concerned by the unwanted effect be carried out and that the absence of risks associated with the unwanted modification be justified by the petitioner.

If the absence of foreign genetic material in the plant obtained using NTGs cannot be demonstrated, in particular following a stable expression phase of the CRISPR-Cas system in the plant in order to obtain the desired mutation, **the WG recommends that the plant be assessed according to the current assessment reference system**, i.e. according to the provisions of Directive 2001/18/EC, Regulation (EC) No 1829/2003 and Implementing Regulation (EU) No 503/2013, according to their respective fields of application.

If the absence of foreign genetic material is demonstrated and the petitioner has a proven track record (cf. section 5.3.3), the WG recommends a simplified assessment framework limited to a comparative study of the plant's composition.

If the absence of foreign genetic material is demonstrated but the petitioner cannot provide a history of knowledge, the WG recommends that an appropriate standard be established. This corresponds to the current assessment framework for genetically modified plants, with the exception of the requirements relating to the expression of a new protein and therefore not directly transposable to plants resulting from directed mutagenesis, and the requirements relating to the risk of gene transfer to micro-organisms (see section 5.1.6), but supplemented by specific requirements relating to the modified species or trait, in accordance with the procedures described in section 5.2.3.

Finally, **the WG recommends that a post-authorisation monitoring plan for environmental risks be put in place for the** entire duration of the authorisation, taking into account the cumulative impacts of growing different varieties derived from site-directed mutagenesis with the same modified trait, as well as the impact of marketing authorisations for plants derived from site-directed mutagenesis on cultivation practices.

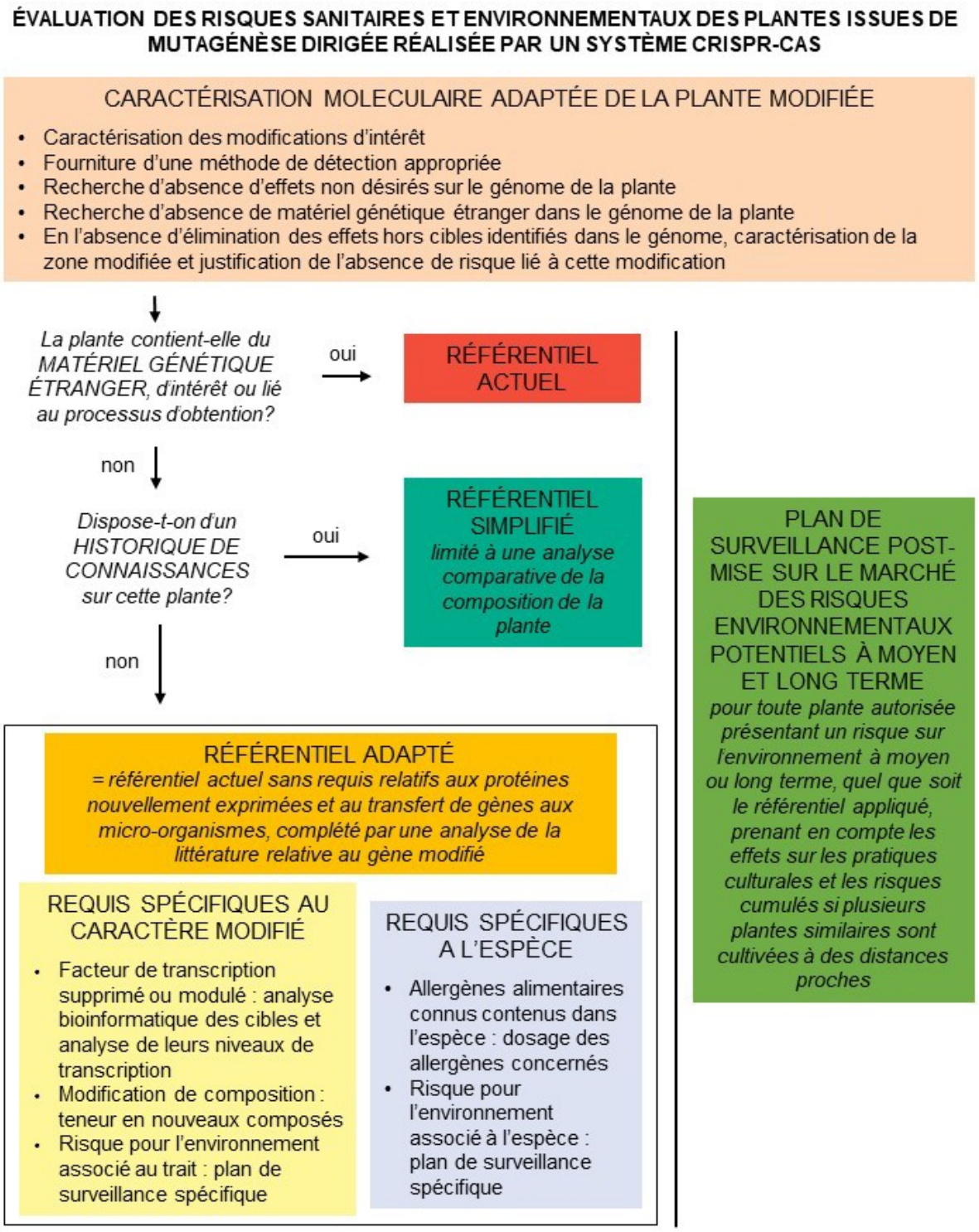


Figure 11. Decision tree corresponding to the NTG WG's proposal for assessing the health and environmental risks of plants derived from site-directed mutagenesis using a CRISPR-Cas system.

7 Socio-economic issues associated with plants and products derived from NTGs: multiple sectors and players

The introduction of plants or products obtained using NTGs could have an impact on the agricultural sectors concerned in France, from upstream to downstream in the value chain. **The WG is** therefore **using the value chain approach to identify the various sectors of activity and the players or groups of players concerned by the plant or product in question and which could potentially be impacted by the introduction of plants or products derived from NTGs (cf. section 7.1). The description of the sectors presented here is general and factual and is not intended to explain how they will be affected by the introduction of plants derived from NTGs.** It concentrates on an analysis of the structure of the sectors concerned by NTG applications in terms of the typology and number of players and the interdependent relationships that may exist between them (cf. section 7.3). The socio-economic issues for these different players or groups of players are then analysed in section 7.4. **The description presented here has also made it possible to identify the type of relevant stakeholders to be interviewed as part of the analysis of these issues, in order to obtain their points of view on the various topics covered in the literature review**.

The value chain approach adopted by the WG is based on the notion of a "value chain". The "value chain" is defined as a set of operations and actors working on a market from upstream (design) to downstream (distribution/consumption) with the aim of offering products (goods or services) on this market (Porter, 1985). The "value chain" concept enables spatio-temporal and technical-economic determinants to be taken into account in economic decisions, by providing a framework for representing meso-economic relationships[32] vertical relationships between players in the value chain (Temple et al. 2011).

However, the value chain approach presented below has certain limitations that should be pointed out. On the one hand, the concept of the "value chain" remains focused on the various stages upstream and downstream of production which make it possible to add value to the product, and does not take into account other more systemic issues on which the introduction of plants obtained by means of NTGs could have an impact (for the development of production systems, for example). Furthermore, in the value chain structure presented below, the value chain considered does not take into account cross-sectoral issues, in particular the relationships that may exist between the production sectors of the crop concerned and other sectors of activity (agricultural equipment, for example) that could be indirectly impacted by the development and adoption of NTG-derived plants in agriculture. Furthermore, this approach does not take into account the territorial dimensions, from the point of view of relocalisation/modification of supply circuits, which the development of NTGs could have an impact on.

With these limitations in mind, an analysis of the sector's integration into international trade is presented to provide a link between the description of the sectors and the analysis of their impact on international trade.

[32] Analysis of economic subsets halfway between macroeconomics and microeconomics, in terms of sectors, groups of companies or industries.

potentially affected by plants and products derived from NTGs and the associated socio-economic issues.

7.1 Identification of sectors potentially concerned by NTG plant applications

NTG applications are not currently marketed in France, but many sectors are potentially affected by the development of NTGs. To understand the effects, the WG has chosen to focus on a few representative sectors. These sectors have been selected as case studies so as to be representative of all the players involved and the potential economic stakes, which is useful for setting up an analysis grid that can later be used to describe other sectors potentially affected by NTG plants.

The selection of case studies for the description of the value chains is based on two criteria:

– the type of trait conferred on the plant obtained using NTG (see **Figure 6**);
– the technical and economic situation of the sector corresponding to plants and products derived from NTG in relation to varietal development (number of authorised varieties), agricultural production, international trade, etc.

Assuming that the plants would be cultivated mainly for their characteristics obtained using NTGs, these two criteria make it possible to identify all the players in the sectors in question and to take account of the various underlying economic mechanisms in terms of incentives for players to adopt plants and products. These economic mechanisms are directly related to the characteristics sought in the various NTG applications already on the market in countries outside the European Union (tomato, carrot and soya) or likely to be marketed in the next 5 to 10 years (see sections 3.3 and 3.4).

On the basis of the data available on the plant species concerned by the NTG applications under development (cf. section 3.2, JRC data[33] data and online data[34]) and economic data on the crops concerned (production, imports and exports)[35]4 sectors were selected as case studies. These sectors are as follows:

- the tomato sector, which is the subject of several potential NTG applications (see Figure 5) with different desired characteristics (one application is already marketed in Japan) and which remains the most widely consumed vegetable in France.[36]) and is still the most widely consumed vegetable in France.
- the common wheat sector, which is a crop with several potential NTG applications and whose production presents major economic challenges given the quantities produced and consumed in France and the sector's involvement in international trade (imports, exports). Durum wheat was not selected by the WG in view of its small share of total wheat production (in

[33] The JRC provided the WG with some of the data used in the publication "*Parisi, C., Rodríguez-Cerezo, E., Current and future market applications of new genomic techniques, EUR 30589 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-30206-3*".
[34] https://www.eu-sage.eu/genome-search, consulted on 18/01/2023.
[35] The data comes from FranceAgriMer's commodity sheets (https://www.franceagrimer.fr/Eclairer/Etudes-et-Analyses/Les-fiches-de-FranceAgriMer) and international trade statistics (http://www.intracen.org/). [36] https://www.genethique.org/japon-une-variete-de-tomates-crispr-mise-sur-le-marche/

volume and value) and the limited number of NTG applications compared to common wheat;

- the vine sector which, although it has relatively few potential applications for the use of NTGs, is the subject of a great deal of work in varietal selection, particularly for resistant grape varieties, and represents a major economic challenge (production, consumption and international trade) for France;
- the carrot sector, which is also the subject of very few potential NTG applications, and where the economic stakes are lower than for wheat and vines, but where an application of interest to the agri-food industry has already been marketed in several countries outside the European Union since 2018[37] ;

These 4 crops have applications covering all the major categories of NTG traits sought (**Table 6.** Types of characteristics sought in NTG applications for the agricultural commodities selected in this **workTable 6**) and different technical-economic situations taking into account the production of the crop in terms of value, the quantity consumed of the product and by-products at national level and international trade. The carrot and tomato sectors will be analysed below under the "vegetable and flower varieties" category. The characteristics sought in the NTG applications covered by the 4 case studies selected should make it possible to capture various economic mechanisms in terms of the willingness to pay of the players (producer and consumer) in these sectors and the economic impact of the NTG applications.[38] and the interest of certain applications in responding to environmental, health and/or societal issues, associated in particular with climate change[39].

Character sought (type of NTG)	Crops/sectors			
	Wheat	Carrot	Tomato	Vine
Improving the quality of food and animal feed	X		X	X
Product colour/flavour		X	X	
Industrial use	X	X	X	
Increased yield and plant growth	X		X	
Herbicide tolerance	X			
Storage performance			X	
Tolerance to biotic stress	X		X	X
Tolerance to abiotic stress	X		X	X

[37] It should be noted that NTG-derived carrots are not marketed as vegetables for consumption, but for industrial purposes for their carotenoid content (see section 3.4).

[38] Willingness to pay is taken to mean the price differential that a farmer is prepared to accept in order to benefit from the trait expressed by the NBT plant compared with a conventional plant. For a consumer, this is the price differential compared with a product not derived from NBT.

[39] The various economic mechanisms and the environmental, health and/or societal issues analysed are presented in Section 7.4.1.

Table 6. Types of traits sought in NTG applications for the agricultural sectors selected in this work

Note: The information in this table comes from the "EU-SAGE" (European Sustainable Agriculture through Genome Editing) database available [online40]. In this database, NTG applications obtained using the CRISPR-Cas technique are grouped into broad categories of desired trait.

7.2 Description of the agricultural sectors potentially concerned by NTG plants and products

7.2.1 General framework for sector analysis

The value chains for selected varieties (tomatoes, common wheat, carrots and vines) consist of 6 stages: variety creation, seed and plant production, variety production, processing, variety distribution and consumption (**Figure 12**). This description shows the links between the various stages and the interdependence between the different operators in the chain.

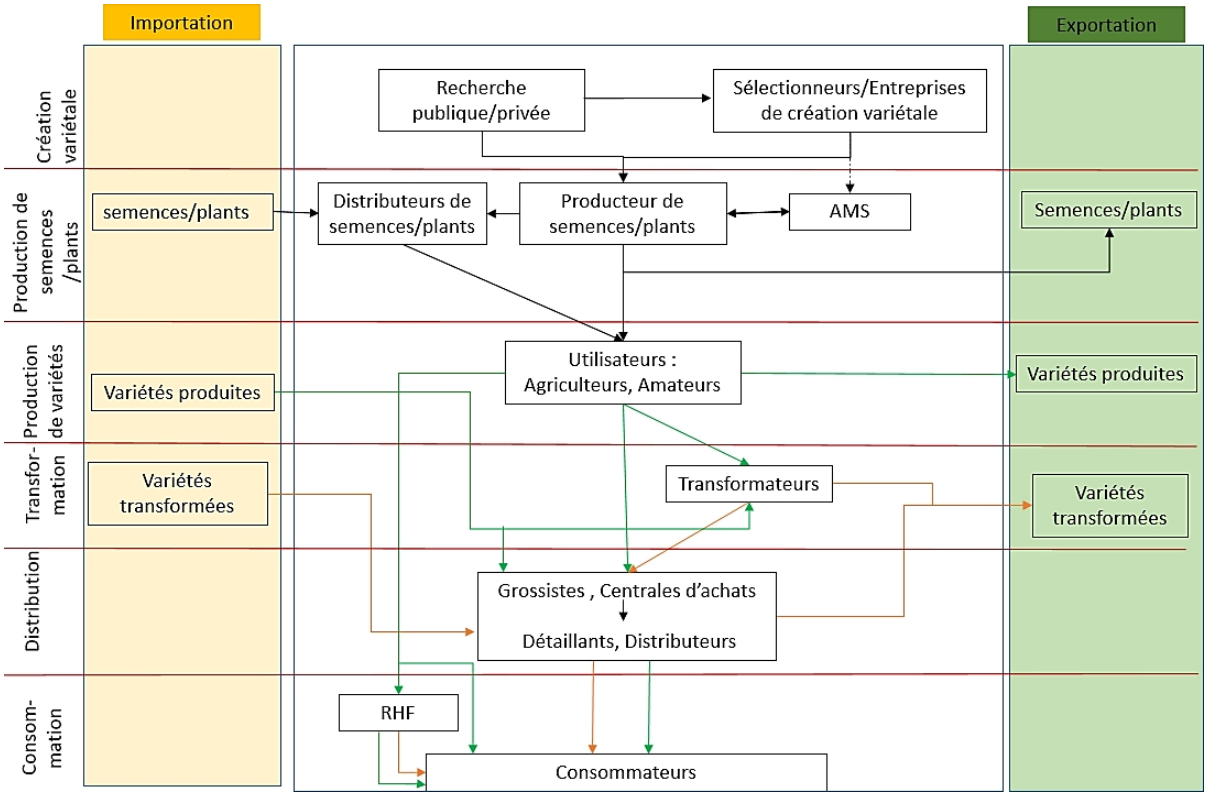


Figure 12. Conceptual diagram of the value chain for selected varieties

Note: The abbreviations AMS and RHF stand for "Agriculteurs-Multiplicateurs de Semences" and "Restauration Hors Foyer" respectively. The arrows show the links between the different groups of players from upstream of variety production to the last link in the value chain. The black arrows represent seed transactions, the green arrows represent direct seed product transactions and the orange arrows represent processed product transactions.

[40] https://www.eu-sage.eu/genome-search?f%5B0%5D=Genome_Editing_Technique%3ACRISPR/Cas, consulted on 18/01/2023.

7.2.1.1 Variety creation stage

Plant breeding is the most upstream sector in the supply chain. This sector includes public and private research bodies and breeders.

Breeders are variety creation companies. Most have their own research laboratories. In 2022, France had **69** breeders of all varieties, according to the SEMAE website. If a breeder creates a new variety and obtains protection for it, evidenced by a property title called the Plant Variety Certificate, then the breeder becomes a **plant breeder** (for more details on the PVC, see Section 7.4.2.1 below). For the variety to be registered in the catalogue, a compliant sample of the variety must be held by a natural or legal person, the **maintainer**. The official maintainer of the variety thus makes it possible to reproduce the variety in accordance with its identity as established at the time of its registration (this is also known as maintenance breeding). For soft wheat, tomatoes, carrots and vines, France has **124** breeders and **86** maintainers (GEVES[41]official catalogue)[42]. Some varieties are also in the public domain, i.e. they are not covered by a PVC. It is therefore possible to freely grow and reproduce seeds from these varieties, without paying or notifying the breeder. As for VOCs, some are the result of collaboration between several public and/or private bodies.

In France, certain **public research bodies** such as INRAE are involved in fundamental studies on plant breeding. However, these players only own a fairly limited number of varieties through the COV.

The varieties selected are sold by their owners to different types of players for seed multiplication.

7.2.1.2 Seed (or seedling) production stage

The seed production sector is made up of seed producers (seed companies), seed farmer-multipliers (henceforth known as AMS) and seed distributors.

Seed producers are responsible for cleaning, processing, packaging and marketing the seeds produced in the fields of the AMSs, with whom they sign production contracts.[43]. In 2022, France will have **252** seed companies producing all types of plant seed.[44]. An **AMS** reproduces identical seeds in large quantities from so-called "basic" seeds. France has 17,271 AMSs and 384,709 hectares of seed production in all plant categories.[45].

Once produced, seeds are sold by seed producers or **distributors**. The latter do not produce, but are responsible for selling seeds and seedlings, plant reproductive material, to all users, professional or otherwise, as well as providing advice on this material. According to the SEMAE website, these include

[41] Group for the Study and Control of Varieties and Seeds
[42] It should be noted that the names of the breeders and maintainers were entered in the first year of registration of the varieties. Some of these players have changed name, have been absorbed by other players or are subsidiaries of the same company. The market is therefore more concentrated than the one presented here.
[43] AMSs can also buy seed. However, in France, all seeds are produced through a contract between an AMS and a seed producer.
[44] Source: SEMAE website.
[45] Source: SEMAE website.

These include a large number of agricultural organisations (cooperatives and retailers) responsible for selling seeds to farmers and green space professionals. Sales to amateur seed users (private individuals and hobby gardeners) are mainly handled by garden centres and DIY superstores. Seeds can also be sold over the internet. The online sales sector is not included in this description. According to figures on the SEMAE website, there were **5,794** seed distributors in France in 2022.

Seeds and seedlings are sold to growers and also to private individuals. The price of seed and seedlings can vary according to category, breed and end use (amateur or professional gardens).

Seeds are imported or exported. Only seeds of varieties registered in the official French or European catalogue may be marketed in France.[46] in France. In addition, according to the customs department[47]an import declaration endorsed by SEMAE is required. Since the introduction of the Guichet Unique National de dédouanement (G.U.N.) in 2015, **the visa request is made via the SEMAE Extranet**. To do this, companies must first register with SEMAE and open an extranet account. Finally, the varieties must be certified in accordance with the OECD Varietal Certification and Seed Scheme[48] and EU rules and standards.

In the case of **exports,** the national regulations of the importing country apply.[49].

7.2.1.3 Variety production stage

The production sector is made up of amateur seed users (**individual or collective amateur gardens**) and professionals (variety-producing **farmers**). Most variety production is carried out by farmers with professional status. Farmers can form cooperatives or producer organisations (POs). **Producer groups" (RP), such as cooperatives or producer organisations, are** formed on the initiative of a group of farmers (who may be AMSs or simple users) who come together with the aim of pooling their knowledge, their demands and their means of production in order to increase their negotiating power with partners upstream and downstream in the supply chain and to reduce transaction costs.

These costs, and the breakdown of them, vary over time. Energy is the biggest item in 2018 and 2019, and despite a significant fall in 2020, it will rise again at the end of this year (**Figure 13**).

[46] The term "marketing" covers any form of distribution, including free distribution.
[47] https://www.douane.gouv.fr/demarche/importer-des-semences-et-plants
[48] Standards for seeds, tractors, forestry equipment and fruit and vegetables - OECD (oecd.org)
[49] The Exp@don database lists the sanitary and phytosanitary conditions for exports to third countries.

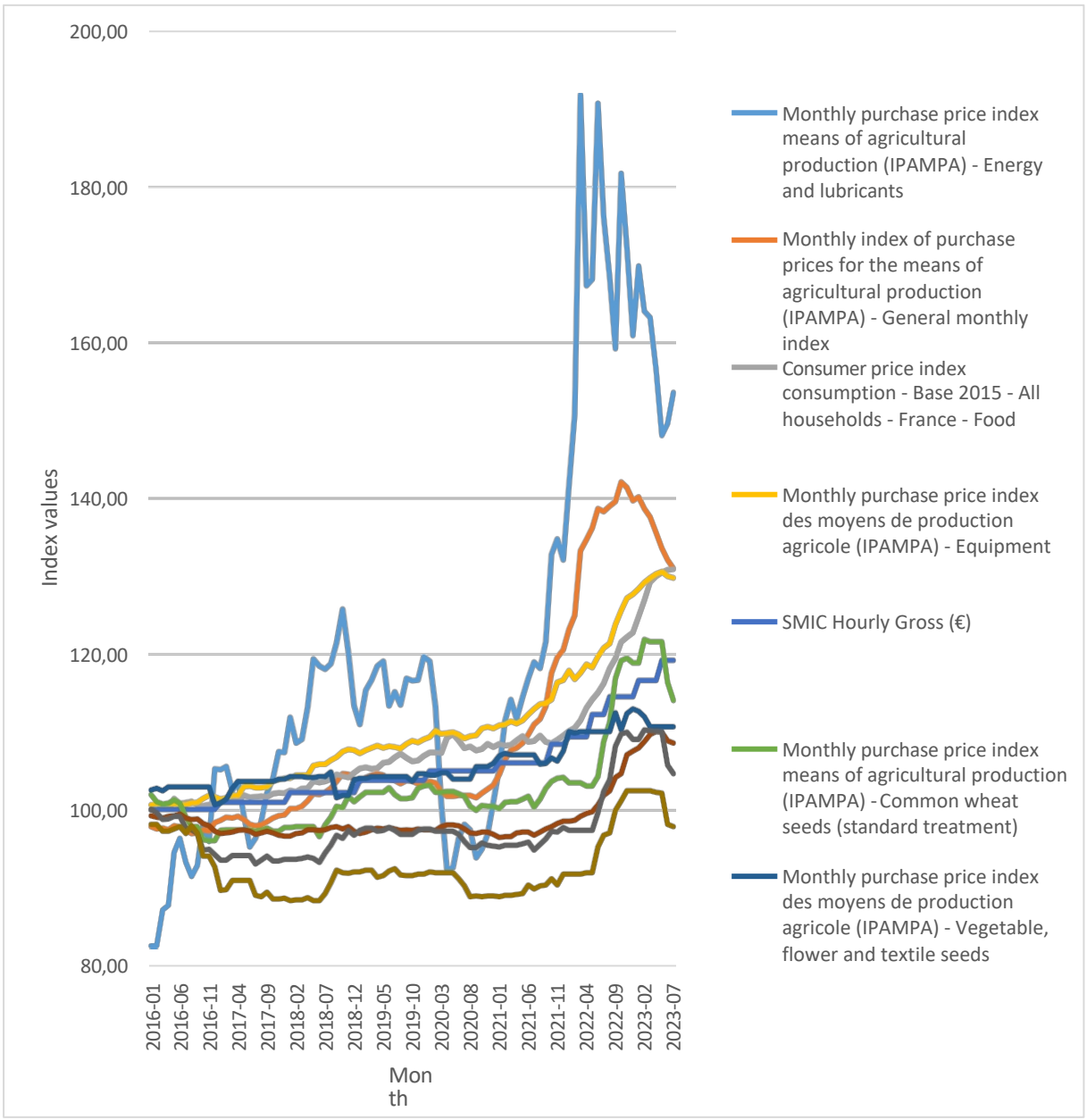


Figure 13. Producer and consumer price trends (from INSEE indices, base 100 in 2015)

7.2.1.4 Variety transformation stage

Variety **processors** carry out operations designed to treat raw materials or materials that have already undergone **processing**, with a view to producing products that can be consumed directly or used in further processing. Processors buy varieties which are intended for them or which were intended for consumption but which have suffered damage making them unfit for direct consumption.

7.2.1.5 Variety distribution stage

First-level producer groups (see section 7.2.1.2)[50] (RP 1) can supply material or seed, the price of which they have negotiated with their suppliers, to user farmers. They also aggregate farmers' production, approve it and package it. These bodies may sell directly to distributors, for example, after negotiating the selling price, or they may group their production together within the same organisation, a **second-level grouping**[51] (RP 2). This organisation brings together the production of several RP 1s within a brand, negotiates prices with the various downstream intermediaries and delivers to them. It supplies its customers (wholesalers, distributors, processors) on its own or with the help of shippers.

The wholesaler is an additional intermediary between the farmer and the distributor. He concentrates the production of the former in order to sell it to the latter. Their main role is allotment. This involves buying goods in bulk to reduce their cost, with a view to reselling them in smaller batches.

Retailers form a heterogeneous group, made up of hypermarkets, supermarkets, grocery shops, specialist shops (organic, for example) and distance selling (or online sales).[52]. Despite the diversity of types of player, the retail sector in France is highly concentrated and dominated by large-scale distribution.[53]. The retail sector is dominated by 6 major groups, which share 90% of the sales market (for all products)[54]. Since 2014, some of the major groups have joined forces to purchase food from suppliers by forming central purchasing groups.[55] The purpose of these groups is to pool members' requests and negotiate supply conditions with suppliers. The members of a central purchasing body no longer deal with suppliers directly, but delegate this task to their central purchasing body. The creation of these joint entities therefore reduces the number of suppliers' customers (concentrating the distribution market faced by suppliers) but leaves the number of distributors unchanged for consumers. The members of a central purchasing body co-operate on purchasing but compete with each other on sales to consumers. These buying groups can be national (including only French players) or international (including at least one French player) and they include

[50] The term "first degree" is used by Bellec-Gauche, Chiffoleau and Maffezzoli (2015).
[51] The term "second degree" is used by Bellec-Gauche, Chiffoleau and Maffezzoli (2015).
[52] A segmentation of predominantly food retailing is described in Opinion No. 15-A-06 of 31 March 2015 of the Autorité de la Concurrence.
[53] Distribution is the activity of "retailing". Its primary function is to make a range of goods or services available to users. Mass retailing is a distribution channel or a type of distributor. Large-scale distribution refers to large-scale food distribution, which includes hypermarkets (NAF code 4711F), supermarkets (4711D) and multi-store outlets (4711E).
[54] Carrefour Group (21.8% in 2014), E. Leclerc (19.9%), ITM Entreprises (14.4%), Casino Group (11.5%), Groupe Auchan (11.3%) and Système U (10.3%) (Kantar, 2014)
[55] Alliances changed in 2021 and are still in the process of stabilising. In 2021, ITM Entreprises and Groupe Casino formed the Auxo purchasing group, which supplies Francap and Cora, part of the Louis Delhaize group. In 2022, Système U will join the European buying groups Everest and Epic Partners, thus joining Colruyt, which is present in Epic Partners. In 2021, E.Leclerc decided to create a central purchasing group with Rewe (a German retailer). In 2021, Auchan created U2A, an entity that centralises the purchases of many Auchan stores in Europe. In 2023, Carrefour also decided to launch a new central purchasing unit, Eureca, which brings together the requests of Carrefours in 6 European countries.

not only branded products (MDF[56]) as well as private label (private label[57])[58].

7.2.2 Vegetable and flower varieties" category: description of the tomato and carrot sectors in France:

According to the SEMAE website, of the **252** seed companies producing all types of plant seed in France in 2022, **99** will be producing vegetable and flower seeds, including tomatoes and carrots. Among the 17,271 AMS in France in 2022, **2,526** AMS produce "vegetable and flower" seeds on 25,982 hectares of seed according to the interprofession, of which **9,746** hectares are destined for the multiplication of fine vegetable seeds. Finally, of the 5,794 seed distributors, **4,620 will be** distributing "vegetable and flower" seeds in 2022 (Source: SEMAE website).

Vegetable seeds, including tomato and carrot seeds, are checked by the importing operator to ensure that imported seeds meet European standards (in terms of purity, packaging, labelling, sanitary quality, etc.). Labels attesting to the quality of the seed are affixed by the suppliers. The information must be translated into French, and the labels must bear the words "EC rules and standards". If the seed is imported from countries outside the European Union, it must also be certified in accordance with the OECD varietal certification and seed control system.[59] accompanied by an International Orange Bulletin (I.O.B.) on which their technological characteristics (germination rate, specific purity, etc.) have been recorded and analysed in accordance with the international rules of the International Seed Testing Association (ISTA).

According to FranceAgriMer data for 2021, most fruit and vegetables are purchased by supermarkets. The market shares of hypermarkets, supermarkets and own-brand stores (formerly hard discounters) are 31.3%, 17.8% and 11.9% respectively. The other distribution channels are markets (10.6%), specialised stores (13%) and convenience stores (6.4%), online sales (3.3%) and alternative specialised stores (5.6%).

7.2.2.1 The tomato industry

The catalogue of **varieties authorised in France**, consulted on 04/09/2023, lists 461 tomato varieties, of which around sixty are in the public domain. Of the 461 varieties, 382 (82.9%) are declared to be "hybrids", 76 (16.5%) are declared to be "non-hybrids", 2 (0.4%) are declared to be "population" varieties and 1 (0.2%) is declared to be a "line" variety, in other words a pure line according to the GEVES categories. All

[56] MDFs are brands created and owned by a manufacturer who designs and manufactures its products and sells them to distributors.
[57] Private labels are brands created and owned by a retail chain. Products sold under private labels are manufactured by independent manufacturers on behalf of the chain and, more rarely, by production subsidiaries belonging to the chain.
[58] See ADLC website: L'Autorité de la concurrence renforce ses investigations et ouvre des enquêtes concernant des rapprochements à l ' achat dans le secteur de la grande distribution à dominante alimentaire.
|Autorité de la concurrence (autoritedelaconcurrence.fr)
[59] Standards for seeds, tractors, forestry equipment and fruit and vegetables - OECD (oecd.org)

of varieties in the public domain are non-hybrid. **Figure 14** shows the trend in the number of tomato varieties authorised each year, which has risen sharply over the last ten years.

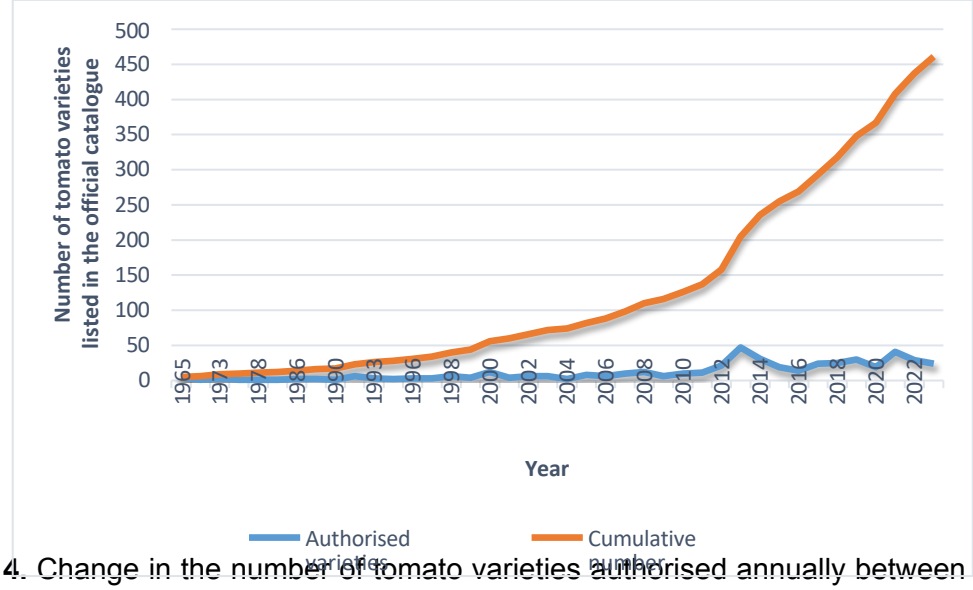


Figure 14. Change in the number of tomato varieties authorised annually between 1965 and 2022 (taken from the official catalogue of plant species and varieties grown in France - GEVES).

According to the official GEVES catalogue, of the 461 varieties, 451 have a breeder and 417 a maintainer. Tomatoes have a maximum of **52** breeders and **33** maintainers. According to figures on the SEMAE website, there are far fewer: **26** breeders create varieties of vegetable and flower species, including tomatoes. Approximately twenty breeders produce tomato varieties authorised for cultivation in France e[60].

Of the 25,982 hectares of "vegetable and flower" seeds worked by AMS, **15** will be dedicated to field tomato **seed production** in 2022 (**Figure 15**).

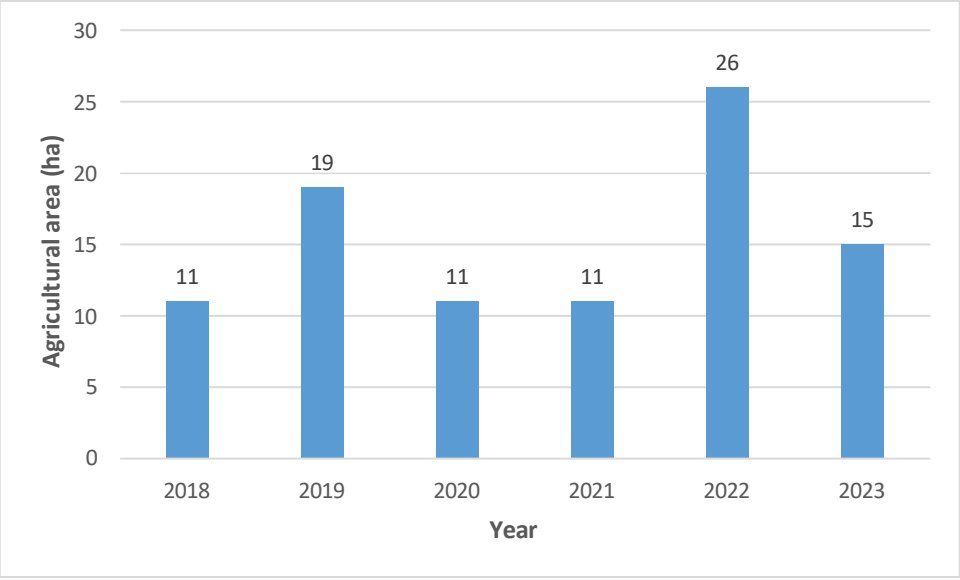


Figure 15. Agricultural areas used for field tomato seed production in France (from the SEMAE website)

[60] This difference is explained by footnote 42.

France has an excellent variety creation industry. In fact, France is renowned for its high-quality mid-range and top-of-the-range varieties.[61]. However, according to a Senate report, tomato seed multiplication and plant production are becoming increasingly internationalised.[62]. Distributors also import tomato seeds for resale on the national market.[63]. In order to **import tomato seeds**[64]operators must file an import declaration with customs[65] and provide a phytosanitary certificate. Measures have been taken within the European Union to prevent the transmission of Tomato Brown Rugose Fruit Virus (ToBFRV). The specific requirements for tomato species are set out in Implementing Regulation (EU) 2020/1191.

There are 2302 **tomato growers** in France, according to the 2020 general agricultural census. According to Agreste's annual agricultural statistics (SAA) published in June 2023[66]in 2021, 5,372 hectares of land in France were used to grow tomatoes. Half of this area, 2,704 hectares, is dedicated to outdoor production for industrial use. This area has tended to increase slightly since 2016 (**Figure 17**). A large part of the area, 2,050 hectares (38%), is dedicated to greenhouse production. This area has remained constant over time. Lastly, 618 hectares (12%) are open-air and intended for fresh produce. This area has remained constant over time, with the exception of 2020, which saw an increase.

According to Agreste's SAA, in 2021 France produced 699,462 tonnes of tomatoes, of which 505,530 tonnes (72%) were greenhouse tomatoes, 34,995 tonnes (5%) were outdoor tomatoes for fresh produce and 158,938 tonnes (23%) were outdoor tomatoes for industry. This production has tended to decrease in volume over the last 6 years (**Figure 16**), despite an area dedicated to tomatoes that has tended to increase since 2016 (**Figure 17**).

[61] FranceAgriMer, Analyse des facteurs de compétitivité sur le marché euro-méditerranéen de la tomate en 2022-Synthèse. May 2022 SYN-FL-2022-VEILLE-TOMATE-2020.pdf (franceagrimer.fr)
[62] https://www.senat.fr/rap/r21-905/r21-90512.html
[63] All companies must make their import declarations via the SEMAE Extranet linked to the GUN (national one-stop shop) Importer / Exporter - SEMAE. Accessed on 16/02/2023
[64] As seeds can be imported from online platforms (particularly for amateur gardens), it would be important to analyse the regulations governing this type of marketing.
[65] 1209.91.80.70 is the nomenclature number for tomato seed.
[66] Data for 2022 is provisional and has not been collected.

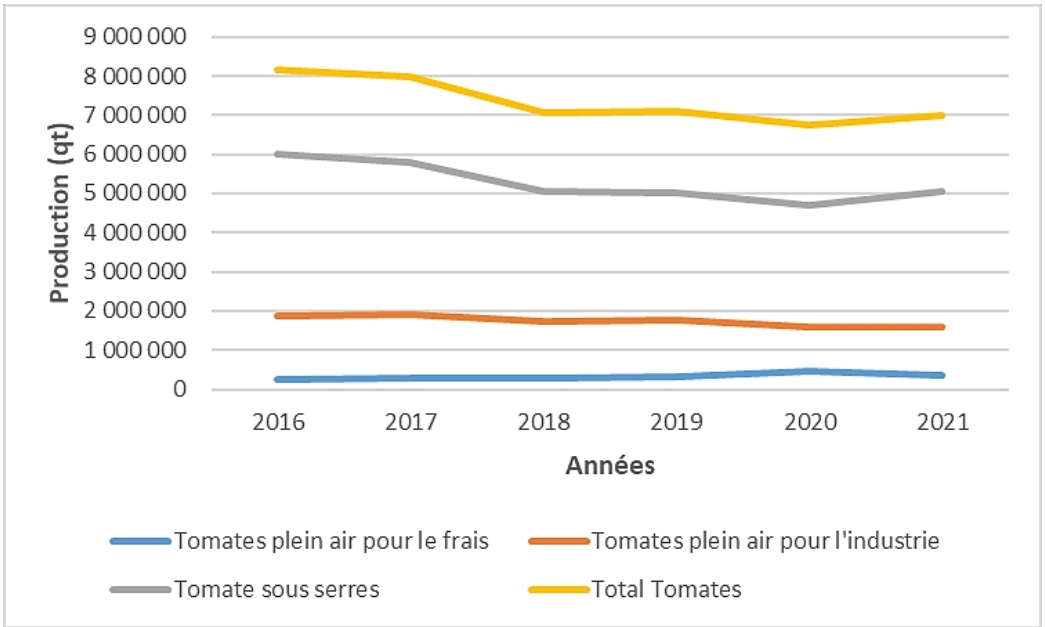


Figure 16. Growth in tomato production (non-garden) in France between 2016 and 2021 (from Agreste)

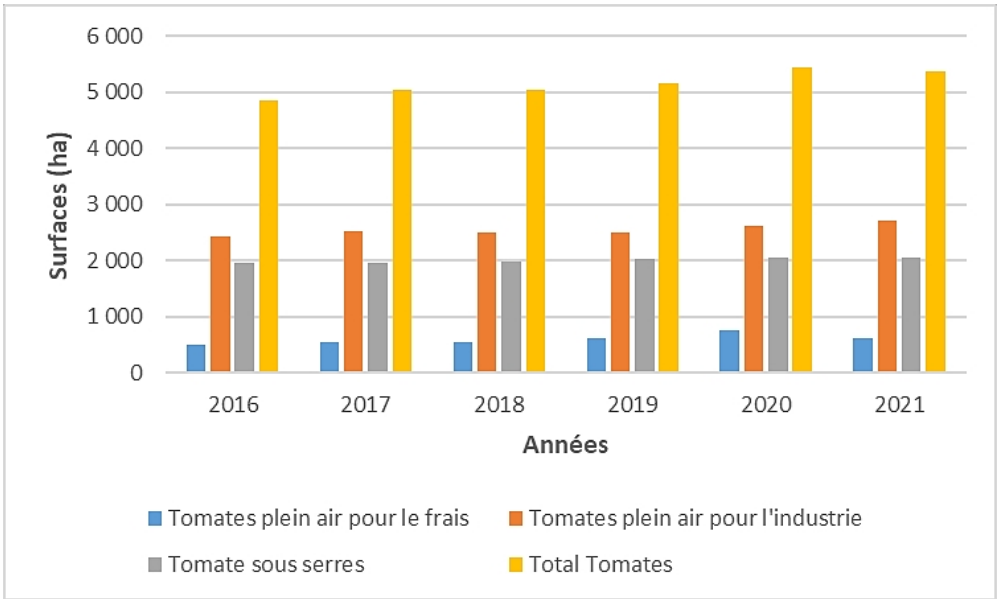


Figure 17. Tomato production areas in France between 2016 and 2021 (from Agreste)

Tomato production in amateur gardens is not included in the SAA data and is therefore not shown in **Figures 16** and **17**. This production is mainly intended for the consumption of fresh tomatoes.

As seen above (**Figure 16**), by 2021, half of the hectares dedicated to tomato production will consist of outdoor production intended for industry, i.e. for **processing**. According to the Société Nationale Interprofessionnelle de la Tomate (SONITO), these

hectares are located exclusively in the South of France[67] operated by 202 growers in 2021. More than three quarters of the area under tomato production for processing is in Bouches-du-Rhône (37% of the national area), Lot-et-Garonne (24%), Drôme (10%) and Vaucluse (8%). These departments account for 83
% of production and producers. Bouches-du-Rhône is the department with the largest surface area dedicated to the production of tomatoes for processing, as well as the highest production (48% of national production), and accounts for 17% of producers in the sector. Lot-et-Garonne, with a smaller surface area and much lower production (16% of national production), accounts for almost 42% of growers in the sector. These differences indicate that producers are smaller in Lot-et-Garonne than in Bouches-du-Rhône. This difference in size can be explained in part by the choice of organic production (AB) in Lot-et-Garonne. This department, with 173 hectares earmarked for AB production, in other words 28% of the area of this department used for the production of tomatoes for processing is AB (hereafter referred to as AB area). The figure for Bouches-du-Rhône is just 17%. The AB area represents more than a fifth of the area (22%) of tomatoes intended for processing, and 31% of this area is in Lot-et-Garonne.

According to SONITO[68]the number of producers of tomatoes for processing varies between 150 and 202. It has been rising since 2018 to reach 202, its highest level since 2010.

According to Agreste figures, 158,938 tonnes[69] of tomatoes for industrial use were produced in 2021, representing 23% of total tomato production of 699,462 tonnes.[70]. According to the fruit and vegetable processing interprofession Anifelt, France has 11 processing units that produced 54,134 tonnes of products in 2021, 66% of which were tomato concentrates, 16% preserves, 14% juices and 4% frozen products (tomatoes and tomato derivatives). Finally, according to Businesscoot (2022), just under a sixth of processed products manufactured in 2020 (16%) were organically produced.

Distribution of fresh and processed tomatoes is dominated by supermarkets. Households buy their tomatoes mainly from hypermarkets, supermarkets and own-brand retailers such as Lidl. According to Businesscoot's tomato market study (2022[71]), 34% of fresh tomatoes sold in 2021 will be sold by hypermarkets, 19% by hypermarkets and 15% by EDMs. Markets and direct sales will account for only 8% and 2% of fresh tomatoes sold in 2021.

In the tomato distribution and processing sectors, the import-export balance for tomatoes remains negative, despite an increase in exports in recent years. In 2021, France exported around 275,000 tonnes of fresh tomatoes, compared with over 500,000 tonnes imported (**Figure 18**). Trade in real terms has increased over the last five years, reaching almost €700 million in imports compared with around €400 million in exports (**Figure 19**). France's main trading partners for tomatoes are Morocco and Spain, which both benefit from lower production costs and higher yields.

[67] It should be noted that SONITO does not provide the same production and surface area figures as Agreste. According to the interprofession's economic studies, France will produce 165,291 tonnes of tomatoes for processing on 2,521 hectares in 2021.
[68] Sonito economic study available on the website: statistics for the 2021 campaign.
[69] 165,291 tonnes according to SONITO.
[70] A description of processing in France is provided in Appendix 15.
[71] The tomato market in France, Businesscoot, 01/08/2022

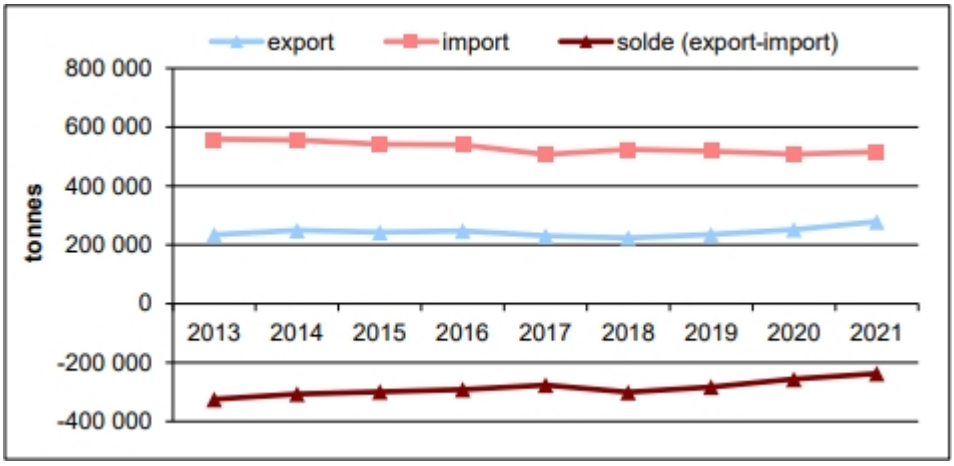


Figure 18. French trade balance for fresh tomatoes between 2013 and 2021 (from FranceAgriMer[72])

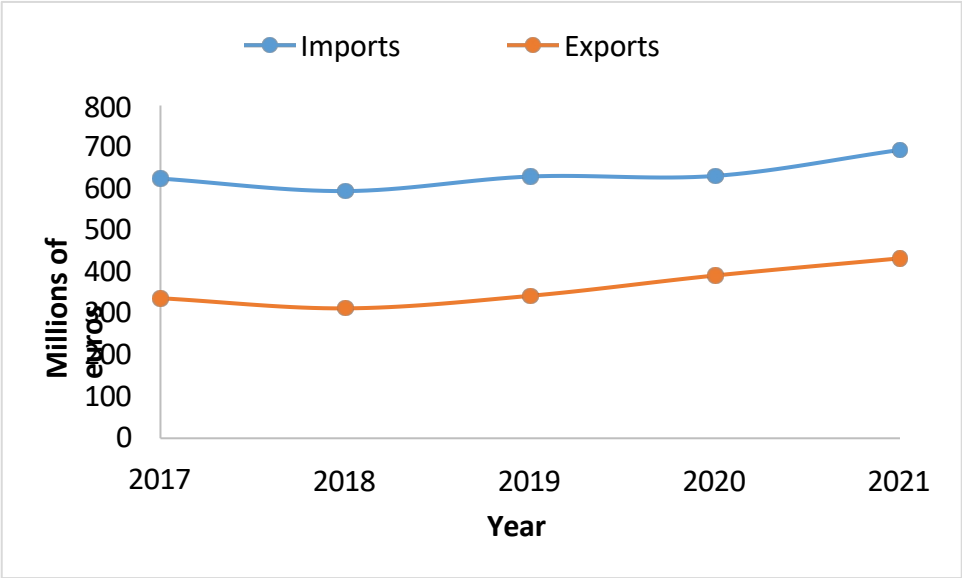


Figure 19. Tomato exports and imports (in millions of euros) in France between 2017 and 2021 (from the International Trade Center[73])

France's dependence on imports is even greater for processed tomatoes (**Figure 20**). According to a Senate report in 2020, France imported almost €404 million worth of processed tomatoes, or 1.2 million tonnes of fresh tomato equivalent.

[72] https://rnm.franceagrimer.fr/bilan_campagne?tomate
[73] ITC - Trade Impact for Good (intracen.org) consulted on 16/02/2023.

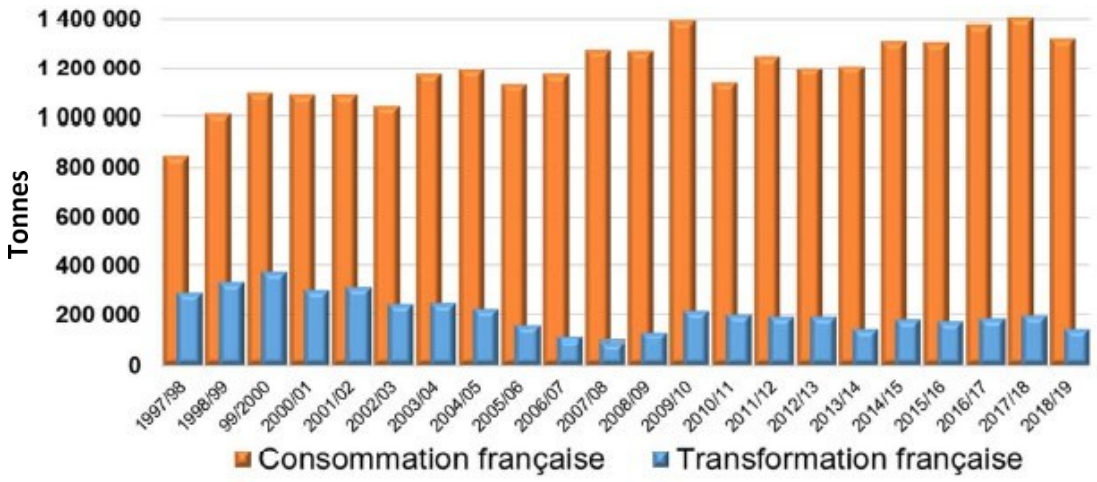


Figure 20: Tomato derivatives processing and consumption (in tonnes) in France between 1998 and 2019 (from SONITO[74])

According to Businesscoot (2022), the annual **consumption of** fresh tomatoes per household in France is 13.6 kg, at an average price of €3.22/kg. In 2021, consumption in France is estimated at 745.9 thousand tonnes. According to the same study, the round tomato and the round vine tomato are the tomatoes most consumed by the French, with 25% and 42% of purchases respectively. A survey in 2021[75] showed that in season (from March to October 2020), the round vine tomato is bought at least once a week by half of respondents, the round tomato is bought by a third of respondents on a weekly basis and the cherry tomato is also bought by a third of respondents. Cocktail tomatoes in bunches, elongated tomatoes, ribbed tomatoes and round fleshy tomatoes are of interest to only one in four respondents. This interest in tomatoes is much lower out of season, but the order of frequency of purchase of the different varieties is similar. Few consumers give priority to buying direct from the grower (8% consider direct sales as their main place of purchase and 5% as their secondary place of purchase).[76]. According to the survey, the French origin of tomatoes, pesticide-free production and bulk buying (no punnets) seem to be the criteria of choice for consumers.

Conclusion

The tomato is one of the most widely consumed vegetables in France, with around 745,900 tonnes in 2021. The different types of tomato on the market offer consumers a wide range of choices. Market prices vary according to the type of tomato (round, elongated, cherry, etc.) and therefore the characteristics of the varieties sold.

Despite a positive trend in varietal development, tomato production in France has been declining in recent years. This fall in

[74] http://www.sonito.org/docs/AG_ET_CA/EVOLUTION_DES_ECHANGES_COMMERCIAUX_EN_2019.pdf
[75] The study on tomato consumption was decided by Interfel's Economic Commission and conducted by Bilendi and CTIFL in the summer of 2021 among a representative sample of 1,000 men and women aged 18 to 65.
[76] The direct sales considered in the study are the delivery of products from the producer to the consumer without going through an intermediary. It includes farm-gate sales, market sales and AMAPs.

This is mainly due to France's positioning in the middle and top of the range, with lower yields than other, more productive bottom-of-the-range varieties. Despite the dynamism of the tomato breeding industry, France is highly dependent on international trade. Trade with third countries takes place at several levels in the industry, in seed distribution and in the distribution of tomatoes and tomato products.

French production, at 699,462 tonnes in 2021, is insufficient to meet French demand. Imported tomatoes are generally sold at a lower price than those produced in France. The lack of competitiveness of this market in France is due to the lower cost of production in the countries (Morocco and Spain, for example) that are the main exporters of tomatoes to France. France's trade balance for tomatoes is largely negative. French imports are around twice as high as tomato exports, with a deficit of around €300 million in 2021.

Given the interdependence between the various players in the sector and the integration of the tomato sector into international trade, the introduction of NTG plants or products into the European Union or elsewhere could have an impact on the sector. A study of the effects of the introduction of Sicilian Rouge in Japan (see section 3.4) on the industry could be of interest in understanding the possible effects of the introduction of this type of product in France.

7.2.2.2 The carrot sector

The catalogue of **varieties authorised** in France, consulted on 30/08/2023, lists 59 carrot varieties, 12 of which are in the public domain. Of the 51 varieties, 38 (64.4 %) are declared to be hybrids, 13 (22%) are declared to be "non-hybrids", 5 (8.5%) are declared to be "three-way hybrids", 1 (1.7%) is declared to be a "single hybrid", 1 is declared to be a "population" and 1 variety is declared to be a "line". All the varieties in the public domain are "non-hybrid". **Figure 21** shows the trend in the number of carrot varieties authorised each year, which has risen sharply over the last 10 years (varieties that have been cancelled but are marketable are not included in this graph).

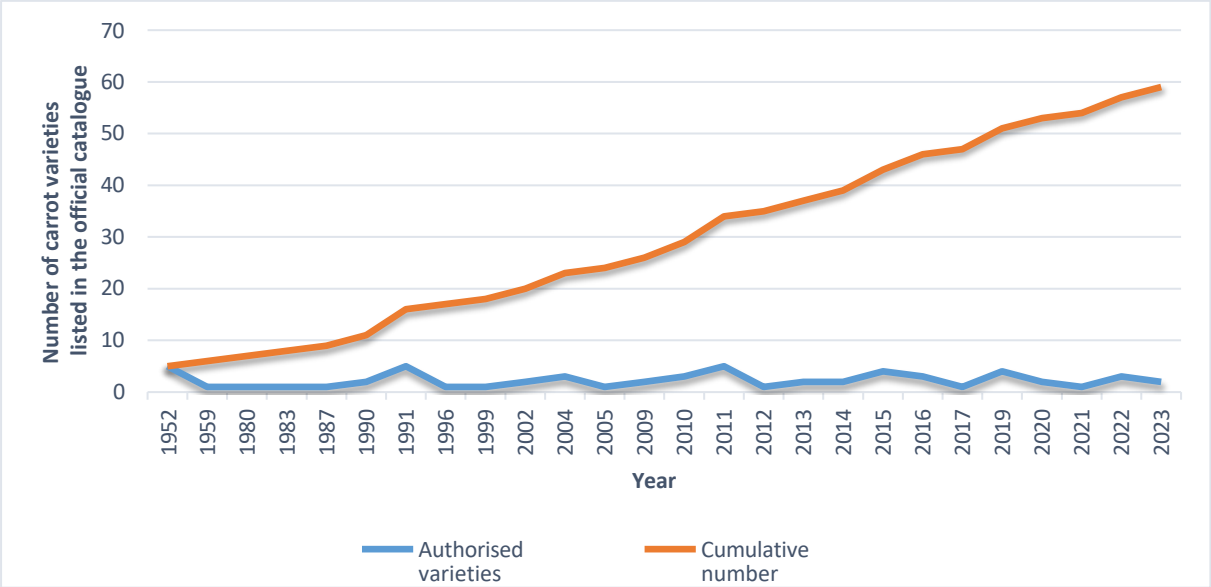


Figure 21. Change in the number of carrot varieties authorised annually between 1965 and 2022 (taken from the official catalogue of plant species and varieties grown in France - GEVES).

According to GEVES, of the 59 varieties of carrot, all have a breeder and 57 a maintainer. Carrots have a maximum of 12 breeders and 10 maintainers.

According to the figures presented on the SEMAE website, of the 25,982 hectares of seeds In 2021, 1,491 of the "vegetable and flower" seeds worked by AMS will be dedicated to field **carrot seed p r o d u c t i o n** , and 1,568 in 2022 (**Figure 22**).

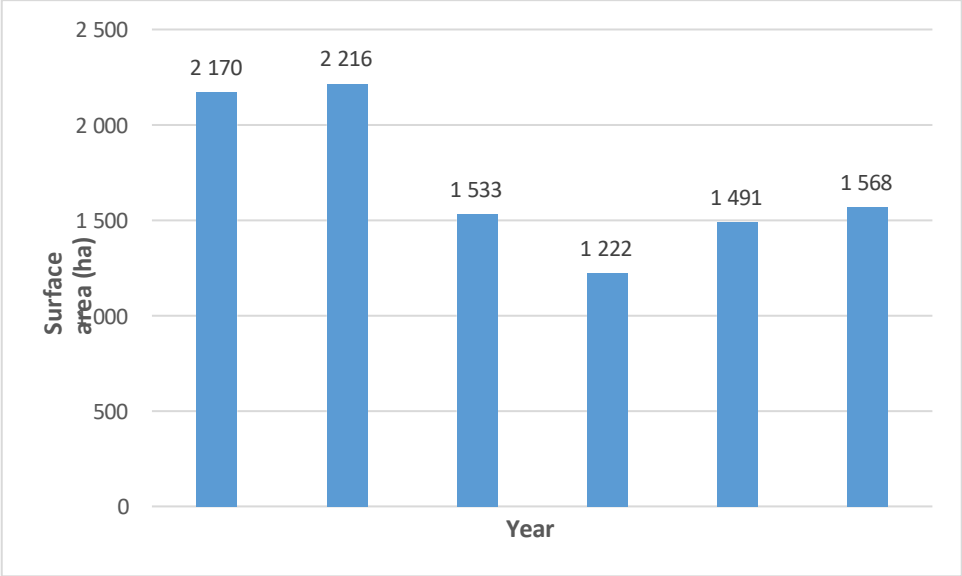


Figure 22. Agricultural areas used for carrot seed multiplication in France (from SEMAE)

Geographically, this operation is concentrated mainly above the centre (departments 18, 28, 6, 41 and 45) of France and not in the West and South-West regions, which according to Businesscoot (2023[77]).

[77] The carrot market in France, Businesscoot, 09/03/2023

The majority of the area is used for non-hybrid carrot seed multiplication, according to a business report published by SEMAE in July 2022 covering the period 2017-2021 (**Figure 23**).

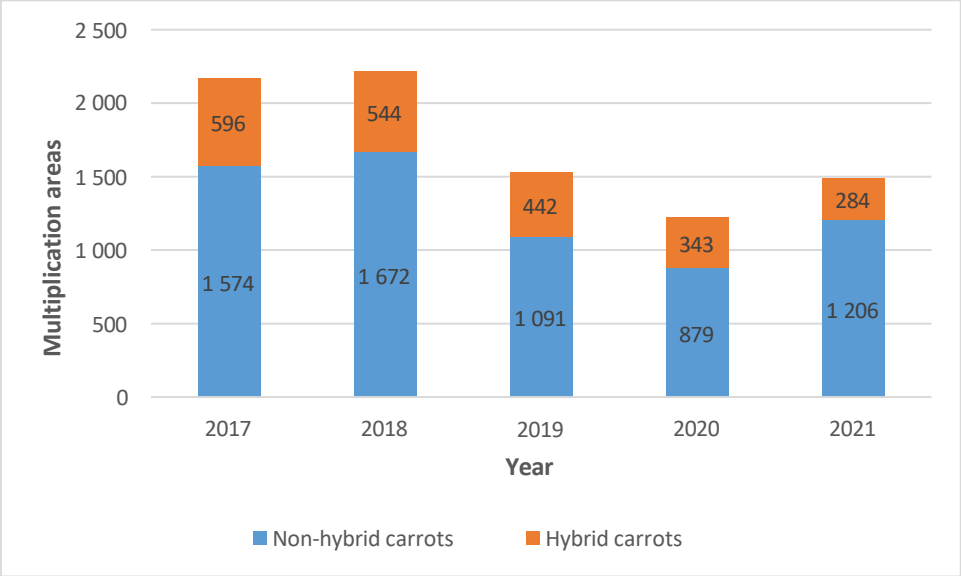


Figure 23. Area used for carrot seed multiplication in France by variety (taken from the note de conjoncture indicateurs 2022, SEMAE)

The low proportion of land used for hybrid seed multiplication could be explained by lower demand due to the higher cost of hybrid carrot production.[78].

As far as carrot production in France is concerned, while French carrot production areas stagnated in 2018 (**Figure 24**), production fell by 11% (**Figure 25**) in the same year. The latter, as well as production areas, increased from 2019 to 2021. These increases follow the rise in prices in 2018, which remain high until 2022.

[78] According to FNAMS, direct costs, i.e. costs that can be immediately allocated to the production cost of a hybrid carrot, are almost twice as high as those for a population carrot. This difference in cost is partly explained by a difference in price, which includes the price of basic seed (which producers

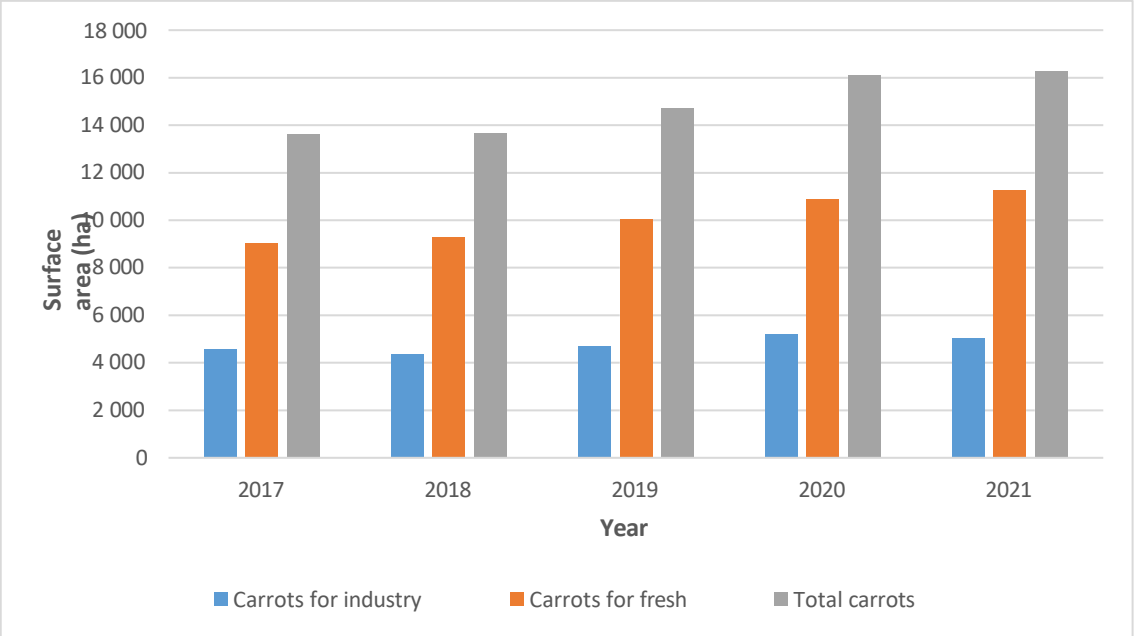


Figure 24. Carrot production area in hectares in France (from SAA 2022)

The area under organic farming (AB) will be 1807 hectares in 2020, i.e. around 14% of the total area under carrot cultivation (Agence bio).

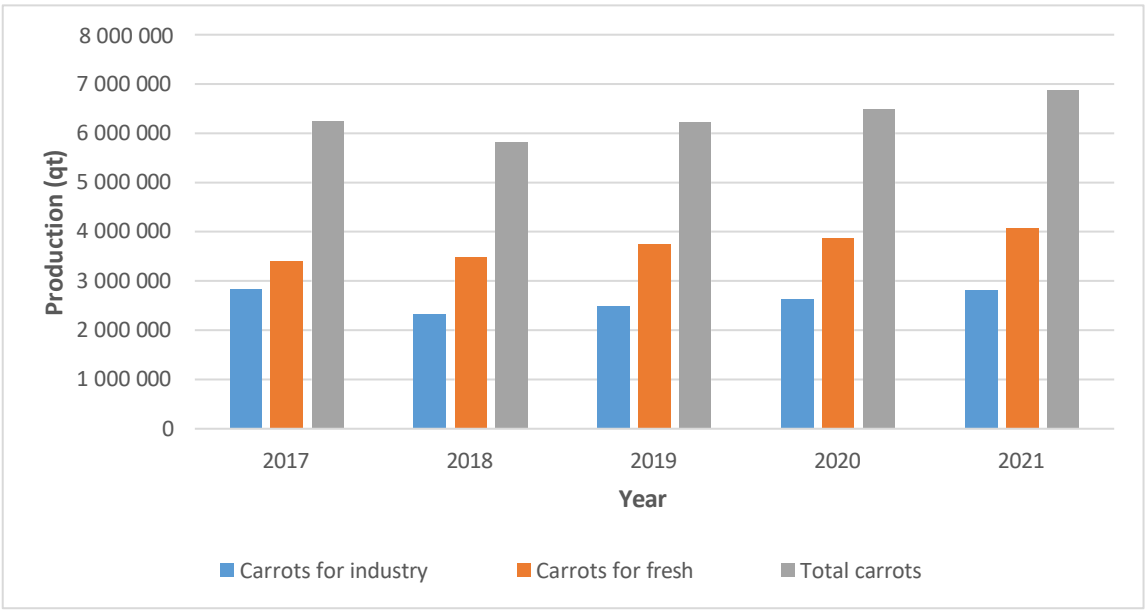


Figure 25. Harvested carrot production in France (from FranceAgriMer)

Carrots account for just 4% of vegetables processed, according to a report by Businesscoot (2023), which uses data from the canned and frozen vegetables interprofession, Unilet, from 2021. However, according to the same report, carrots are used in 35% of canned vegetables produced, in the form of canned carrot peas, mixes and carrots, and account for 16% of frozen vegetables produced.

France is Europe's fifth largest carrot producer, but has a negative trade balance (**Figure 26**).

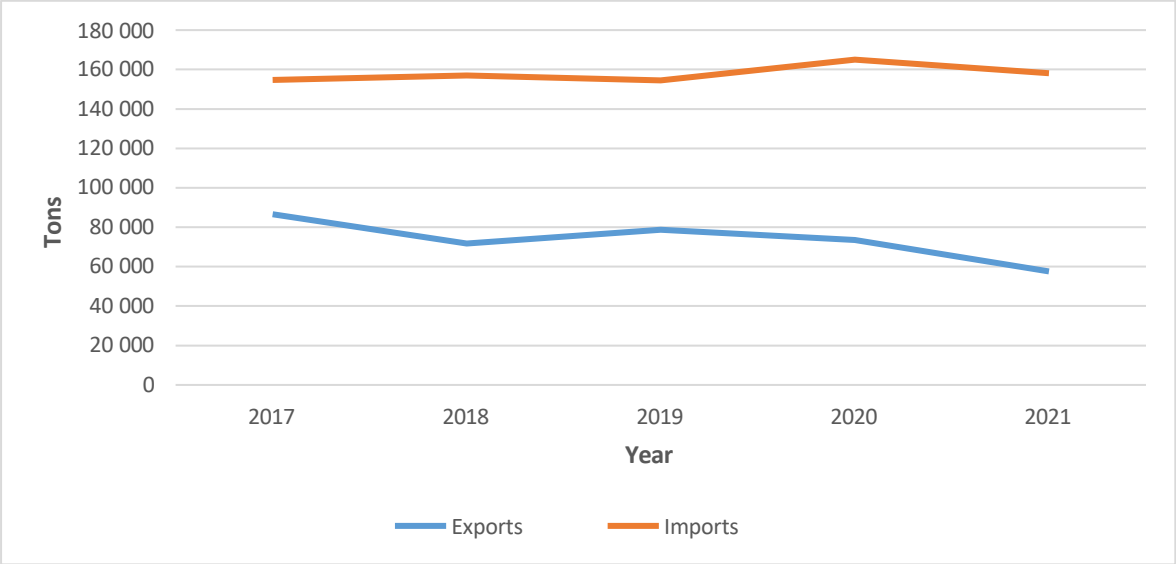


Figure 26. French carrot trade balance between 2017 and 2021 (from FranceAgriMer)

France imports carrots almost exclusively from the European Union, with the bulk coming from Belgium and Spain. In 2021, these two countries will account for almost 70% of French carrot imports (Businesscoot, 2023). These two countries are also the two main destinations for French carrots, accounting for 60% of French carrot exports.

According to the Institut Technique de l'Agriculture Biologique (ITAB), carrots are one of the most widely consumed and sought-after organic vegetables in France. According to the Carottes de France producers' association, using Kantar Wordpanel 2021 data, French households consume at least 9 kg of carrots a year at an average price of €1.43/kg. This would make carrots the second most consumed vegetable in France in terms of volume, after tomatoes. By analysing searches for the term 'carrots' in Google Trends, Businesscoot has observed a seasonal pattern in demand. This is explained by the seasonal nature of the supply of different categories of carrot. There are three categories:

- Early carrots are harvested very young, from the end of May to July. They can only be kept for a maximum of three days in the crisper.
- In-season carrots: available from July to October.
- Storage carrots are on the market from October to March.

Conclusion

Varietal development for carrots has been sluggish, but this does not seem to be holding back the dynamism of seed and carrot production in recent years. Between 2018 and 2021, the area under cultivation and carrot production increased from 13,679 hectares and 581,518 hectares respectively.
tonnes in 2018 to 16,092 hectares and 688,114 in 2021. These increases follow a rise in carrot selling prices.

Carrots are still one of the most widely consumed vegetables in France. French production is not sufficient to meet French demand, and the carrot sector is highly dependent on international trade. French imports will be around twice as high as carrot exports in 2021.

Given the interdependence between the various players in the sector and the integration of the carrot sector into international trade, the introduction of NTG plants or products into the European Union or elsewhere could have an impact on the sector and on import and export flows.

7.2.3 Description of the soft wheat sector in France

There are two types of soft wheat: winter wheat and spring wheat. In the catalogue of **varieties authorised** in France, consulted on 30/08/2023, 12 spring wheat varieties are listed, all of which are "line varieties". France has 8 spring wheat breeders and 6 maintainers. There are 389 winter wheat varieties, of which 360 (93%) are declared to be "line varieties", 27 declared to be "simple hybrids" (7%), 1 declared to be "male-sterile line varieties" and 1 declared to be "male-sterile line varieties".
A "fertility restorer line". France has 55 winter wheat breeders and 29 maintainers.

Figure 27 shows the trend in the cumulative number of soft spring and winter wheat varieties authorised each year, which has risen sharply over the last 10 years (varieties that have been cancelled but are marketable are not included in this graph).

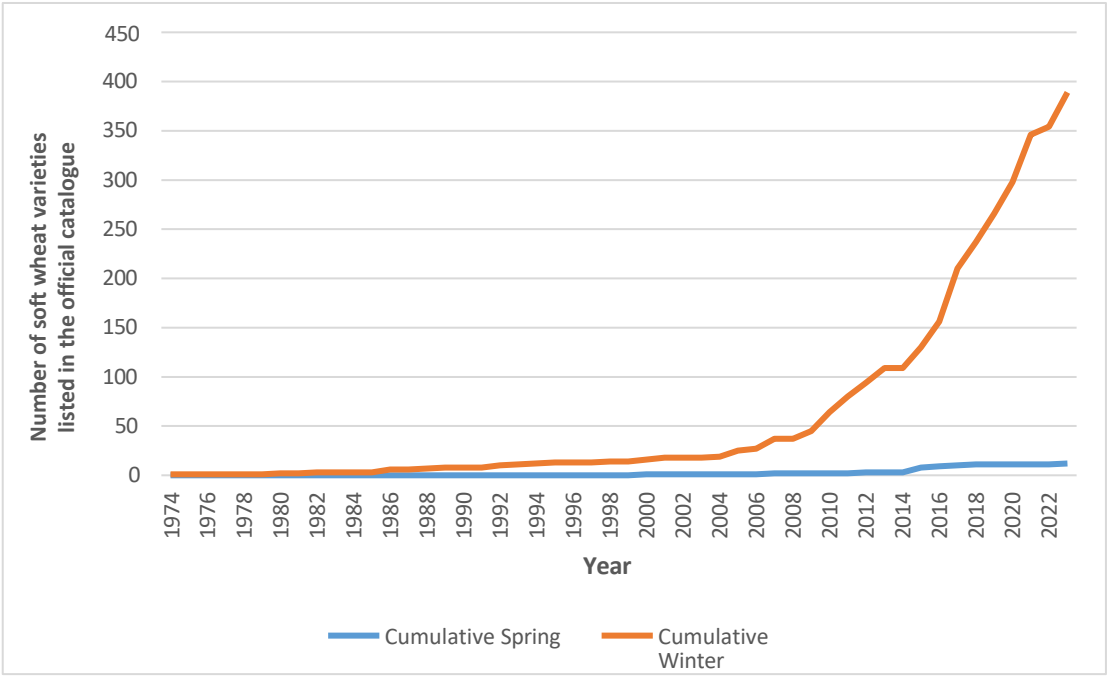


Figure 27. Change in the cumulative number of soft wheat varieties authorised annually between 1965 and 2022 (taken from the official catalogue of plant species and varieties grown in France - GEVES).

According to SEMAE figures for 2022, there will be far fewer breeders in France than previously indicated: **21** breeders create straw cereal and protein crop varieties (of which soft wheat is one).[79].

There are **89** seed producers of these species, **826** distributors and 5997AMS in 2022.

Soft wheat seed production will occupy **66,710** hectares in 2023 according to the SEMAE website consulted on 27/11/2023 (**Figure 28**). It is concentrated mainly in the north of France.

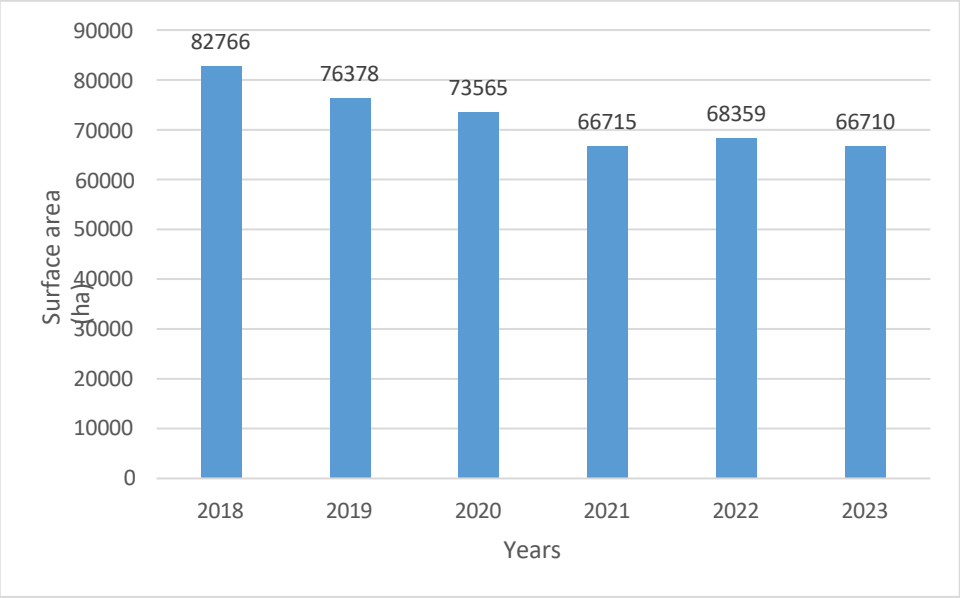


Figure 28. Agricultural areas used for soft wheat seed multiplication in France (taken from the SEMAE website, consulted on 27/11/2023)

In order to **import common wheat seed,** operators must be certified. Agricultural seed may only come from countries that have obtained equivalence with the European Union (Council Decision 2003/17/EC on the equivalence of field inspections carried out in third countries on seed-producing crops and on the equivalence of seed produced in third countries). For seeds treated with plant protection products, the treatment product must be approved in France. In order to be marketed in the European Union, seeds of these varieties are subject to "product" certification. This certification is compulsory and official. It is set up by the public authorities in each Member State (packaging bears blue labels).[80].

According to Agreste, there were 150,762 **soft wheat** farms in France in 2020. According to figures from the SAA (Agreste), around 5 million hectares will be farmed in France in 2021[81] to produce common wheat. The area devoted to soft wheat production has been decreasing slightly since 2016 (**Figure 29**), and is almost exclusively devoted to soft winter wheat.

[79] This difference in figures can be explained in the same way as for tomatoes (see footnote 60).
[80] Source: SEMAE website
[81] SAA data from 2010 to 2021 are studied, as data for 2022 are considered provisional by Agreste.

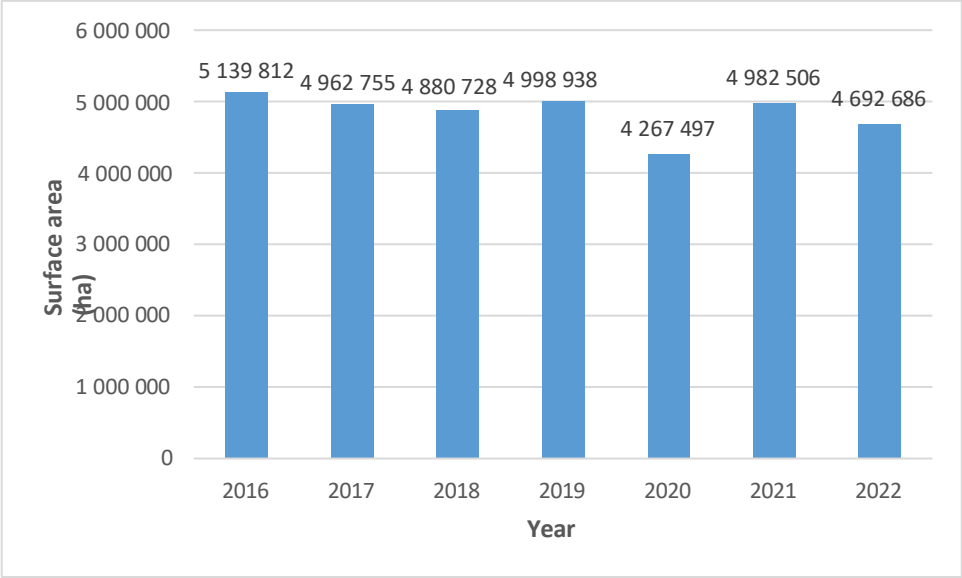


Figure 29. Soft wheat production areas in France between 2016 and 2022 (from Agreste)

In 2022 (provisional figures), France produced almost 33.7 million tonnes of soft wheat (**Figure 30**), almost all of which (99%) was soft winter wheat (and spelt).[82].

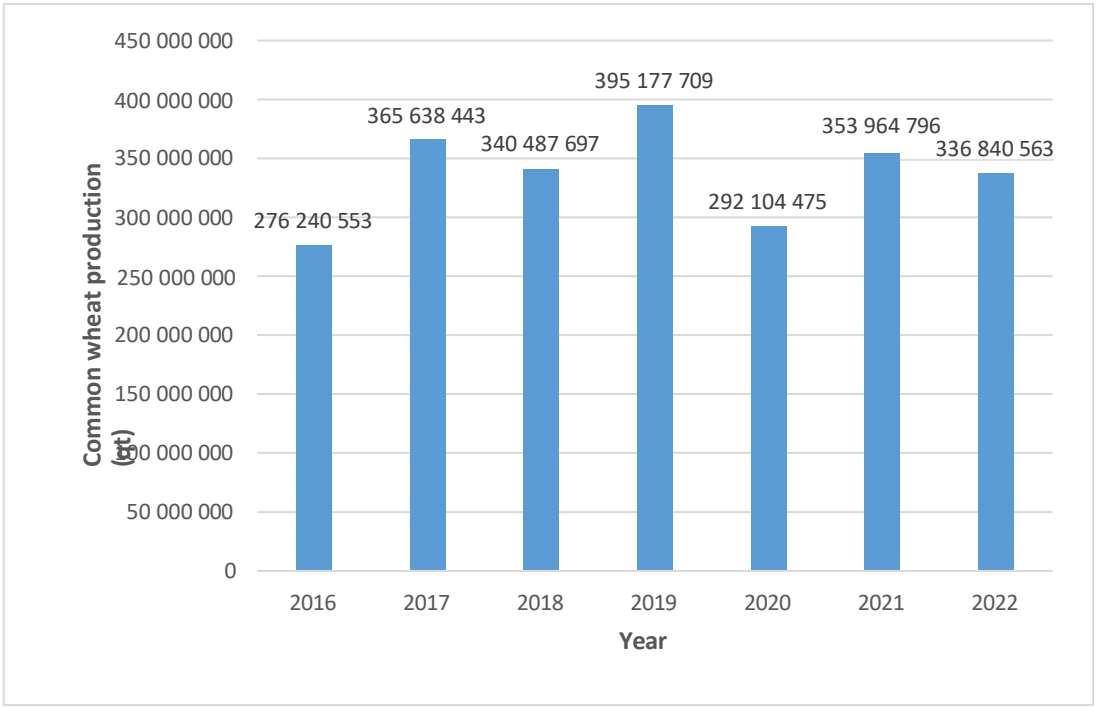


Figure 30. Soft wheat production trends in France between 2016 and 2022 (from Agreste)

According to FranceAgriMer's soft wheat data sheet, of the 35.4 million tonnes (Mt) of soft wheat produced in 2021, 3.1 Mt will be stored and consumed on the farm, 16 Mt will be destined for the French market and 16.9 Mt for **export**, i.e. 48% of production. 8,8

[82] Source: Annual Agricultural Statistics, Agreste

million tonnes were exported to third countries[83]Algeria in particular (29% of French exports according to Businesscoot 2021[84]) and China[85]. The import-export balance for soft wheat is positive. According to the FranceAgrimer bulletin, wheat plays a very favourable role in the balance of trade (**Figure 31**).

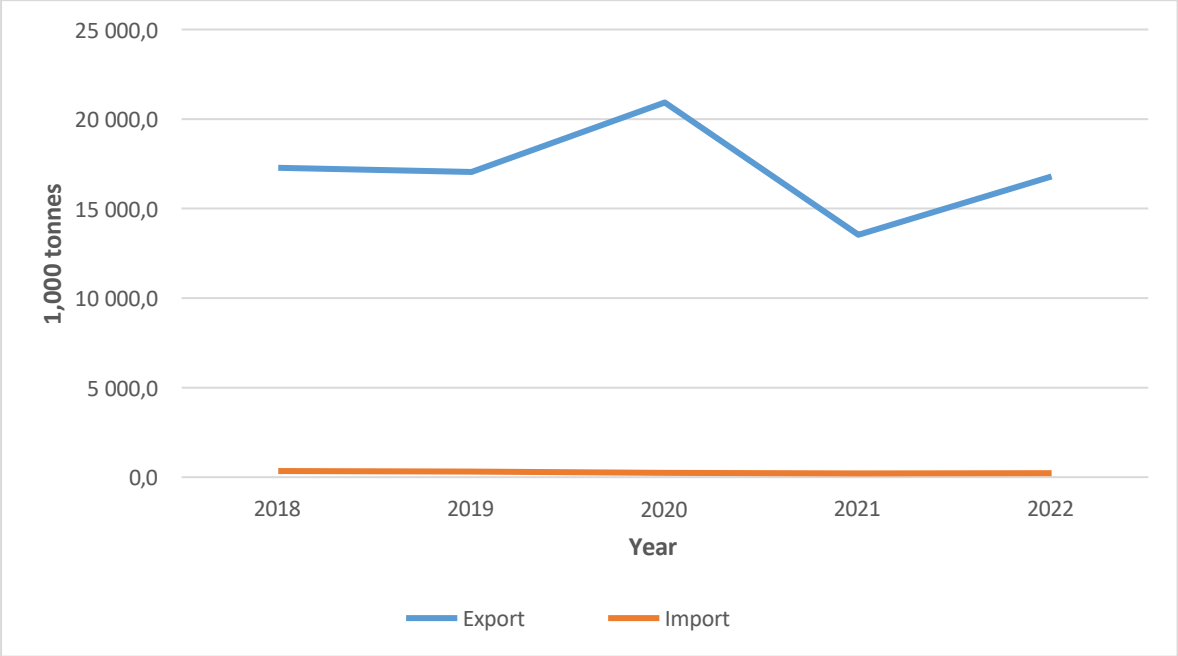


Figure 31. French soft wheat trade balance between 2018 and 2022 (taken from the FranceAgrimer bulletin)

Once produced, the wheat is collected by cooperatives or traders. Half of the production is sold to domestic processors. The latter process the soft wheat either to produce animal feed (in 33% of cases) or for human consumption. The milling and starch/gluten industries each use a fifth of the wheat used by processors (20% and 19% respectively). More than a tenth (11%) is used to manufacture alcohol and less than a tenth (8%) is used by the biscuit/biscuit/pastry-making industry (FranceAgriMer, **Figure 32**).

[83] Third countries are countries outside the European Union.
[84] The wheat market in France, Businesscoot, 20/04/2021
[85] According to the Perspective-agricole website, China is the second-largest destination for French wheat exports outside the EU after Algeria, and France will be China's third-largest supplier of soft wheat in 2021.

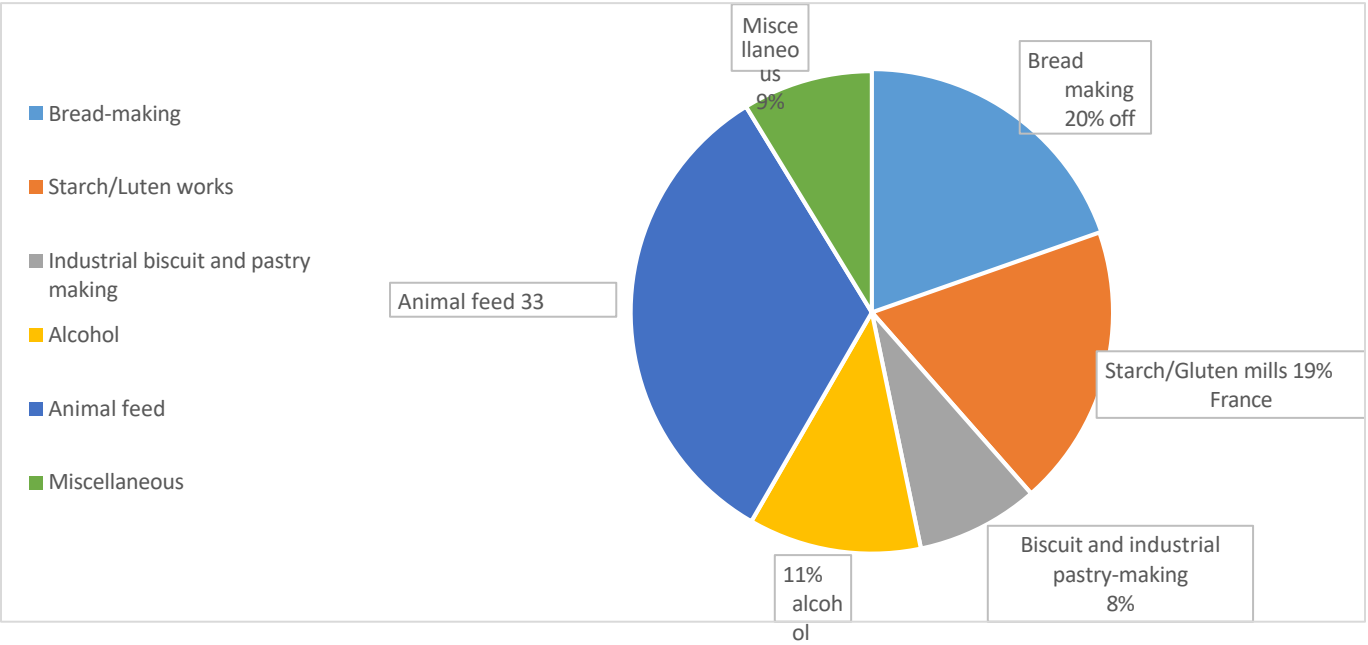


Figure 32. Soft wheat use in France in 2022 (from FranceAgriMer)

In 2022, according to a statistical study by the French National Milling Association (ANMF), the French milling industry comprised 395 mills belonging to 337 companies. It employed around 6,100 people. It uses 5.1 million tonnes of wheat and produces 3.96 million tonnes of flour, 99% of which is French wheat. 3.92 million tonnes of flour were marketed in France in 2022 (T65 wheat flour is the main type), 63% of which was used for bread-making. According to the ANMF, flour production and the number of mills fell between 2015 and 2020, only to rise again slightly in the last two years (although without returning to its 2015 level) (**Figure 33**).

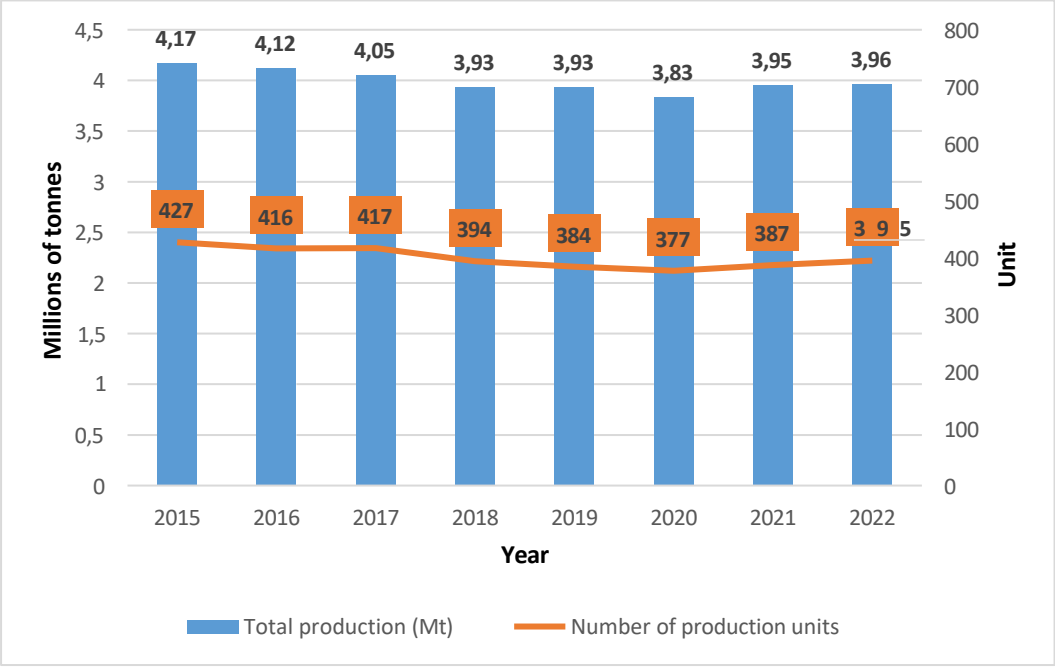


Figure 33. Flour production and number of mills in France from 2015 to 2022 (from ANMF)

The milling industry is made up of a wide variety of companies and mills. The vast majority of companies (77%) and mills (71%) crush less than 5,000 tonnes a year (**Table 7**).

Overwhelming companies	Companies	% companies	Crushing in Mt	% crushing
>150 000 t	6	2 %	2,79	55 %
>50,000t and <150,000t	15	4 %	1,27	25 %
>5,000 and < 50,000t	55	16 %	0,82	16 %
< 5 000t	261	77 %	0.22	4 %
Total	337	100 %	5,10	100 %

Table 7. Market structure of the French milling industry **(**ANMF data)

According to the ANMF, flour produced from common wheat is mainly intended for human consumption, which accounts for over 98% of flour use. Bakeries and breadmakers account for 58% of flour users. According to Intercéréales, the French cereals trade association, there were 35,000 bakeries in France in 2021, employing around 180,000 people. According to Intercéréales, small-scale bakeries had a 55% share of the market. Industrial bakeries would employ 50,000 people in 2021 and 48,000 in 2020.

According to the ANMF's 2022 statistics sheet, Europe is the leading destination for wheat flour **exports** (80%) in 2022, notably Spain (23%), Ireland (19%), Belgium (11.5%) and the UK (7.9%). Germany accounts for just 4.3% of French exports, but 67% of our **imports**. It should be noted that France imports more flour than it exports, and has done so since 2018 (**Figure 34**).

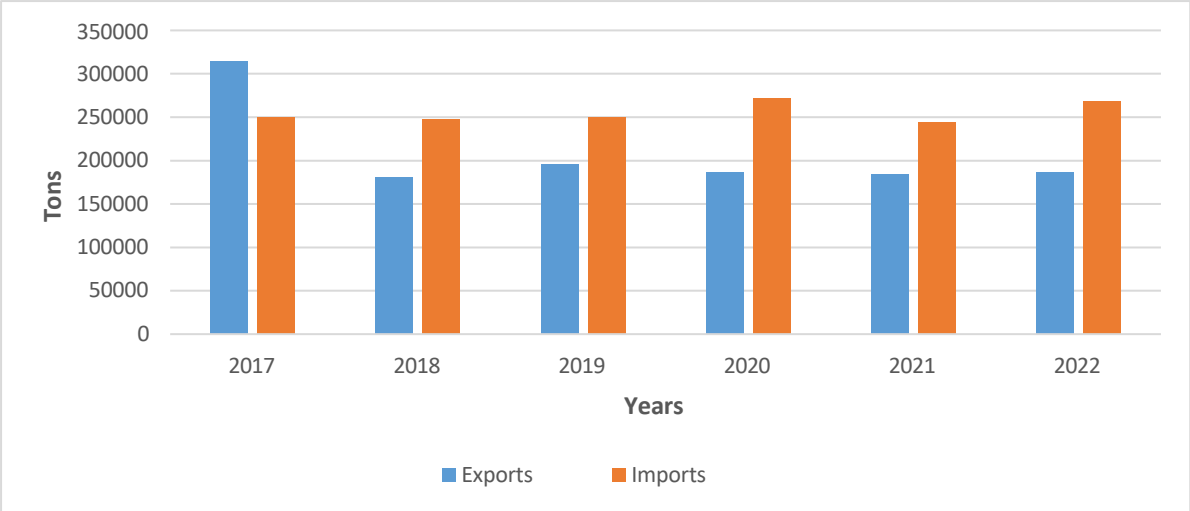


Figure 34. French soft wheat flour imports and exports between 2017 and 2022 (from ANMF)

The fact that France is both an importer and exporter can be explained by intra-branch trade. Imported and exported flours may have different qualities or different uses. According to the France Grandes Cultures website, the main difference is due to packaging. The vast majority of mills in France produce 10 or 25 kg bags for use by manufacturers and bakers. The market for small packagings intended for mass distribution, 500 gram or 1 kg bags, requires specific bagging lines, which are longer and more restrictive than large packagings. Small packs are mainly manufactured in Germany, where production costs are lower, and to a lesser extent in Italy. Commercial strategies to avoid customs may also explain this trade.

In terms of **consumption**, after bakeries, food industries such as biscuit manufacturers are the biggest consumers of wheat flour, with 28% of the flour produced consumed by this industry. The biscuit industry represents 115 production units and employs 12,133 people. Despite the number of production units, the sector is oligopolistic[86] Only 4 companies accounted for 85% of production in France in 2018, according to a 2019 FranceAgrimer study.[87]. In 2021, according to Intercéréales, the industry used more than 1 million tonnes of soft wheat flour to produce 921,773 tonnes of biscuits and cakes, 60% of which were sold to French supermarkets, with the remaining 40% being exported.

A small proportion of the flour (5%) is used by supermarket laboratories, in other words the bakery and pastry shops of supermarkets. The same proportion is used for household flour sachets. This rate is set to rise to 6% by 2022. Given the development of household bread production, this rate could increase in the future.

Conclusion

Despite a positive trend in varietal development in France, the area used for soft wheat seed multiplication is shrinking, while the area used for soft wheat production remains constant. However, this has not affected the trade balance. The common wheat sector is very well integrated into international trade, and plays a very favourable role in the trade balance. Common wheat exports are 79 times greater than imports.

Given the interdependence between the various players in the sector and the integration of the common wheat sector into international trade, the introduction of NTG plants or products into the European Union or elsewhere could have an impact on the sector and on France's balance of trade.

[86] A market in which a small number of companies compete for a large number of buyers.
[87] Competitiveness of secondary processing products in the French agri-food industry.

7.2.4 Description of the vine industry in France

Any seed or plant to be propagated is registered in the National Catalogue, the vat varieties are classified for vinification and marketing of wine (website of the French Institute of Vine and Wine, IFV[88]) and approved clones.

In the catalogue of **varieties authorised** in France, consulted on 17/09/2023, 153 vine varieties are listed, 105 of which have a breeder and 151 of which have a maintainer. France has 20 breeders and 17 maintainers at most. Of the 153 varieties, 41 (27%) are declared "1 is declared "hybrid" (7%) and 1 is declared "lineage" (7%).[89]. The first variety was registered in 1975 and the last in 2023. Half of the registrations took place after 2010 and a quarter after 2016.

Figure 35 shows changes in the cumulative number of vine varieties authorised each year, which has risen sharply over the last ten years (varieties that have been cancelled but can be marketed are not included in this graph).

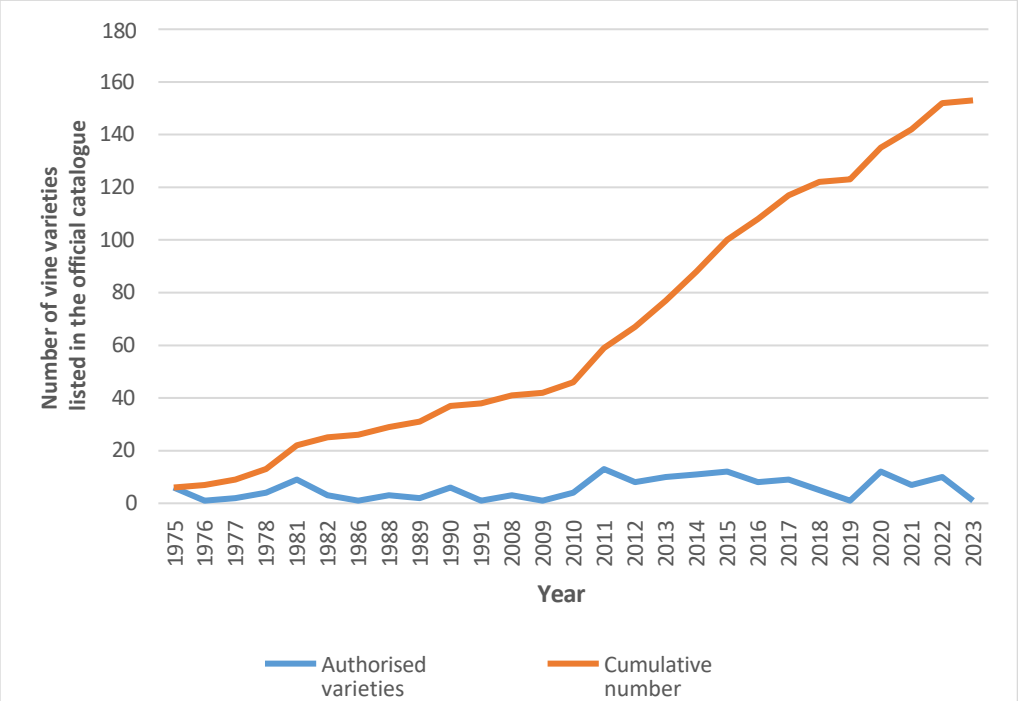


Figure 35. Change in the cumulative number of vine varieties authorised annually between 1975 and 2022 (taken from the official catalogue of plant species and varieties grown in France - GEVES).

According to the IFV website, the industry has organised a pyramid-shaped propagation process involving three categories of material: initial material, basic material and certified material. The **initial material** is produced from the head of the clone and allows the installation of pre-multiplication plots. These will enable the production of **basic material**, which can be used to plant mother vines for grafts or rootstocks at nurseries or winegrower-propagators. The result is the mass production of **certified material** (grafts and rootstocks) used by winegrowers. This material is marketed with a blue label. For material not produced by this selection process, it is marketed as "standard material" with yellow labels (site

[88] https://www.vignevin.com/article/histoire-dun-plant-de-vigne-de-linitial-au-certifie/ consulted on 06/12/2023
[89] The remaining percentage corresponds to vine varieties declared "unknown".

Geves website[90]With regard to **production**, the number of professionals registered to inspect wood and vine plants will be 794 in 2022 (**Figure 36**). This number has fallen by 3.6% in one year and by 11.2% in 3 years (i.e. 100 fewer professionals).

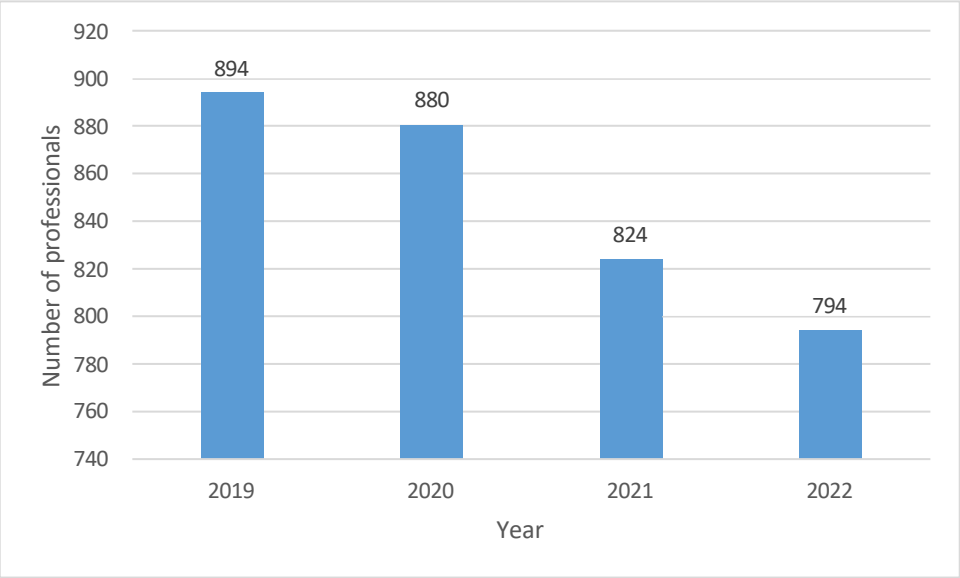


Figure 36. Number of professionals registered to inspect wood and vine plants between 2019 and 2022 in France (from FranceAgrimer)

According to FranceAgrimer, the 794 vine professionals are made up of 433 plant producers (compared with 523 in 2017, a drop of 17% in 6 years) and 219 merchants (a number that has remained stable for 6 years).

Plant producers are located close to the major wine-producing areas. Nearly a third of plant producers are located in south-east France (Provence-Alpes-Côte d'Azur and Corsica) and nearly a quarter in south-west France (New Aquitaine).

The stock of mother vines comprises 3,981 hectares, 60% of which (2,356 ha) is made up of rootstock mother vines and 40% (1,625 ha) is made up of graft mother vines (FranceAgrimer, key figures for the sector). Since 2018, the surface area (ha) of rootstock mother vines and graft mother vines has only increased before decreasing in 2022 (**Figure 37**, **Figure 38**).

[90] https://www.geves.fr/expertises-varietes-semences/vignes/commercialisation-semences-plants/, consulted on 21/11/2023

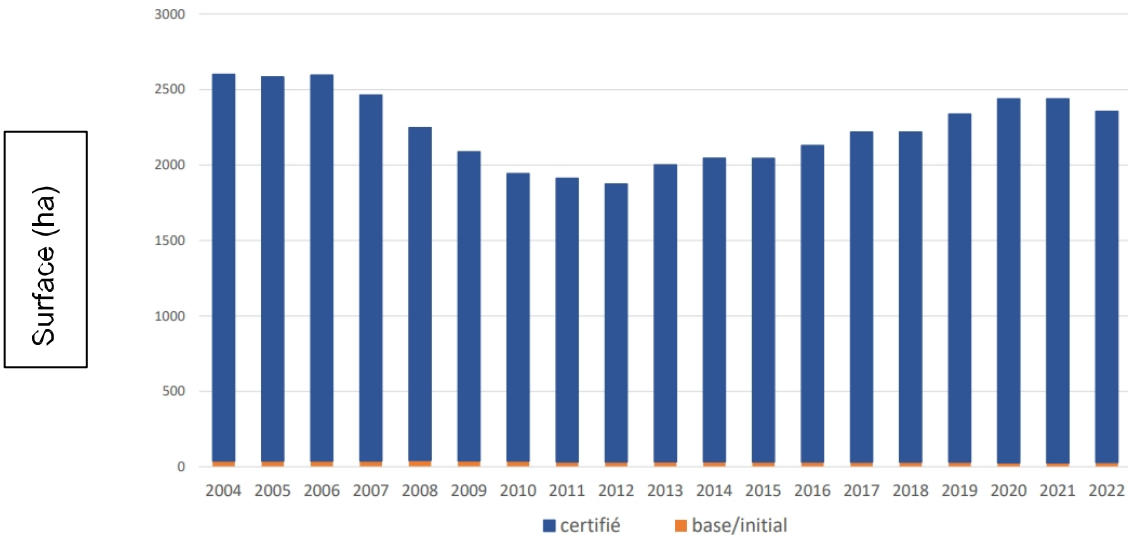


Figure 37. Change in the area (ha) under rootstock parent vines in France (from FranceAgrimer, key figures for the wine nursery sector 2022)

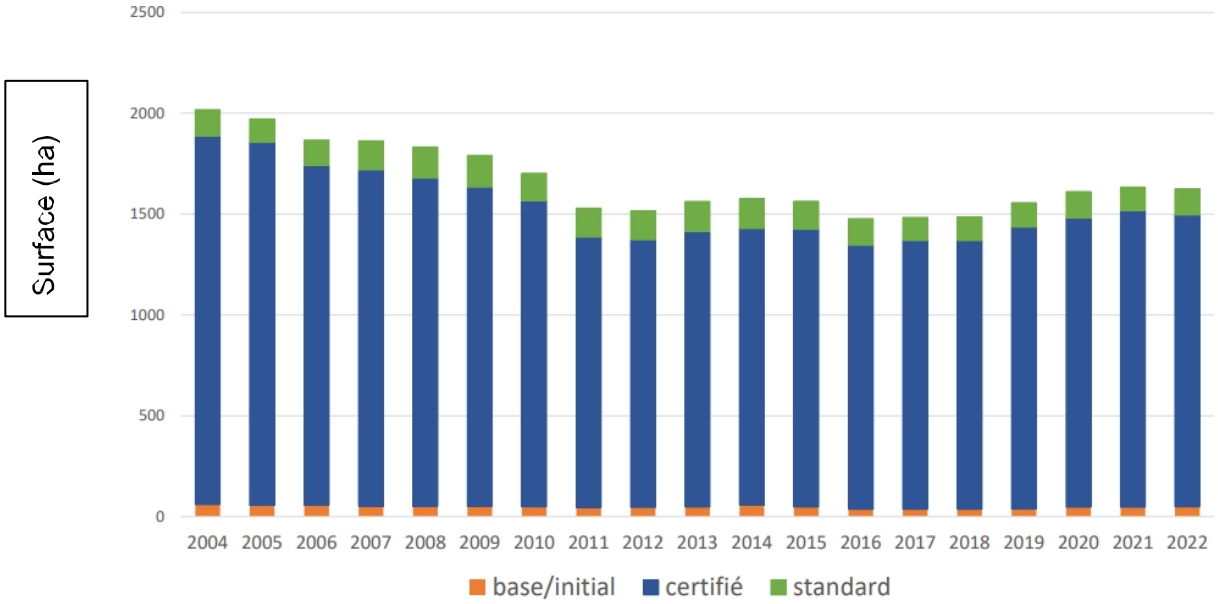


Figure 38. Change in area (ha) under **graft** nurseries (from FranceAgrimer, key figures for the wine nursery sector 2022)

According to FranceAgrimer, the stock of mother vines is getting younger. More than half of the stock of graft nurseries (VMG) and rootstock nurseries (VMPG) is less than 15 years old. The majority of VMG and VMPG production areas are located in the south of France: 32% in the PACA region and 24% in Occitanie. The PACA region alone produces 42% of VMPG. However, the Nouvelle-Aquitaine region produces the most VMG (26%).

Despite the fall in the number of professionals and the fall in areas dedicated to the **production of wood[91] and vine seedlings**, the total number of seedlings used has risen from 220 million in 2021 to 235 million in 2022, according to FranceAgriMer.

[91] The vine shoots are sold for barbecues (they give a different flavour).

Part of the production of vine plants is **exported**. The three main destinations are Italy, Mexico and Spain, while Germany, Italy and Canada are the main export destinations for vine cuttings. Total exports of vine seedlings will be worth €20.8 million in 2022, and cuttings €4.8 million. According to FranceAgriMer, these values have fallen between 2020 and 2021. Imports are (at least) twice as low. Italy accounts for 87% of vine plant imports and 8% of cuttings imports, while Spain, although accounting for only 3% of plant imports, will account for 68% of cuttings imports into France in 2022.

After this stage comes the **production of grapes**.

According to Agreste, there were 70,266 grape-growing farms in France in 2020, with 795,426 hectares under cultivation in France in 2021.[92] 99% of which are used to produce wine grapes (for the production of wine, must and grape juice). The remaining 1% is used to produce table grapes. The area under grape production increased until 2020, before declining (**Figure 39**).

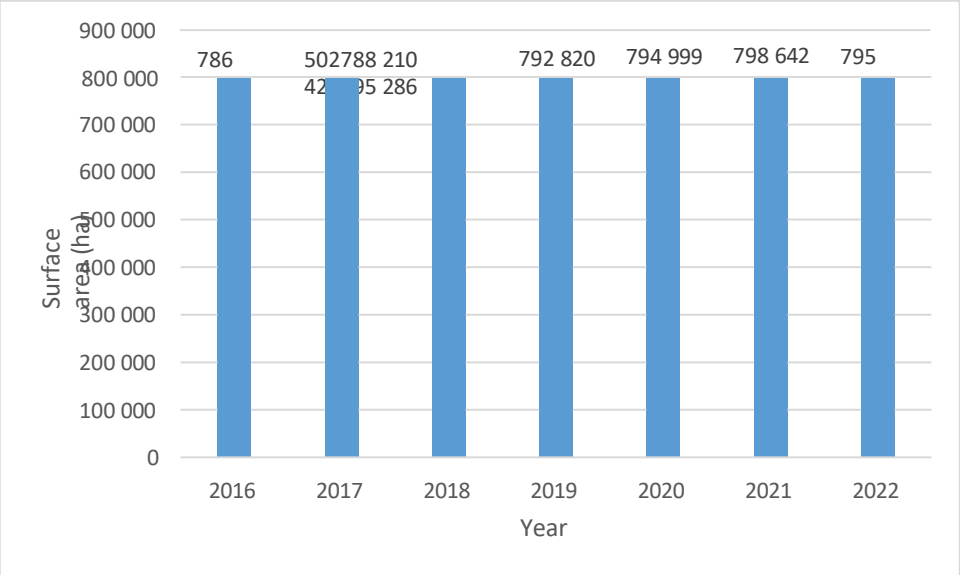


Figure 39. Grape production areas in France between 2016 and 2022 (from Agreste)

According to Agreste, France produces between 5 million (for the lowest harvests) and 6 million (for the highest) tonnes of grapes (**Figure 40**), almost all of which (99%) are wine grapes.

[92] Figures for 2022 are provisional.

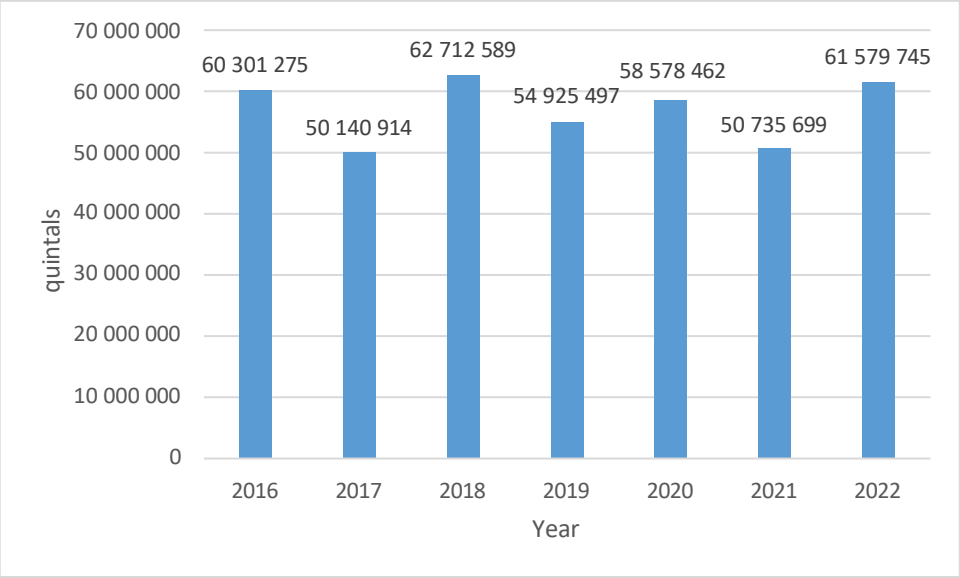


Figure 40: Grape production in France between 2016 and 2022 (from Agreste)

With this level of production, France will be Europe's second largest grape producer behind Italy in 2022 (Source: Eurostat). As for exports and imports, the only figures available concern table grapes. The lack of information on wine grapes can be explained by the special nature of this wine and its specifications, which include geographical indications.[93]. Exports and imports of table grapes amount to 114,510 quintals and 1,342,990 quintals respectively in 2021.

As far as **processing is** concerned, wine grapes are mainly used to produce wine or must. Grape juice production is fed by surplus wine production. PDO wine production will represent 43% of wine production in 2022, PGI wine 28% and wine suitable for cognac production 22% (**Table 8**). According to FranceAgriMer's "Wine sector" fact sheet, wine producers are organised into cooperatives (570 cooperative cellars accounting for more than 44% of the volumes vinified in France, excluding Cognac) and private cellars.

The négociants (700 wine merchants in France[94]) buy grapes, bulk wine or bottled wine, and vinify all or part of the grapes purchased or produced on their own estates.

The entire sector is grouped around 24 interprofessional associations for geographical indications (GIs) covering all vineyards, or at national level with an interprofessional association for wines without geographical indications. Actions to promote their wines, monitor markets and carry out research and development are financed by the interprofessions.

[93] Site of the Institut National de l'Origine et de la qualité (Cahier des charges (inao.gouv.fr)), consulted on 25/10/2023.
[94] Fiche filière du vin de FranceAgrimer, January 2022

Catégorie de vins	2022	2021	Moyenne 2017-2021	2022/2021	2022/ Moyenne 2017-2021
	millier d'hectolitres			%	
Vins AOP	19 581	15 976	18 921	23	3
Vins pour eaux-de-vie	10 281	9 533	8 951	8	15
Vins IGP	12 591	10 190	11 792	24	7
Autres vins (dont vins sans IG)	3 377	2 142	3 012	58	12
Total vins*	45 830	37 841	42 672	21	7

Table 8. French wine production in 2021 and 2022 (from Agreste)

AB production will account for 17% of total wine production and 21% of PDOs by 2020.

According to the FranceAgriMer fact sheet, French wine **exports will** total 14.6 million hectolitres, worth €11.1 billion in 2021. France is the world's third-largest exporter by volume, but the leading wine exporter by value. This is due to the high quality of French wines. In 2021, still PDO wines and Champagne will account for 49% and 32% respectively of the value of French exports. The United States, the United Kingdom and China are the main destinations for French wine exports. Exports have fallen slightly over the last two years, and the price of Appellation wines, with or without GI, has also fallen slightly.

The wine trade plays a favourable role in the trade balance (the balance is positive), with exports twice as high as imports (**Figure 41**).

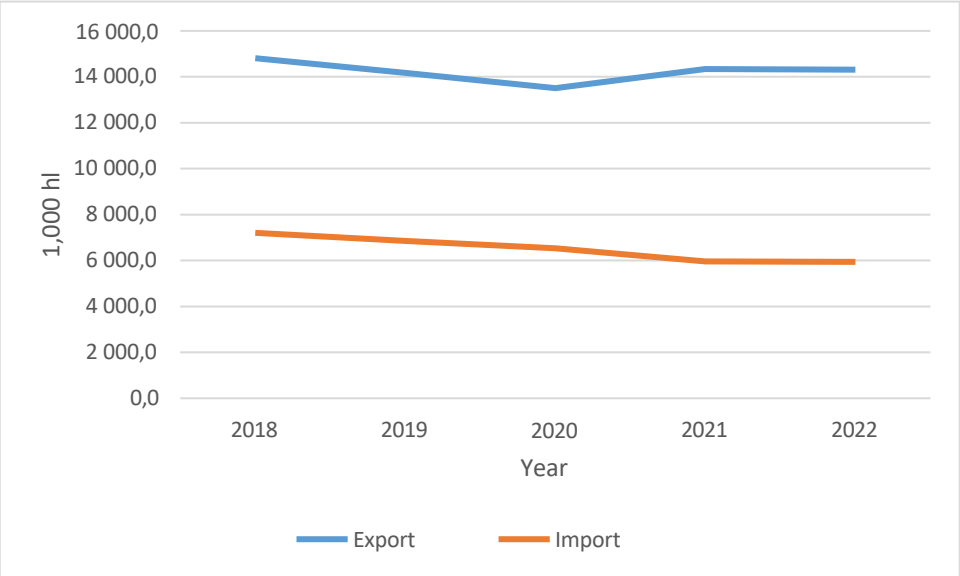


Figure 41. French wine trade balance between 2018 and 2022 (from FranceAgriMer bulletin)

It should be noted that the French offer is losing market share in lower-range wines. France mainly imports bulk wines and wines with no geographical indication in order to cover the demand for entry-level wines on its own market.

As far as **distribution** is concerned, only table grapes or products made by processing grapes from vats (wine, grape juice, must, balsamic vinegar) are distributed. For wine, the wineries sell their products to end consumers either directly or indirectly through distributors. Table grapes and grape juice are sold through wholesalers or retailers.

Conclusion

Varietal development in the vine sector has a positive dynamic. The areas used to propagate grape plants and those used for grape production have remained constant in recent years. Production, on the other hand, varies according to weather conditions and disease. These variations are mainly due to wine grapes, which account for 99% of grapes produced in France. Table grapes account for just 1% of grapes produced in France, with 45,726 tonnes produced in 2022.

Only the downstream players in the wine industry, processors and distributors, are heavily involved in international trade. Imports of table grapes (124,000 tonnes) are almost two and a half times greater than French production. Wine grapes, on the other hand, are not included in international trade, given the specifications for these wines. Wine production, on the other hand, is very well integrated into international trade, with exports twice as high as imports.

Given the specific features of the wine industry in international trade, the introduction of NTG plants or products into the European Union or elsewhere could have an impact not only on the "table grape" industry, which is dependent on imports, but also on the "wine grape" industry. The latter could be interested in NTG-derived plant varieties with increased resistance to pesticides and drought. This would require a change in specifications. However, the use of such plants could damage the quality image of French wine. The introduction of NTG plants or products could therefore have an impact on France's trade balance through the wine industry.

7.2.5 Conclusion concerning the description of the sectors in France

The description made it possible to identify the different types of players and to perceive the stakes for the industry if NTGs were introduced. However, given the absence of plants derived from NTGs or their by-products in France, no impact analysis could be carried out.

7.2.5.1 Varietal development and production

Variety creation is a dynamic sector for all four sectors, although to a lesser extent for the carrot sector. This dynamism does not always translate into dynamism in production. In fact, in recent years, production of

tomato production is tending to fall, soft wheat production is not changing, grape production is fluctuating with no clear trend, and carrot production, a sector where there is the least variety creation, is increasing. These different trends are linked to the strategic choices made by producers (the choice of high quality tomatoes), weather conditions, prices and diseases (vines).

7.2.5.2 International trade

The four sectors are not equally dependent on international trade.

The tomato and carrot sectors depend on imports to meet demand. Each imports twice as much as it exports. The carrot sector imports almost exclusively from the European Union, while the tomato sector depends mainly on countries outside the EU. Morocco alone accounts for 66% of tomato imports into France.

The wine industry is differently integrated into international trade depending on whether the grapes are table or wine grapes. Imports of table grapes are significant, while imports of wine grapes are non-existent (according to the various institutions that record trade). The wine industry is highly integrated into international trade. Unlike the first two sectors above, this sector exports more than it imports, and imported wines come primarily from Italy, a member of the European Union.

The soft wheat sector is very well integrated into international trade, and plays a very favourable role in the trade balance. Exports are 79 times greater than imports of common wheat.

7.2.5.3 Prospects for the sectors in the event of NTG being introduced

Given the specific characteristics of each sector, it is likely that the introduction of NTG plants or products into the European Union will not affect them in the same way. The effects could be significant for sectors that are highly integrated into international trade. Industries that are dependent on imports, such as tomatoes and carrots, could be encouraged to use NTG-derived varieties in order to become more competitive. As for the soft wheat sector, the introduction of plants or products from NTG could enable it to maintain its market share. The wine grape sector could be tempted for the same reasons, but this would require a change in specifications and could have an impact on the quality image of the wine. Finally, industries that are highly dependent on non-EU countries will be affected to a greater or lesser extent depending on the regulations governing NTG-derived plants.

7.3 Method for analysing the socio-economic issues associated with plants derived from NTGs

To analyse the socio-economic issues associated with plants and products derived from NTGs, a systematic review of the literature was carried out. The socio-economic issues are analysed under the following headings:

- The supply of plants and products obtained using NTGs in relation to the legal aspects of intellectual property rights, patents and licensing.
- NTG adoption dynamics and impacts upstream of the supply chain
- Trade, competition and international impact
- Coexistence, segregation costs, contractual relations and market segmentation
- Consumers and NTGs
- Choice of regulation
- Identifying stakeholder positions and controversies surrounding NTGs
- Controversy governance

In addition to the scientific controversies over the potential impacts of plants and products derived from NTGs, the last two themes enable us to understand the points of divergence between the different types of stakeholders concerned by NTGs and the impact of the governance of these controversies (i.e. the political consideration given to the different visions and debates on the subject) on the positions of the stakeholders.

For each of these themes, an initial literature search was carried out to analyse the socio-economic issues by searching the Scopus and CAB Abstracts databases using keywords defined for the different themes identified. Details of the PICO structure used in this systematic review are presented in Appendix 9 of the report.

A search of the 2 bibliographic databases identified 96 references selected after sorting by title and abstract and sorting by full text[95]. It should be noted here that this search was carried out both on original articles and on reviews and meta-analyses on the socio-economic issues associated with plants and products derived from NTGs. Only articles in English published in peer-reviewed journals were included in the analysis.

The topic of "NTG supply in relation to the legal aspects of intellectual property rights, patents and licensing" was analysed through a hearing of experts from outside the WG. Mr Fabien Girard (Senior Lecturer in Private Law at Grenoble Alpes University, Centre de Recherches Juridiques, junior member of the IUF) and Mr Stéphane Lemarié (Director of Research at INRAE, Grenoble Applied Economics Laboratory) were interviewed on 24 January 2023. A questionnaire containing the WG's main questions was sent to the experts prior to the hearing (see Appendix 10). Information from the hearing is also used in the treatment of the topic concerning "NTG adoption dynamics and impacts upstream of the sectors".[96].

Stakeholder hearings were also held to provide an understanding of the socio-economic issues and the positions of the various types of players potentially affected by plants and products obtained using NTGs. Between June and July 2023, 9 stakeholders sitting on the dialogue committee
"biotechnologies" of the Anses were interviewed:

- National Federation of Farmers' Unions (FNSEA)
- France Nature Environnement (FNE)
- Federation of Commerce and Distribution (FCD)
- Syndicat des entreprises bio agroalimentaires (Synabio)
- Confédération Paysanne

[95] See Appendix 9 for the list of keywords used in the bibliographic search and the article selection process.
[96] See appendices 10 and 11 for the questionnaire and the minutes of the hearing.

- Groupement national interprofessionnel des semences et plants (Semae)
- National Federation of Organic Farming (FNAB)
- National Association of Food Industries (ANIA)
- National Council of Secular Family Associations (CNAFAL)

Of the stakeholders initially approached, UFC Que Choisir did not respond to the WG's request and was replaced by the CNAFAL (Conseil National des Associations Familiales Laïques) as the consumer representative. The stakeholder hearings are not intended to be exhaustive in terms of the stakeholders potentially affected by NTG plants and products. However, they have been chosen by the WG in such a way as to ensure that they are properly representative of these stakeholders.

A questionnaire was sent to the interviewees at least one week before the interview.[97]. Information from the hearings was used to support certain points raised in the analysis of controversies based on the scientific literature (see section 7.4.2.7). The verbatim reports of the hearings and a table summarising the main points of view of stakeholders (see section 7.4.2.7; Table **10**) were validated by the people interviewed. For more details, the verbatim transcripts of the hearings are attached to the expert report.[98]. A second literature search was carried out to produce a critical analysis of the results of the literature on the socio-economic issues associated with plants and products derived from NTGs. This critical analysis is based on the literature on transgenic plants. The bibliographical search was also carried out on Scopus and CAB Abstracts, taking into account the themes in the two registers identified by the WG by replacing the keywords relating to NTGs with keywords relating to GMOs (cf. appendix 9). In view of the abundant literature on transgenic plants and the time required to process the report, only meta-analyses and literature reviews were selected. A total of 18 meta-analyses and literature reviews were identified. However, these studies must be treated with caution, both because of certain methodological limitations (most of the meta-analyses published do not follow the procedures recommended today, particularly in terms of transparency in the selection of articles retained; the studies summarised are generally based on very heterogeneous approaches and data, etc.), and because most of these studies are based on data collected in the early 2000s, and therefore do not allow us to know whether these conclusions would be confirmed over the long term. In view of these limitations, an analysis of these publications is appended to the report (see Appendix 13).

7.4 Socio-economic issues associated with NTG plants and products

Documenting and analysing the socio-economic issues associated with plants and products obtained using NTGs is a prerequisite for a better understanding of the impact of these technologies on the sectors. **The aim of this section is to describe the socio-economic issues associated with NTG-derived plants and products for the various players involved.**

[97] The questionnaire for the hearings is presented in Appendix 12.
[98] The verbatim transcripts of the hearings are available online via the link in Appendix 13.

without going as far as an analysis and quantitative assessment of the associated impacts (which are outside the scope of the referral).

7.4.1 Socio-economic mechanisms involved in NTGs

Generally speaking, the literature analysed emphasises that the economic and social impact of the use of NTGs on the sectors will depend first and foremost **on the regulatory choices** made at European level. By affecting the economic trade-offs of the various types of players as a result of regulatory constraints involving additional costs (including in terms of time and responsiveness), these will have a direct influence on the incentives to develop and adopt these techniques. This will determine (i) the risk assessment procedures and the methods used to regulate marketing authorisations for seeds obtained using NTGs (which will have an impact on R&D costs), and (ii) the methods used to identify (detection and labelling) products derived from plant varieties obtained using NTGs on the markets, and those used to ensure their coexistence with products derived from varieties not obtained using NTGs (which will have an impact on segregation, control and preservation costs).[99]control and preservation of product identity). In addition, the degree of harmonisation and synchronisation of regulatory developments between countries may influence the choices made by players and have major effects on the place of plants and products obtained using NTGs in international trade.

The economic and social impact of plants and products obtained using NTGs will also depend on the **nature of the traits** being innovated. On the basis of the literature, innovations can be distinguished according to the objectives pursued by the players who develop them (objectives which may overlap):

- Varietal innovations aimed at increasing the **effectiveness and/or efficiency of agricultural and agro-industrial production.** The main objective here is to reduce unit production costs and, for the same product range, seek to be more price-competitive, for example through traits that increase yields, provide resistance to certain herbicides (Wan et al. 2021), improve product health (e.g. reduction in mycotoxins) or improve the ability to extract substances from agricultural raw materials for industrial purposes (e.g. carotene as a natural colouring agent). We can assume that it is the economic interests of producers and the upstream levels of the sectors that will be decisive in the development and adoption of these innovations for this objective of effectiveness and/or efficiency.
- Varietal innovation as part of a **product differentiation and diversification strategy** on the part of companies in the sector. The marketing of varieties with new properties (e.g. allergen-free products, different sensory and nutritional qualities, etc.) may meet the needs or expectations, expressed or more latent, of certain consumers. The success of these innovations will depend directly on the acceptability and willingness of consumers to pay for these distinctive characteristics (Bearth et al. 2022), but also on the marketing conditions for the new varieties (size of

[99] Segregation costs refer to all the investment and expenditure involved in cleaning equipment and infrastructure to ensure a NTG-free product.

markets concerned, degree of acceptability of NTGs, margins for industry players, etc.). While these innovations seek to improve the non-price competitiveness of professionals, the production costs of these innovations and the ability to generate margins for players will remain important for their adoption.

- Varietal innovations designed to **meet environmental, health and/or social challenges**, particularly those associated with climate change. This last type of innovation can sometimes also meet the economic and financial objectives of industry players (securing production in a context of uncertainty, reducing yield losses in deteriorating water conditions, etc.), encouraging their adoption. However, this is not automatically the case, as shown by the example of intermediate crops between two cash crops that can be used to provide permanent soil cover, but which have few or no commercial outlets (Jordan et al. 2022). The private costs of these environmental or health innovations may exceed the anticipated private benefits. This shows the importance, if net collective benefits (economic cost/benefit or environmental risk/benefit balance) are proven, of public support to encourage their development, production and adoption.

The literature analysed also notes that the economic and social impacts associated with plants and products obtained using NTGs will also depend on the **intrinsic characteristics of these technologies** (Bartowski et al. 2018), such as their development costs, the traceability issues they raise, or the speed of scientific advances in the field. The question here is, in particular, whether these intrinsic characteristics can make it possible for developments to differ from those observed in the case of plants derived from transgenesis.[100].

Finally, publications on the possible impacts of plants and products obtained using NTGs lead us to consider **different time horizons**[101]. In addition to short-term effects, long-term issues need to be considered in relation, for example, to the dynamics of the European varietal research and development sector, or that of the agricultural and food model. These issues have economic components, but they are also part of broader questions (political, ethical, societal). They give rise to confrontations between highly differentiated stakeholder positions, reflecting the controversies on the subject (see section 7.4.2.7). They raise questions about the governance arrangements put in place to express agreements and disagreements on the role of NTGs in the development of the agricultural and food sectors (Bechtold, 2018). These modes of governance may themselves have economic and social impacts, for example by reducing or increasing uncertainties about future modes of regulation (cf. section 7.4.2.8).

Figure 42 identifies the main points on which the economic and social impacts associated with the introduction of plants and products obtained using NTGs need to be considered (right-hand side of the figure). The socio-economic literature available is fairly limited and largely made up of *position papers dealing with* the challenges of these innovations rather than their impacts (see Lemarié and Marette, 2022 for a summary of the economic literature on the subject). Few empirical studies have been conducted to date. A few articles are based on survey data and, in a way, make it possible to assess the impact of these innovations.

[100] As NTGs are considered to be GMOs under current regulations, the term GMO is used in the remainder of this document for applications resulting from transgenesis compared with NTGs.
[101] It should be stressed here that this time/risk dimension is increased for perennial crops such as vines. The costs of an NTG passage are concentrated, while the benefits are uncertain and diffuse.

However, few studies have quantified the real impact of choices to regulate plants and products obtained using NTGs on seed prices, agricultural and food prices, costs and gains for the sectors, or the economic risks for the various types of player. Quantitative assessments are therefore very partial. They are mentioned when they are available, specifying the origin and nature of the data used.

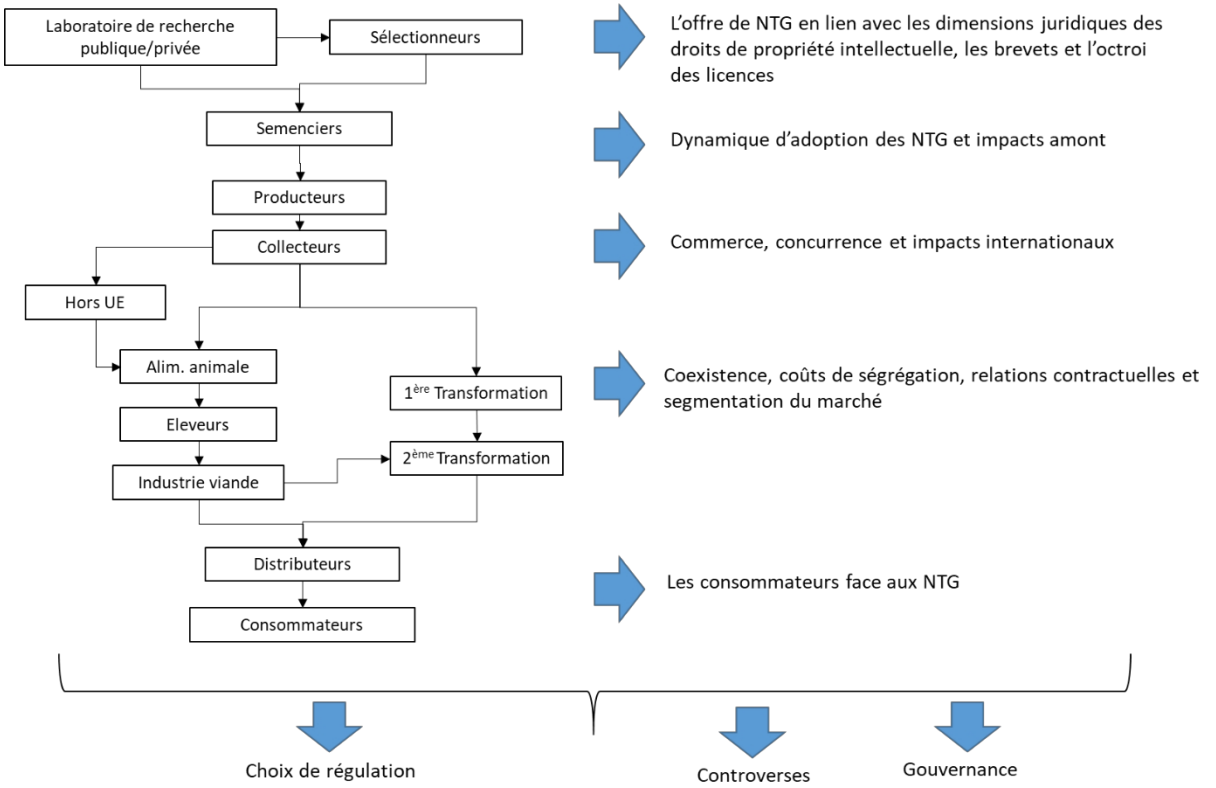


Figure 42. Conceptual diagram of the analysis of the socio-economic issues associated with NTG plants and products.

As NTG-derived plant varieties are not currently on the European market, the analyses are prospective and aim to assess the possible economic and social impacts that would result from the strategies of the players and public regulatory choices. Assessment of these possible impacts presupposes that the NTG-derived plants under consideration have been subject to a health or environmental risk assessment (if they are not considered equivalent to conventional plants). The abundant literature on GMOs derived from transgenesis can provide benchmarks and illustrate certain economic mechanisms. **However, most of the elements in the available economic literature on plants and products obtained using NTGs should be considered as hypotheses that have yet to be confirmed rather than as proven results.**

The WG's approach of comparing NTGs with the first GMOs may have certain limitations, given the differences between the two technologies. Other approaches, using examples that are completely external to the seed sector, could prove just as relevant in helping to consider possible developments in the absence of data. However, the WG has chosen to compare the situation of plants obtained by means of NTGs with that of plants obtained by transgenesis, given that the regulations in force

makes no distinction between the two types of technique in the context of plant breeding.

7.4.1.1 The supply of plants and products obtained using NTGs in relation to the legal aspects of intellectual property rights, patents and licensing.

This section presents the different forms of intellectual property rights in the field of plant breeding (see Box 1). However, it does not deal with the coexistence of the plant variety certificate (PVC) and the various types of patent. The legal aspects relating to the inclusion of varieties in the catalogue were not addressed during the expert hearings. These aspects, which may represent major issues, have been the subject of several HCB reports[102].

Box 1: Regulatory landscape for plants

When it comes to plants, there are two industrial property rights that apply in Europe: plant breeders' rights and patents.

Plant variety rights

The plant variety certificate (PVC) for seeds was created by the Paris Convention of 2 December 1961 (known as the UPOV Convention, the latest version of which dates from 19 March 1991)[103] and has been incorporated into French law since 1970. Regulation (EC) No 2100/94 of 27 July 1994[104] now makes it possible to obtain a PVC valid throughout Europe.

In the European context, a plant variety can only be protected by a PVC (and not by a patent)[105]. This protection is based on a set of criteria that give the new plant variety its DUS characteristics (distinctness-homogeneity-stability).

Industrial property rights give the holder of a plant variety a monopoly on exploitation for a period of 25 to 30 years. Exclusive rights apply only to products, allowing breeders to reproduce processes to obtain other marketable varieties. Since the 1991 revision, the farmer's right to resow (farm-saved seed) has been an (optional) exception to the breeder's right. It is known as the "farmer's privilege" and is tightly controlled.

All breeders also benefit from the breeder's privilege, which allows them to use a protected variety as a source of variation. A breeder does not need the consent of the breeder of another protected variety, either to develop his new variety or to market it. The consent of the breeder of the initial variety is only required if the production of the new variety requires the repeated use of the protected variety or if the new variety is an essentially derived variety (EDV) of the initial variety[106]. In both these cases, the breeder must negotiate a licence with the holder of the protected variety to exploit the new variety.

Patents

[102] See the reports duHCB :https://www.researchgate.net/profile/Fabien-Girard/publication/315366083_Biotechnologies_vegetales_et_propriete_industrielle/links/58cd5a9da6fdcc5cccbbda48/Biotechnologies-vegetales-et-propriete-industrielle.pdf; https://hal.inrae.fr/hal-02791518/document; https://www.actu-environnement.com/media/pdf/news-26203-avis-cees.pdf

[103] https://www.upov.int/edocs/pubdocs/fr/upov_pub_221.pdf

104 https://cpvo.europa.eu/sites/default/files/documents/lex/394R2100/FR394R2100.pdf

[105] In the United States, a plant variety may be protected (including simultaneously) by a plant variety right and by a patent.

[106] See *below*.

Patents are governed in Europe by the 1973 Munich Convention (European Patent Convention - revised in 2000). This framework has been adapted in the EU to the development of biotechnologies by Directive 98/44/EC[107].

Only inventions that are new, involve an inventive step and are capable of industrial application are patentable. A patent confers a 20-year monopoly on exploitation and covers both manufacture and sale. However, a distinction must be made depending on whether the patent relates to a product or a process.

The farm-saved seed exception also exists for patents under Directive 98/44/EC. In some countries, such as France and Germany, there is an extended research exception that allows breeders to use biological material to develop other varieties without the agreement of the patent holder. However, a breeder cannot market varieties with patented elements without the prior agreement of the patent holder.

Plants derived from genetic modification and new genome-editing techniques

The deliberate release of plants derived from biotechnology (GMOs) and their placing on the internal market in Europe are regulated by Directive 2001/18/EC of the European Parliament and of the Council[108]. The scope of the directive covers a range of genetic mutation techniques, with the exception of certain exemptions such as mutagenesis and cell fusion, even though they are genetic modification techniques (Annex I B). However, the Ruling of 25 July 2018 (Confédération paysanne and others, C-528/16) of the Court of Justice of the European Union (CJEU)[109] provided additional clarification by restricting these exemptions to mutagenesis methods that appeared or were developed before the directive and for which safety has been proven. These exemptions therefore exclude directed mutagenesis techniques (genome editing) and random *in vitro* mutagenesis techniques that subject plant cells to chemical or physical mutagenic agents[110]. **For plants derived from these techniques and considered to be GMOs, there is an obligation to carry out a risk assessment, a specific authorisation and recommendations on labelling, traceability and post-market monitoring.**

The regulation of GMOs (which currently includes NTGs) has no direct impact on the patentability of plants and products derived from these techniques. However, the supply of these plants and products may be indirectly affected by the regulatory situation. Changes in regulations can influence patenting decisions depending on whether they are perceived as flexible or rigid by biotech companies.

7.4.1.1.1 Legal implications of NTG patents

- ***Patentability of processes***

The analysis presented in this section relates only to genome-editing techniques (*Oligonucleotide-directed mutagenesis (ODM), Site-directed nucleases (SDN) - targeted mutagenesis*) and in particular to the CRISPR-Cas9 technique, which is comparatively cheaper to use than other genome-editing techniques (see Collonnier,

[107] https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:31998L0044&from=EN
[108]https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0007.02/DOC_1&format=PDF
[109]https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:62016CA0528&qid=1675081531484&from=FR
[110] A judgment of the Court in Case C-688/21 | Confédération paysanne and Others (Random in vitro mutagenesis) was published after the hearing on 03 February 2023. https://curia.europa.eu/jcms/upload/docs/application/pdf/2023- 02/cp230022en.pdf

2021[111]). According to the IPStudies database (2020), there are approximately 1,232 patent families linked to CRISPR techniques that relate to plant improvement[112]. [113]. Patent applications relating to CRISPR-Cas techniques have been increasing since 2013 (**Figure 43**).

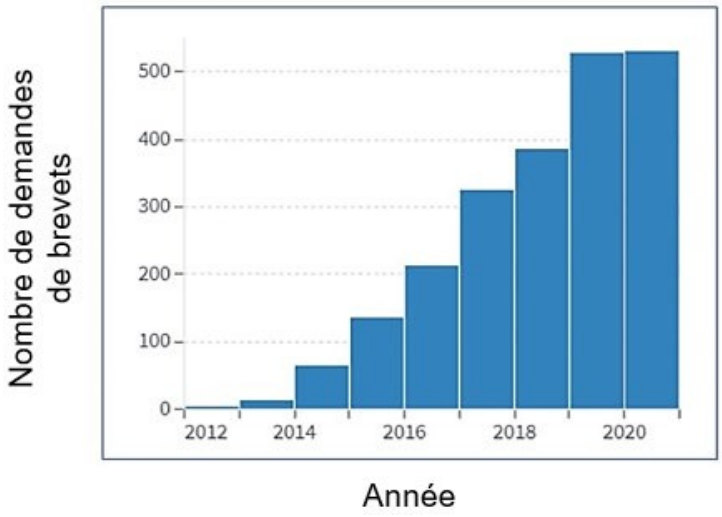


Figure 43. Number of patent applications (by year) relating to CRISPR- Cas technologies of interest to plants (adapted from Kock, 2021)

First and foremost, the patent protects the process itself. Any breeder wishing to use a process protected by a patent will have to negotiate a licence. It is important to note that, depending on the breeding objectives, several processes will be necessary. Depending on the context, a simple edition may require the negotiation of several licences.

The process patent normally also extends to the **product obtained** by the process. Article 25 of the Agreement on a Unified Patent Jurisdiction 2013/C 175/01 states that :

"A patent confers on its owner the right to prevent, in the absence of his consent, any third party: [...]

c) offer, place on the market, use or import or possess for these purposes a product obtained directly by a process which is the subject of the patent".

The scope of the rule varies from one legal system to another. This is an important issue, since the scope of a process patent can be extended to any product obtained by the said process. In this respect, the rules can be divided into three categories:

[111] Cécile Collonnier, Webinar: New breeding techniques & the challenges of their IP protection, CPVO & European IPHelpdesk, 8 June 2021.

[112] A "patent family" is a set of patents that share the same technology and priority date. (https://www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/). The priority date is that of the first patent application, which gives the invention provisional protection in other countries for up to 12 years until the patent is granted (https://www.ipside.com/fr/guide-pi/foire-aux- questions-faq/faq-brevets-questions/all-faqs-brevets/82-what-is-priority-for-a-patent, consulted on 27/02/2023).

[113] A "patent family" is a set of patents that share the same technology and priority date. (https://www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/). The priority date is that of the first patent application, which gives the invention provisional protection in other countries for up to 12 years until the patent is granted (https://www.ipside.com/fr/guide-pi/foire-aux- questions-faq/faq-brevets-questions/all-faqs-brevets/82-what-is-priority-for-a-patent consulted on 27/02/2023).

- in some cases, such as in the United Kingdom, the scope of the patent extends only as far as the patent holder.
  "Directly obtained product", which means that it only covers the parental line, but not the seed, which is obtained after several generations of propagation.[114]
- in other cases, such as in the United States, the patent extends to all downstream products (35 U.S.C. 271(g)[115]).
- Directive 98/44/EC takes an intermediate position. A claim to a method for producing biological material with "specific properties" as a result of the process extends to the descendants if it has the same properties (the properties must therefore still be present).

A reasonable interpretation of this last rule is that, in the case of a patent extended to descendants, the properties determined must clearly be disclosed in order to avoid infringement in the use and exploitation of the plant obtained by means of NTGs.

- ***Product patentability***

The European Patent Convention established by the EPO (European Patent Office) allows patents to be granted for products. However, in accordance with Article 53 of the Convention, the EPO has revised Rule 28(2) of the Implementing Regulations to specify that "*European patents shall not be granted for plants or animals obtained exclusively by means of an essentially biological process*[116] "an exception that was already applied in certain countries such as France, Germany, Italy and the Netherlands through their respective national laws.[117]. As a result, the granting of a patent on a product that can be obtained by an essentially biological process requires the introduction of a "*disclaimer* [118]"The purpose and effect of this clause is to limit the claim to products obtained by technical means. The situation is therefore different depending on the technique used to develop the plant (

Table 9).

Techniques/mechanisms	Product	Patentability (process) Art. 53(b)	Patentability (product) Art. 54	Need for a disclaimer
Transgenesis	Synthetic sequence	Yes	Yes	No
Intragenesis	Synthetic sequence	Yes	Yes	No

[114] E.g., UK High Court of Justice, Monsanto Technology LLC v Cargill International SA (Case No: HC06C00585; decision of Oct. 10, 2007) HJ Pumfrey - no extension of the breeding process to descendants: the phrase "*directly obtained by means of the process*" means "*the immediate product of the process*", (No. 35). Consequently, "*all the RR soybean plants in Argentina... can be described as the ultimate product of the original transformation of the parent plant. But I cannot see that it can be properly described as the direct product of that transformation, a phrase I would reserve for the original transformed plant. This aspect of the claim must fail*. (No.37 of the ruling). https://www.casemine.com/judgement/uk/5a8ff75f60d03e7f57eabda1

[115] Subsection (g) of 35 U.S.C. 271. https://www.bitlaw.com/source/35usc/271.html

[116] Processes that rely exclusively on natural phenomena such as crossing or selection. Article L611-19 - Intellectual Property Code - Légifrance (legifrance.gouv.fr)

117 https://www.epo.org/law-practice/legal-texts/official-journal/2017/07/2017-07.pdf In Germany, Patentgesetz, PatG, section 2a (amended in 2013); in France CPI, art. 611-19, I 3° bis (amended by L. n° 2016-1087 of 8 August 2016 pour la reconquête de la biodiversité, de la nature et des paysages); in Italy, Codice della proprietà industriale, art. 81quater (1)e); in the Netherlands, Rijkswet van 15 december 1994, houdende regels met betrekking tot octrooien, art. 3(1)d).

[118] A "disclaimer" is a clause which allows a patent to be annulled if the conditions of intellectual property law are not met (G1/03, point 2 of the grounds). https://www.sedlex.fr/brevets-ep/conditions-de- brevetabilite/clarte/.

Techniques/mechanisms	Product	Patentability (process) Art. 53(b)	Patentability (product) Art. 54	Need for a disclaimer
Cisgenesis	**Native" sequence**	**Yes**	**? (yes)**	**Yes**
Site-directed mutagenesis (SDN-3)	Synthetic sequence	Yes	Yes	No
Site-directed mutagenesis (**SDN-3)**	**Native" sequence**	**Yes**	**? (yes)**	**Yes**
Site-directed mutagenesis (SDN-2)	Desired mutation - non-native	Yes	Yes	No
Site-directed mutagenesis (**SDN-2)**	**Desired native mutation**	**Yes**	**? (yes)**	**Yes**
Site-directed mutagenesis (ODM, SDN-1)	Random mutation - not yet identified "in the wild".	Yes	Yes	Yes
Site-directed mutagenesis (**ODM, SDN-1)**	**Random mutation - native**	**Yes**	**? (yes)**	**Yes**
Random mutagenesis	Random mutation (not yet identified in nature)	Yes	Yes	Yes
Random mutagenesis	**Random mutation (already identified in nature)**	**Yes**	**? (yes)**	**Yes**

Table 9. Patentability of processes and products according to the genome modification technique used (adapted from Collonnier, 2021[119]).
Note: the question mark preceding certain statements (lines in bold) expresses the legal uncertainty that characterises the patentability of certain products.

7.4.1.1.2 Essentially derived varieties (EDVs)

A VED is a variety that is clearly distinguishable from the initial variety in all its characteristics except for the characteristics resulting from the derivation.[120]. It therefore conforms to the initial variety in the expression of the essential characteristics ("indispensable" or "fundamental" characteristics of an economic, agronomic and cultural nature) that result from the genotype or combination of genotypes of the initial variety. The VED can be protected but cannot be exploited without a licence granted by the breeder of the initial variety. In the case of plants obtained using NTGs, a potential difficulty lies in the fact that there is a high degree of **genetic conformity between the** VED and the initial variety, but **a clear distinction in the essential** (phenotypic) **characteristics** depending on the desired trait.

[119] https://cpvo.europa.eu/en/news-and-events/webinars/webinar-new-breeding-techniqueschallenges-their-ip-protection.
[120] UPOV, EXPLANATORY NOTES ON ESSENTIALLY DERIVED VARIETIES ACCORDING TO THE ACT OF 1991 OF THE UPOV CONVENTION, Document adopted by the Council at its thirty-fourth extraordinary session on 6 April 2017, UPOV/EXN/EDV/2, 6 April 2017, https://www.upov.int/edocs/expndocs/fr/upov_exn_edv.pdf
UPOV, EXPLANATORY NOTES ON ESSENTIALLY DERIVATIVE VARIETIES UNDER THE 1991 ACT OF THE UPOV CONVENTION, DRAFT (Revision), 3 September 2021, UPOV/EXN/EDV/3 Draft 2, https://www.upov.int/edocs/mdocs/upov/fr/wg_edv_4/upov_exn_edv_3_draft_2_marked_version.pdf

The impact of the VED concept on plants obtained by NTG will depend on the interpretation given to VED (Girard and Noiville, 2014):

- A first approach, supported by the major NTG-producing companies, is based on phenotype;
- The second approach, advocated by breeders (small and medium-sized companies), is based on genotype.

From a legal point of view, it is difficult to decide, but we can consider that the
The term "essential characteristics" refers more to the phenotype.

However, the genotypic approach is more generally used as it seems to be favoured by case law and international arbitration proceedings (Girard and Noiville, 2014). For example, in the ISF (*International Seed Federation) guidelines*, an analysis of genotypic components may be requested to justify the distinction between a VED and an initial variety[121].

Taking these factors into account, the impact of the development of NTGs on the sector could be different depending on the regulations adopted for VEDs. In any case, companies producing plants using NTGs point out that a molecular approach would have the effect of limiting the use of the best germplasm (a plant's genetic resources) in genome-editing selection programmes.

7.4.1.1.3 Types of patents for plants obtained using NTG: what solution(s) for the future?

There are a large number of patent applications for traits in plants modified using NTGs. There will be at least 138 patent applications for biotechnologies developed with CRISPR-Cas in 2020 (Kock, 2021). However, a limited number of varieties are covered by at least one patent (around 1.85% according to the catalogue of varieties authorised in Europe). The development of NTGs could therefore have an impact on the number of varieties with patents. Kock (2021) estimates that the number of varieties with plant patents could increase to 30% by 2030 depending on the country, and to over 80% by 2040 in the United States, compared with almost 50% in Europe. The evolution of the number of patents on plant varieties, in Europe in particular, will depend not only on the evolution of the regulatory landscape but also on several other factors such as the acceptability of these technologies and certain technical obstacles linked to their development and adoption.

The development of NTGs is also likely to accelerate the pace of innovation and facilitate the stacking of traits in the same plant variety, which would contribute to the creation of new varieties.
"patent bushes[122] "(Kock, 2021). In this case, the development of a new variety from a patented variety would require the negotiation of several licences.

Several solutions have been proposed in the literature to regulate/framework the development of patents on NTGs. These proposals range from certain forms of patent (*patent pools, clearinghouses, licensing pledges, open source*) to legislative reform of the system, with various possible options (abandonment of patents, in-depth revision and adjustment of patent law (Van Overwalle, 2009; Kloppenburg, 2014, Luby et al. 2015; Kotschi and Horneburg,

[121] https://worldseed.org/wp-content/uploads/2015/10/Guidelines_EDV_Ryegrass_Nov_2009.pdf
[122] "Patent thickets" are situations where an innovation depends on a very large number of earlier patents. https://doi.org/10.4000/cdst.215

2018; Montenegro de Wit, 2019; Kock and ten Have, 2016)). The interest in and use of these different types of patents (in the development phase) depend on the type of players/companies developing these technologies.

Summary

Analysis of the regulatory landscape for plants shows that, even if GMO regulations (including NTGs) have no direct impact on the patentability of plants and products derived from these techniques, the supply of these plants and products may nevertheless be indirectly impacted by the regulatory situation. Changes in regulations can influence patenting decisions, depending on whether they are perceived as flexible or rigid by biotech companies.

As far as plants are concerned, there are two industrial property titles that apply in Europe. Firstly, plant variety certificates (PVCs), which confer rights only on products, enabling breeders to reproduce processes to obtain other marketable varieties. On the other hand, patents apply to products and processes, the use of which requires the negotiation of a licence with the holder. In the European context, a plant variety can only be protected by a PVC (and not by a patent), unlike in the United States, for example, where a plant variety can be protected (including simultaneously) by a PVC and by a patent. The scope of patent regulations also varies from one legal system to another. Exceptions applied in European regulations make it possible, for example, to protect the natural characteristics of plants by including a "disclaimer" in patents.

Several solutions have been proposed in the literature to regulate/framework the development of patents on NTGs. These proposals range from specific forms of patent (patent pools, clearinghouses, licensing pledges, open source) to legislative reform of the system, with various possible options: abandonment of patents, in-depth revision of patent law or adjustments. The interest in and use of these different types of patent (in the development phase) depend on the type of players/companies (small breeders, large biotech companies, etc.) developing these technologies.

7.4.1.2 NTG adoption dynamics and impacts upstream of the supply chain

- ***Faster, less costly R&D processes***

Compared with other available breeding methods, most publications consider that NTGs increase the precision in targeting the traits to be developed and the probability of success in the upstream phases of R&D (Lassoued 2019a). This has a number of consequences in terms of economic impact for players who produce plants and products using NTGs.

Assuming that regulatory choices are not too restrictive (for more details on this point, see section 7.4.2.6), most publications note that NTGs make it possible to develop varieties that could reach the end market at lower cost.

and in a shorter time than plants obtained by transgenesis. A survey of biotechnology experts (scientists, public authorities, agri-food professionals) attempts to put a figure on the differences in the costs of obtaining plants obtained using NTGs under two scenarios (plants obtained using NTGs regulated as GMOs resulting from transgenesis or not) by considering all the phases of the R&D process, from the upstream research stages through to marketing authorisations (Lassoued et al. 2019a). The orders of magnitude of the differences, which must be treated with caution due to the non-systematic nature of the study, are as follows: the duration of the process is estimated at 14 years in the first case compared with 5 years in the second. This is also what emerges from an empirical study conducted in Argentina (Whelan et al. 2020), which suggests that NTGs follow a much faster pace of development from the laboratory to the market than plants derived from transgenesis. The R&D costs of developing a varietal innovation are estimated at 24.5 million dollars for GMO-type regulations applied to plants derived from NTGs, compared with 10.5 million dollars for regulations imposing fewer constraints in terms of risk assessment. One third of the reduction in costs (-$4 million) is linked to the reduction in upstream research costs (the remainder is linked to the cost of marketing, see *below*).

- ***Greater diversity in the types of players involved in the production of new characteristics***

Comparative analysis of NTG-derived plants and transgenic plants developed in Argentina (Whelan et al. 2020) also suggests more diverse company profiles in the case of NTG-derived plants, with significant involvement of small and medium-sized enterprises and public bodies. This greater involvement of the public sector (academic research) and SMEs in the development of varietal innovations is highlighted in several publications (Bartowski et al. 2018; Jorasch, 2020; Ricroh and Hénard-Damave, 2016).

This observation is modulated in certain articles. Lemarié and Marette (2022) note that NTG technology exists in a different context to transgenic plants, for which the range of applications widely disseminated around the world is limited (herbicide tolerance and insect resistance) and for which patents are held mainly by multinational companies. However, this difference needs to be treated with caution, as the first transgenic plants were also developed by start-ups that were acquired by multinationals in the late 1990s. It was only later that the number of operators involved in the production of GM varieties was reduced. The deployment of innovations sometimes requires investment that SMEs do not have. This type of market development cannot therefore be ruled out in the case of NTG-derived plants.

The possible diversity of operators that could enter the plant breeding market may appear to be a positive point (more competition, greater diversity of traits sought and species concerned, lower prices), but it also raises a risk highlighted by Bartowski et al. (2018). These authors highlight the fact that if plants obtained using NTGs are produced by a larger number of companies, there will also be more diversity in the genetic modifications applied. This statistically increases the risk of an undesired effect appearing, and must therefore be set against the arguments highlighting the precision of the techniques used.

- ***Smaller market size required to cover R&D costs for companies***

NTG technologies could reduce the market size required for profitable investment. This is suggested by an economic analysis (Bullock et al. 2021) based on the modelling of the R&D process, taking into account the uncertainties existing at each stage, from the research phase to the product marketing phase.

The authors show, for a wide range of parameter values, that NTGs significantly reduce the duration and total cost of the R&D process and greatly reduce the size of the market required to cover the associated costs compared with transgenic plants (Bullock et al. 2021). In their estimates, this difference is linked to the fact that during the R&D phase, the costs are lower and the probability of success higher for NTG-derived plants than for transgenic plants. Such an estimate might suggest that applications based on NTGs could be made on plant species considered to be minor crops, unlike plants derived from transgenesis. These estimates have been made taking into account the North American regulatory context, which is less restrictive than the European context. Furthermore, minor crops, by definition, have limited access to the market. As a result, reducing the cost of developing an innovation may not be enough of an incentive, given the prior investment required in knowledge of genome expression.

One important consequence is that NTG-derived plants would allow more diversified varietal innovations in terms of desired traits and species covered (Venezia-Krainer 2021) and for production that does not *a priori* represent large market volumes. Plant varieties obtained using NTGs could thus be used in differentiation strategies in targeted (niche) markets, targeting specific consumer segments (Bullock et al. 2021).

However, these arguments are based on just two studies (Bullock et al. 2021; Venezia-Krainer 2021). As these innovations are not yet on the market (with rare exceptions), more research is needed to confirm or refute these results.

- ***Less impact on the concentration of the plant breeding sector?***

The plant breeding industry has undergone a strong process of concentration at international level (Sumpter, 2021; Torshizi and Clapp, 2021; Quaim, 2009), to which the strategies of companies developing products derived from transgenic plants have contributed. In countries where producers make extensive use of transgenic seeds, the structure of the upstream market is such that their prices essentially involve transferring the value associated with productivity gains to seed companies and breeders.

An important part of the challenge for companies is the granting of licences. There are studies on the licences obtained for processes, but the analysis presented in this section refers only to patents for products. Since very few products obtained using NTGs are already on the market, the literature on plants derived from transgenesis is used here to analyse the situation of plants derived from NTGs. However, the potential of NTGs to produce modified varieties more quickly than conventional technologies for producing plants derived from transgenesis

could affect the licensing process and therefore have different economic implications.

In the case of transgenic plants, business strategies are essentially based on the sharing of value between two companies which manage to market a variety combining existing characteristics (conventional seed) and a new characteristic (transgenic seed) (**Figure 444**).

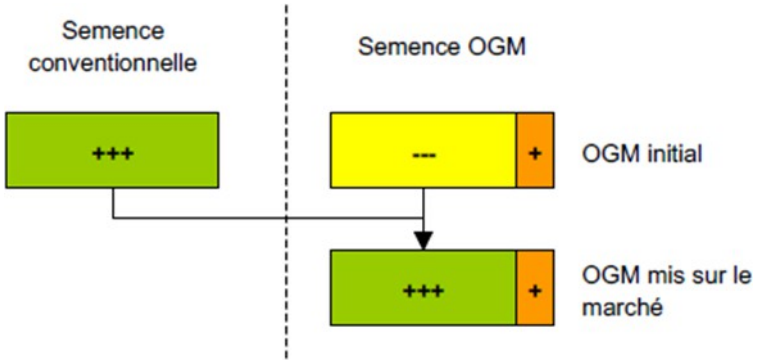


Figure 44. Illustration of the combination of a conventional variety and a new transgenic trait on the market (from Lemarié, 2023[123])

Note: in green, the traits of a high-performance conventional seed that is already on the market; in yellow, the traits of a low-performance seed to which a new trait derived from transgenesis has been added (in orange), such as resistance to a total herbicide, for example; seed derived from transgenesis only has economic value if the GMO trait is combined with other traits of a high-performance conventional variety.

The strategy of companies with patents for the production of transgenic plants depends on the company's position in the market. A patent holder has less bargaining power if it is not present on the seed markets. As a result, the development of GMOs has led to seed companies being bought out by firms holding patents relating to new traits resulting from transgenesis (vertical integration). If the company has its own seed production subsidiary, it can reserve the GMO solely for its own subsidiary (foreclosure strategy). However, some companies may continue to sell licences to other companies (non-exclusive licensing strategy). This latter strategy has been used by certain biotech companies such as Monsanto (now Bayer), which has resulted in the widespread dissemination of its GMO traits. Since their introduction in 1996, the share of international sales accounted for by GM seeds has risen, levelling off from 2012 onwards. This trend is accompanied by a high level of concentration in the global seed market (Bonny, 2017). However, the level of market concentration varies depending on the crops concerned and the countries (Deconinck, 2019).

The important question in the case of NTGs is to know to what extent their intrinsic characteristics (precision in the selection of desired traits, lower development costs, etc.) and the regulatory choices made could reduce the barriers to entry into the varietal innovation market, in contrast to the observations just made in the case of GMOs derived from transgenesis.

[123] This figure was produced by Stéphane Lemarié as part of the hearings to illustrate the marketing of a combination of a conventional variety and a GMO trait.

At this stage, the available literature does not allow us to answer this question, which is the subject of considerable controversy (see section 7.4.2.7). **With regard to the effects of the intrinsic characteristics of NTG technology, the hypothesis that markets will be more open to companies of different types and sizes has been put forward in a number of publications, but has not really been demonstrated.** It will have to be confirmed by monitoring innovations and the contribution of small biotech companies and public institutions to their development (Bullock et al. 2021; Bartowski et al. 2018). Egelie et al. (2016) note, with regard to crops based on gene editing, that the major players in the industry already seem to have control (patents) over the agricultural and food applications of this technology (cf. section 7.4.2.1). One of the consequences to be studied in particular will be the effects of the concentration of players in plant breeding, as well as their impact on seed prices for producers (Bartowski et al. 2018).

- ***More or less significant effects depending on the choice of regulation***

In addition to the intrinsic characteristics of NTGs, regulatory choices can also influence the degree of concentration in the sector and, *ultimately*, the way in which value is shared between industry players. The impact of regulations is seen in the costs incurred in R&D and the uncertainties faced by companies.

Purnhagen & Wesseler (2019) develop an analysis of this point by modelling the process of developing an innovation in four stages: an R&D phase, a regulatory approval phase, a commercialisation phase and a liability phase in the event of *ex post* litigation. Before embarking on this process, a company must assess the potential costs and gains, taking into account the uncertainties that exist at each stage. Regulatory policies affect the benefits and costs, but also the uncertainties, associated with each phase. The simulations carried out by these authors indicate that marginal changes in the costs and duration of R&D can have significant consequences on the overall economic interest in embarking on an R&D investment. Using parameter values that can vary from one country to another, the authors show that a one-dollar increase in R&D costs increases the benefits that must be obtained for R&D investment to be profitable by 14 dollars. By influencing this ratio, regulatory choices affect the structure of the market, by making it possible or impossible for small and medium-sized companies to enter.

For these reasons, some authors (Purnhagen & Wesseler, 2019; Wesseler et al. 2019; Jorasch, 2020) consider that the effects of greater openness of the plant breeding market (due to the characteristics of NTGs) could be strengthened/accentuated by more flexible European regulations that would lower barriers to entry by reducing the costs of obtaining marketing authorisations. On the other hand, these regulations could increase the concentration of players in plant breeding, limit the capacity of European companies to operate on export markets (but would have little effect on companies producing only for the domestic EU market), encourage a reduction in R&D investment and encourage the relocation of R&D activities on these innovations outside the EU (Marette et al. 2021). The reduction in such investment could, however, enable the development of innovations in plant production as alternatives to NTGs to meet the same types of challenge.

Jorasch (2020) and Wesseler et al. (2019) present the results of two surveys of seed companies in the European Union. The sample surveyed by Jorasch (2020)

includes 62 seed companies that are members of Euroseeds or national seed associations. The survey covers companies of different sizes (53% small, 37% medium; 10% large).

The results of these surveys show that the proportion of these companies investing in NTGs differs according to size category (100% of large companies, 86% of medium-sized companies; 47% of small companies). Research efforts cover a wide range of plant species, regardless of company size (**Figure 45**). There is also a very wide range of traits being worked on (**Figure 46**). However, this point needs to be qualified, as the same observation was made for GMOs derived from transgenesis in the early 2000s, when a very limited number of agronomic traits were ultimately disseminated. The market filter is therefore significant. A large proportion of companies (67% of large companies, 40% of medium-sized companies and 36% of small companies) anticipate that plants obtained using NTGs will be marketed within the next 10 years (Jorasch, 2020).

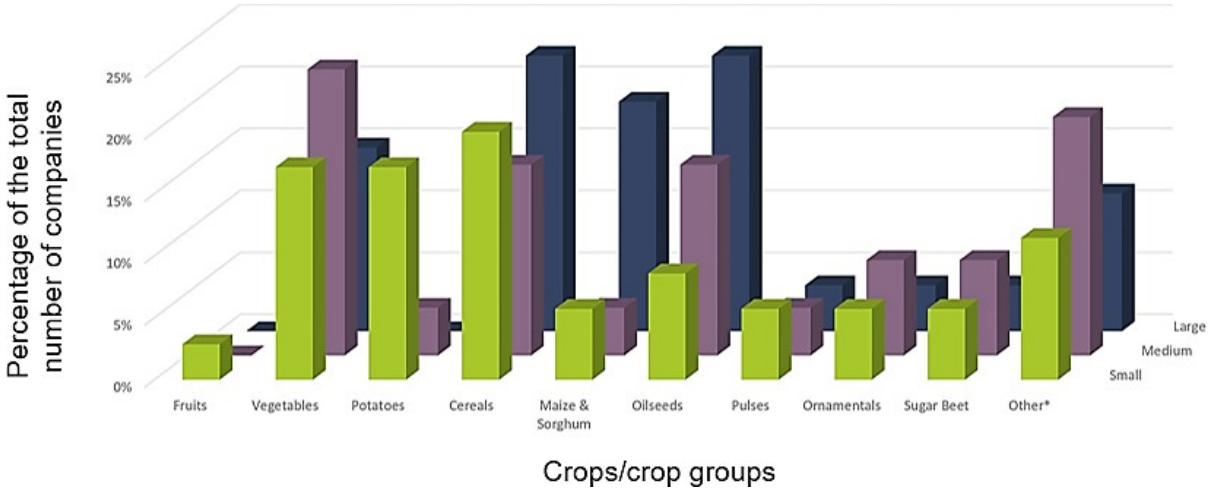


Figure 45. NTG research efforts by plant species targeted by seed companies in the European Union (adapted from Jorasch, 2020)

Note: The percentage is relative to the total number of respondents to the questionnaire for the category of company concerned: 27 large, 26 medium and 35 small; "other" means soya, cotton, rice, forage crops (grasses, legumes), chicory, model plants for gene discovery research, poppies for the pharmaceutical industry, groundnuts, ornamental plants as food and medical plants, hemp, dandelion, legumes and stevia.*

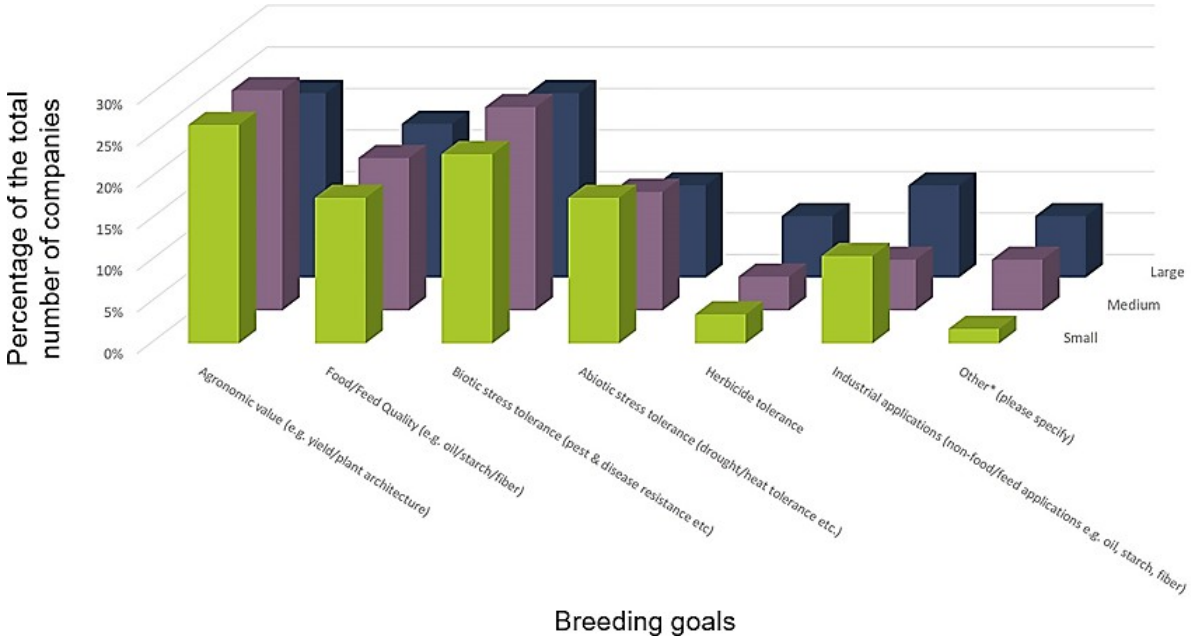


Figure 46. NTG research efforts by type of trait sought (adapted from Jorasch, 2020)

Note: The percentage is relative to the total number of respondents to the questionnaire for the category of company concerned: 27 large, 49 medium and 57 small. The characteristics mentioned under "other" relate to flavour, shelf life, digestibility, ornamental value (flower colour) and post-harvest quality.*

The survey results also show that issues related to NTG regulation (e.g. uncertainty and regulatory costs) are among the main factors that could influence NTG investment. More specifically, the decision of the Court of Justice of the European Union (CJEU) on 25 July 2018 concerning NTGs[124] could have an impact on companies' strategies. Indeed, according to these surveys, a high percentage of companies (100% of large companies, 86% of medium companies, 68% of small companies) would choose to invest in seeds obtained using NTGs if they were regulated as conventional seeds. In addition, large companies (100%) in particular acknowledged in this survey that they had changed their strategies to focus on products with outlets on markets outside the European Union following the CJEU ruling. Finally, companies anticipate a delay in the marketing of NTG applications on an international scale as a result of the CJEU ruling.

The authors suggest that uncertainties about the future of regulation, and the differences and non-synchronisation of regulatory developments between countries, are having a greater impact on investment decisions, leading them to be reduced or transferred outside the EU.[125].

However, we might wonder about the differing effects of these regulations depending on the type of NTG and, in particular, the characteristics sought and market segments targeted. We

[124] The judgment of the Court of Justice of the European Union (CJEU) of 25 July 2018 clarified that only organisms obtained by means of mutagenesis techniques/methods which have traditionally been used for various applications and whose safety has long been proven are excluded from the scope of Directive 2001/18/EC. As a result, the use of new mutagenesis techniques must comply with the regulatory framework as designed for GMOs derived from transgenesis, particularly in terms of risk assessment, authorisation procedure, traceability, labelling and control.

[125] It should be noted that this argument is not shared by all players. One of the possible consequences could be investment in alternative technologies in the EU (see section 7.4.2.7).

It can be assumed that the impacts will differ depending on whether we are dealing with commodity markets or differentiated markets (cf. section 7.4.2.4). The analysis by Bullock et al (2021) suggests that, even in the event of restrictive regulation, there could be a place for plant varieties obtained using NTGs targeting specific consumer segments.

Summary

Compared with the other selection methods available, most publications consider that NTGs increase the precision in targeting the traits to be developed and the probability of success in the R&D phases. As a result, NTGs could make it possible to develop varieties likely to reach the end market at a lower cost and in a shorter time than GMOs derived from transgenesis. As a result, (i) the profiles of companies involved in R&D appear, at this stage, to be more diversified in the case of NTGs, with a significant involvement of small and medium-sized companies and public bodies; (ii) NTGs would make it possible to reduce the size of the market needed to ensure profitable investments for those who use them; (iii) NTGs would allow more diversified varietal innovations in terms of desired traits and species covered.

The plant breeding industry has undergone a strong process of concentration at international level, to which the strategies of companies developing GMO products from transgenesis have contributed. In the case of plants obtained using NTGs, the question is to what extent their characteristics (precision in the selection of desired traits, lower development costs, ease of use, etc.) could amplify the process of concentration in the plant breeding and seed sector, or on the contrary contribute to reducing the barriers to entry into these markets. At this stage, the available literature does not allow us to answer this question. Among the consequences to be studied in particular are those relating to the effects on the market power of the players in plant breeding, on the sharing of value within the sectors and on seed prices for growers.

The literature analysed also emphasises that the economic impacts associated with plants and products obtained using NTGs will depend heavily on the regulatory choices made at European level. By affecting the economic trade-offs of the various types of players, these will have a direct influence on the incentives to develop and adopt these techniques. These regulatory choices may also influence the degree of concentration in the sector and decisions on R&D investment and location, and will have an impact on the ability of European companies to operate on export markets.

7.4.1.3 Trade, competition and international impact

International trade and the competitiveness of products derived from NTG plants are at the centre of current debates on technological options and their socio-economic implications. While these issues are crucial to understanding the gains and costs

research in this area remains limited. The literature review identified the few scientific studies that analyse the potential impacts of plants and products derived from NTGs on the basis of hypothetical scenarios. These studies offer insights into the future challenges and opportunities of international trade in products derived from NTG plants. However, they have limitations inherent in the methods used, and as a result, the perspectives derived from them should be interpreted with caution.

International trade scenarios and the implications of NTGs

Smith et al (2021) have studied how new plant breeding technologies affect the global economy and trade, particularly for exporting and importing countries. A major point of attention is the position adopted by importing countries regarding the approval or prohibition of products derived from NTG-derived plants. These authors point out that the integration of these technologies could lead to a significant increase in a country's agricultural production capacity.[126]transforming the global trade landscape. Taking their analysis a step further, Smith et al (2021) explored various scenarios relating to the adoption of these technologies in agriculture, with particular emphasis on the economic implications of these scenarios. They highlight that the effects on farm incomes can be complex, with potential global benefits but varying regional effects. In addition, the study discusses the possible changes in trade dynamics if the main exporting countries adopt the new technology.

Also focusing on the position of importing countries, particularly those in the EU, Gocht et al (2021) created scenarios for 2030, focusing on the EU, to investigate how current policies might affect the agricultural economy in the future. Focusing on the main cereal crops, such as wheat, barley, maize and soybeans, the study explored several scenarios related to NTG product regulations, based on the Comparative Regionalized Agricultural Sector Model (CAPRI). Two main scenarios were developed: a baseline scenario and a scenario in which EU imports from all non-EU countries would cease. The baseline scenario is a projection of the most likely development of the agricultural sector, taking into account current trends such as population growth, inflation, GDP growth and technological progress. The import halt scenario incorporates all the specifications of the reference scenario, but adds a halt to imports of all cereal products. This stop is technically implemented by prohibitive tariffs on imported products. As an alternative to this formulation, the authors considered continuous imports from regions with regulations similar to those in the EU. However, simulations have shown that stopping imports only from certain countries would lead to a shift in import flows towards other regions, such as Russia or African countries. These regions could then export to the EU, presenting a risk of 'contamination' by NTG varieties. By

[126] According to the authors, when a country adopts these technologies, it gains access to plant varieties that may be more resistant to disease, drought-tolerant or even biofortified. These advantages can lead to an increase in agricultural production, even in conditions that would have been unfavourable to traditional varieties.

The scenario was therefore applied to all countries, regardless of their regulations on genome editing. The study also highlighted that the adoption of strict regulations could slow down innovation in the EU agricultural sector, putting European farmers at a disadvantage vis-à-vis their international counterparts. In the long term, this could have an impact on the competitiveness of European agriculture on world markets.

In the scenario where all imports are halted, major economic changes have been anticipated. EU consumers could suffer considerable losses, estimated at €18.6 billion, as a result of higher prices. On the other hand, the agricultural sector could benefit from these higher prices, with a potential €20.8 billion available to pay for land, labour and capital. Notably, despite the reduction in imports of genetically modified crops, tariff receipts could increase, particularly for products such as rapeseed, sunflower seed and certain fish products.

The study by Gocht et al (2021) highlights the complexity of world agricultural markets and the consequences of a reduction in EU agricultural imports. However, the scenarios put forward should be approached with caution, as they are simulation models used for *ex-ante* evaluation based on a certain number of hypotheses, in order to study the economic mechanisms at play and help decision-making.

- ***Historic trade tensions***

At the time of writing, there are no documented cases of real disruption to international trade in genetically modified crops or products, although the experience with GMOs derived from transgenesis is often cited to anticipate such tensions, particularly in the context of the current regulation of NTGs as GMOs within the EU (Gocht et al. 2021). Historical precedents illustrate these tensions. For example, one notorious case involves Syngenta's Agrisure VipteraTM (MIR162) maize variety. In 2013, Syngenta's corn variety Agrisure VipteraTM (MIR162), although approved in several countries, had not been validated by China, leading to a drastic drop (85%) in US corn exports to that country. Similarly, in 2006, the presence of unapproved genetically modified rice ("LL Rice" or "LibertyLink Rice") in shipments destined for Europe and Asia caused major trade disruptions.

The European Commission has recently proposed to review the regulation of certain genomic techniques (see section 2.3). This proposal could have repercussions for the commercial landscape. On the one hand, it could reduce tensions with countries that support this new direction. On the other hand, it could generate friction with countries that were in agreement with the Union's previous position.

In this context, operators could opt for a cautious approach when shipping products, particularly if the selection method is not explicitly defined. This caution stems from the uncertainties associated with the various national regulations. Traceability remains a major issue (see section 7.4.2.6). Current detection and control protocols based on the search for exogenous DNA in GMO plants are not adapted to plants obtained by NTGs. In this changing landscape, it is possible that European players will give greater preference to local products, as suggested by Gocht et al (2021).

- ***Regulatory disparities and compliance costs***

In addition, regulatory disparities could potentially lead to trade imbalances and hamper the competitiveness of EU farmers on the global market due to higher compliance costs compared to their counterparts in other countries (see section 7.4.2.4). As mentioned in a previous section, Lassoued et al (2019b) conducted a survey providing information on the likely cost of bringing genetically edited plants to market. Their results indicate that the overall cost of bringing a genetically edited plant to market is on average lower if it is regulated as a conventional plant than if it is regulated as a transgenic plant (see section 7.4.2.2). These estimated values are likely to vary between regions due to divergent policies and different national regulatory frameworks (Lassoued et al. 2019b).

As well as the cost to business, it is also important to consider the cost to society as a whole. Environmental implications, public health concerns and socio-economic impacts are all factors that can influence this cost. Regulation and enforcement play a key role in the cost to society. It is therefore crucial to take these elements into account when assessing the cost of bringing NTG products to market (Lassoued et al. 2019b).

- ***Prospects for international agreements***

The 2018 Nagoya-Kuala Lumpur protocols add a new layer of complexity to the international agreements that influence world trade. They call for greater coherence and harmonisation between different international agreements. Indeed, some authors, such as Smith et al (2021), have highlighted the legal uncertainty they generate for plant breeders, due to ambiguous guidelines regarding the sharing of benefits arising from the commercial use of genetic resources. This situation could reduce the use of these resources, especially in southern countries. As a result, the adoption of new technologies could slow down in southern countries, creating imbalances in world trade (Smith et al. 2021).

In the face of regulatory complexity, several institutions and countries have raised the possibility of establishing mutual recognition agreements between different regulators as an alternative (Jin et al. 2019). These agreements aim to create a framework in which different regulators recognise the validity of each other's regulatory processes and decisions. This approach has the potential to reduce trade barriers and compliance costs for companies operating in multiple jurisdictions. The principle of mutual recognition has been raised in this context, opening up prospects for simplifying international trade. Mutual recognition agreements and mutual recognition of goods[127] exist in various sectors such as pharmaceuticals[128] (including those relating to gene therapy) and various

[127] It is important not to confuse the principle of mutual recognition with mutual recognition agreements. The principle of mutual recognition ensures market access for goods that are not or only partially subject to EU harmonisation legislation, while Mutual Recognition Agreements (MRAs) facilitate market access between the EU and non-EU countries. The aim of MRAs is to reduce technical barriers to trade and facilitate access for products to foreign markets. There are two categories of MRA: "traditional" agreements and "extended" agreements.

[128](https://www.seco.admin.ch/seco/en/home/Aussenwirtschaftspolitik_Wirtschaftliche_Zusammenarbeit/Wirtschaftsbeziehungen/Technische_Handelshemmnisse/Mutual_Recognition_Agreement_MRA0.html).

areas of the agricultural sector[129]. In the UK, discussions are currently underway on the impact of these agreements, particularly in the case of products derived from genome editing[130]which are no longer considered to be GMOs. Similar considerations are underway in the United States, notably as part of the renegotiation of the North American Free Trade Agreement (NAFTA)[131]and in the context of transatlantic regulatory cooperation[132]. However, it is important to note that these proposals have already given rise to controversy and met with opposition from various stakeholders[133] (see section 7.4.2.7).

- ***International coordination for the monitoring of products derived from NTG plants in world trade***

Some studies stress the need for international coordination to establish an adequate and constantly updated database on genetically-edited products (Ribarits et al. 2021). Such a database would provide real-time information on the diversity of genetically-edited products, their characteristics, their regulatory status in various countries, and the environmental and health monitoring data associated with them. This international cooperation would promote transparency and simplify informed decision-making on the trade and regulation of plants and products obtained using NTGs.

An interesting example of this approach, which could serve as a model, is the "New genomic techniques" database[134] database developed by the European Commission's Joint Research Centre (JRC), although its public scope and updating remain limited.

Other commonly cited examples include the Human and Agriculture Gene Editing: Regulations and Index[135]the EFTA Surveillance Authority databases[136]databases, and the World Health Organisation's Environment and Health Information System (ENHIS)[137] initiatives of the World Health Organisation. The creation and maintenance of similar initiatives concerning products derived from NTGs raises interesting questions relating to governance, reliability and the obligation to inform.

[129] Mahalatchimy A, Lau PL, Li P, Flear ML. Framing and legitimating EU legal regulation of human gene-editing technologies: key facets and functions of an imaginary. J Law Biosci. 2021 Aug 16;8(2):lsaa080. doi: 10.1093/jlb/lsaa080. PMID: 34408900; PMCID: PMC8366714.

130https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1109849/2022-06-16-RPC-DEFRA-5170_1_-_Genetic_Technologies__Precision_Breeding_Techniques__Bill.pdf

[131] https://www.iatp.org/blog/nafta-genetic-engineering-trade

[132] Peter Chase, Reframing and Energizing Transatlantic Regulatory Cooperation, Dec 2021. In RED Volume 3, Issue 2, pages 85 to 90

[133] https://corporateeurope.org/en/trade/2013/05/open-door-gmos-take-action-eu-us-free-trade-agreement

[134] https://www.eu-sage.eu/genome-search

[135] https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org

[136] https://www.eftasurv.int/internal-market/food-safety/food-and-feed-safety

[137] https://gateway.euro.who.int/en/datasets/

Summary

On the basis of the corpus analysed, the discussion on international trade, competition and impacts focused mainly on the implications of differences in regulatory frameworks for crops and products derived from genome editing. The threat of unpredictable and restrictive trading environments was highlighted, in that they can lead to trade barriers and impact on competition. Although there have been no documented cases of disruption to international trade in crops or products derived from genome editing, the experience of GMOs derived from transgenesis is frequently cited as an early warning of such tensions.

Scenario-based studies show that regulatory differences could affect trade and the competitiveness of EU farmers on world markets using NTGs. These studies offer insights into the future challenges and opportunities for international trade in products derived from NTG plants. However, as these studies are few in number, the perspectives they offer should be interpreted with caution. Opportunities linked to trade barriers caused by differences in regulatory choices (such as protecting national or European economic activities, encouraging the development of alternative technologies, etc.) have not been studied.

7.4.1.4 Coexistence, segregation costs, contractual relations and market segmentation

- ***Case of varieties obtained using NTGs whose desired characteristics improve the efficiency of production processes***

Different types of plant traits obtained using NTGs are aimed at meeting the objectives of improving the efficiency of production processes, by increasing yields, saving on inputs or reducing product losses due to plant diseases. Noleppa and Cartsburg (2021) study the impact of various innovations on farmers' average incomes and margins. One example is a variety that increases resistance to pod breakage in oilseed rape in France, which could lead to a 9% yield gain and an additional margin of €100/ha.

Maaβ et al. (2019) study the possible effects, on the whole wheat sector, of the development and adoption of a varietal innovation increasing resistance to fusariosis limiting the accumulation of mycotoxins in wheat grains. Overall, such an innovation could reduce product losses in the sector. The distribution of potential gains depends on the costs incurred by fungal diseases and the presence of mycotoxins at each stage of the value chain. These gains are highest in the upstream links of the value chain, particularly in agricultural production, grain collection and trading, milling and animal production. On the other hand, the food processing and starch production stages are less affected, because the fight against fungal diseases is mainly carried out by selecting batches of wheat at the start of the process that comply with the limit values for concentrations of

mycotoxins. Downstream players would therefore have less incentive to adopt this type of NTG-derived plant, especially as there is a risk of the product being devalued by consumers.

If NTG products are regulated in the same way as conventional production, and therefore in the absence of strict rules on coexistence and product segregation, we can expect the variety to develop if the reduction in costs in the production chain is deemed sufficient. Conversely, in the presence of GMO-type regulations (imposing, for example, isolation distances between crops in plots and the separation of product flows along the supply chain), this could act as a brake on the development of these varietal innovations in the food sectors, particularly for purely agronomic traits, as Maaβ et al. (2019) point out. These difficulties would be amplified by the issues raised by plants and products obtained using NTGs in terms of traceability and the ability to distinguish, using analytical methods, between varieties depending on whether they are derived from NTGs or not (see section 7.4.2.6). All in all, the additional costs and the probable lack of consumer appreciation of these products (see section 7.4.2.5) are likely to be higher than the gains made in the sector.

- ***Case of varieties obtained using NTGs whose desired characteristics could be part of product differentiation strategies***

Other varietal innovations resulting from NTG may be aimed directly at traits likely to be valued by consumers. Here, we are more in the context of product differentiation strategies aimed at taking advantage of an additional willingness to pay by some consumers for certain product characteristics. Maaβ et al. (2019) illustrate this by considering the (fictitious) case of a *gluten-free* wheat variety for consumers suffering from celiac disease.

The authors anticipate a higher seed price than for conventional wheat and additional costs for setting up logistics to preserve the identity of the product throughout the value chain. The main question raised is the level of consumers' willingness to pay (maximum amount agreed) for this type of product (cf. section 7.4.2.5).

Provided that consumers are willing to pay, this type of strategy could be implemented, even in the case of restrictive GMO-type regulations, because traceability (documentary) and segregation requirements would be imposed, in any case, for reasons of commercial credibility in the eyes of consumers. This would mean defining selection objectives in a coordinated way between players in the industry, with commitments on production volumes and methods, as well as logistical organisations. It would also mean developing contractual relationships between seed companies, growers and suppliers of the final product. In addition, as soon as the characteristic that differentiates the product (the seed or the plant) is developed in the field, the development of varietal innovation could lead to a sharing of value that is more favourable to the producer. Given the additional costs and the complexity of the co-ordination arrangements to be put in place, the first condition is that the distinctive characteristic should be significantly valued by consumers. Furthermore, documentary traceability is unlikely to be a complete substitute for analytical traceability. It therefore remains to be defined on what basis NTG products can be identified and distinguished from other products (see section 7.4.2.6).

It is interesting to note that this scenario (which also depends on the level of acceptability of the consumers concerned) could be more easily envisaged with products obtained by means of NTGs, than with those obtained from GMOs produced by transgenesis, because of the lower development costs (Bullock et al. 2021) (cf. section 7.4.2.2). The smaller market size required to ensure a return on investment could therefore make segmentation easier for small volumes and narrower consumer targets.

- ***Varieties obtained by means of NTGs with* characteristics *designed to meet environmental and social objectives***

Numerous publications have focused on NTG innovations in response to 'common good' issues, particularly environmental issues such as soil quality, water resources, biodiversity and climate change.

An example of varietal innovation could be plant resistance to water stress and control of production in the face of water resource shortages. By avoiding production losses, such varieties could ensure a higher average yield in a deteriorated climate. For growers, the reduction in yield losses may create economic incentives to adopt such varieties (see section 7.4.1). For breeders and seed companies, the issue is the size of the markets concerned. In countries where the regulation of NTG-derived plants is not very restrictive, it is this balance between yield gains (less losses) and market size that could be a factor, bearing in mind, as mentioned earlier, that NTGs could make investments possible for smaller market sizes than transgenic GMPs (Bullock et al. 2021). In countries where regulations are more restrictive, it is the balance between yield gains and the additional costs associated with this regulation that will be decisive. In the absence of consumer value for such varieties, we find here the case of varieties derived from NTGs for production efficiency purposes.

Another example concerns species that could be used for permanent soil cover (Jordan et al. 2022). Diversification of production is seen as an important means of reducing the environmental impact of farming practices. In this context, the use of crops that provide permanent soil cover can play an important role. While the environmental benefits of these production systems are well established, their economic interest remains low, as these crops, which complement the predominant crops, generally have a low commercial value. The hypothesis put forward by the authors is that the new methods of varietal selection could facilitate genetic improvements for this type of production, where the economic interest is a priori low but the environmental interest is high. However, it is not certain that market mechanisms will be sufficient to enable their development.

- ***Coexistence and segregation costs***

The EU has established rules to ensure the coexistence of GM crops with conventional crops, involving a number of technical and legal specifications, ranging from minimum distance requirements for cultivation to liability and damage measures. In addition, compulsory labelling of GMO products implies market segregation and a system of identity preservation throughout the value chains. These measures lead to additional costs, which are negatively correlated with the thresholds.

authorised for the adventitious presence of GM material, and can have the effect of increasing prices (Fulton & Giannakas, 2004). These coexistence rules are all factors that discourage farmers from adopting GM plants (Demont & Devos 2008).

There are no published figures for the costs of segregation and coexistence in the case of plants obtained using NTGs. However, it can be assumed that, in the presence of similar regulations, the effects would be of the same nature as in the case of GMOs produced by transgenesis.

One particular point concerns the question of product traceability. Several publications deal with this subject, considering that an important characteristic of NTG applications lies in the difficulty of distinguishing, using analytical methods, the products derived from them from those resulting from conventional varietal selection (non-NTG). If consumers are to be informed of the type of product they are being offered by means of compulsory labelling, then the question arises as to how they can be guaranteed this information and how it can be checked using standardised detection methods on these products.

In the event of varieties obtained using NTGs arriving on the market, there would also be the question of the interaction between products derived from them and products complying with specifications that exclude these technologies, such as organic farming in particular (see section 7.4.2.7).

Firstly, as in the case of GMOs derived from transgenesis, the aim would be to prevent unintentional contamination, which would result in traces of NTG appearing in products derived from organic farming and penalise these products, which would be downgraded to conventional products. This point raises the question of the arrangements for coexistence in the field (distances between plots of NTG crops and organic farming plots), segregation throughout the chain (storage cells, modes of transport, etc.) and coverage of the damage caused by the downgrading of organic farming products. There is no specific analysis of these points in the economic literature on NTGs, but the conclusions would probably be the same as for GMOs derived from transgenesis. As the costs of coexistence, segregation and damage are borne by the GMP producer, this would make it difficult for NTG-based crop sectors to emerge.

Moreover, as Hamburger (2018) notes, in the event of NTG-derived varieties entering the market, specifications excluding NTGs from organic farming products may, on the one hand, increase consumers' willingness to pay for the organic farming product. But the entry onto the market of lower-priced products based on NTGs (thanks, for example, to productivity gains) would increase the price gap with organic farming products, which would have a negative effect on organic market shares, unless the prices of these products were lowered, which would make it more difficult to maintain demanding specifications. The weight of each of these effects is difficult to estimate a priori, and would require empirical studies if coexistence were to be established.

Summary

The economic impact of the introduction of plants obtained using NTGs on the sectors will depend on the nature of the traits being innovated.

The first type of innovation involves varietal innovations aimed at increasing the effectiveness and/or efficiency of agricultural and agro-industrial production. The economic interests of producers and the upstream levels of the supply chain will be decisive in the development and adoption of these innovations. In the presence of GMO-type regulations, based on strict rules of coexistence and product segregation, the additional costs associated with these rules are likely to be higher than the gains for the players in the sector, due to the probable devaluation of the product by consumers (as products derived from NTGs offer nothing more to consumers than conventional products, suppliers of products derived from NTGs could only enter the market at a lower price than conventional products). As with GMOs derived from transgenesis, there is little chance of these varietal innovations developing in the human food sector.

A second type of varietal innovation is part of companies' product differentiation strategies (allergen-free products, different sensory and nutritional qualities, etc.). The aim here is to capitalise on the potential willingness of a proportion of consumers to pay for these distinctive characteristics. This type of strategy could be envisaged, even in the case of restrictive regulations on coexistence, since traceability and segregation requirements would be imposed, in any case, for reasons of commercial credibility in the eyes of consumers. However, this would require selection objectives to be defined in a coordinated way between players in the industry, based on contractual relations between seed companies, producers and final product marketers. Given the additional costs and the complexity of the co-ordination arrangements to be put in place, the first condition is that the distinctive characteristic should be significantly valued by consumers.

A third type of innovation concerns varietal innovations designed to meet environmental, health and/or social challenges, for which there is not necessarily an economic incentive to adopt them (e.g. restoring biodiversity). The private costs of these environmental or health innovations may exceed the anticipated private benefits.

7.4.1.5 Consumers and NTGs

Box 2: Perceptions of food biotechnology in Europe (Eurobarometer, EFSA)

The Eurobarometer survey on food safety, commissioned by EFSA in 2022, provides information on the perception of genetic modification in food by 26,509 European citizens.

In response to the question "Please tell me which of the following topics you have heard of", 56% of respondents have heard of "genetically modified ingredients in food and drink", and 29% have heard of "the use of new biotechnologies in food production, e.g. genome modification". The proportions of the population in France (N=1034) are 59% and 28% respectively. By way of comparison, at European level, the least familiar subject is 'nanotechnologies applied to food production' (25%) and the most familiar is 'the use of new biotechnologies in food production, e.g. genome modification' (25%).
"Additives such as colourings, preservatives or flavourings used in food or drinks" (70%). In this respect, France's position is in the central zone of distribution, near to

of the European average. Germany has proportions of 68% and 35%, i.e. almost 10 percentage points higher than France for each measure. Between the two measures, the difference in points ranges from 12 points (Luxembourg: 54% and 42%) to 47 points (Lithuania: 68% and 21%). Slovenia (77% and 46%) and Sweden (70% and 55%) have the highest proportions, while Romania has the lowest (39% and 20%). There is relatively wide disparity between the different European countries in terms of their knowledge of genetic modification in food.

The table (Tab.1) below compares these results with those of the 2019 survey (it is not possible to compare with the 2010 survey, which only considered levels of concern for these different subjects). Both in Europe and in France, the proportion of respondents who have 'heard of' 'genetically modified ingredients' has fallen (by 6 points in France). This may indicate a reduction in people's awareness of the subject. However, with regard to interventions on the genome, even though the question has changed significantly, the proportion of respondents who are aware of this has increased by 9 points.

Tab. 1: Proportion of respondents "having heard of" EU27 in France, in 2019 and 2022 (Eurobarometer 2019, Eurobarometer 2022)

	2019		2022	
A entendu parler :	UE27 (n=26603)	France (n=1029)	UE27 (n=26509)	France (n=1034)
Des ingrédients génétiquement modifiés dans les aliments et les boissons	58%	65%	56%	59%
De la correction du génome	20%	19%		
De l'utilisation de nouvelles biotechnologies dans la production alimentaire, p. ex. la modification du génome			29%	28%

Note: the EU figures are significantly different from the reports because here we have removed the UK in 2019.

A question was asked about the concerns of the subjects the respondents had heard about. The table (Tab.2) below shows the percentage of respondents concerned (first and second concern) about the subjects they had heard about. While concern about GMOs has not changed at European level (26-27%), it has dropped by 7 points in France to 21% of respondents. In addition to the table (Tab.1) above, we can emphasise that the French are hearing less about GMOs and are less concerned about them in terms of food. Concern about genome modifications is relatively low at both European and French level, but has increased significantly between the two surveys. By way of comparison, the percentages of concern in Germany are 30% for GMOs (unchanged since 2019) and 7% for genome modifications (up since 2019).

Tab. 2: Proportion of respondents concerned about issues they have "heard about" in the EU27 and France, in 2019 and 2022 (Eurobarometer 2019, Eurobarometer 2022)

	2019		2022	
Sujets vous préoccupant le plus (2 premiers) en matière d'alimentation :	UE27 (n=25848)	France (n=1015)	UE27 (n=26132)	France (n=1026)
Les ingrédients génétiquement modifiés dans les aliments et les boissons	27%	28%	26%	21%
La correction du génome	4%	3%	-	-
L'utilisation de nouvelles biotechnologies dans la production alimentaire, p. ex. la modification du génome	-	-	8%	5%

By way of conclusion, the results of the Eurobarometer surveys show that, on average, respondents will be less concerned about "genetically modified ingredients" in 2022 than in 2019.

- ***Consumers and the acceptability of products derived from genetically modified plants in the literature***

NTGs are seen in the literature (2010s, for example: Lucht, 2015) as a potential response to the rejection of transgenesis technologies commonly referred to as 'GMOs' by consumers and citizens. There is a large body of literature on the perception and evaluation of food biotechnologies (GMOs) by consumers. An exhaustive review of this literature is not included in this report, but a number of major findings are mentioned that could provide food for thought on genome-editing technologies. The meta-analyses carried out (Lusk et al. 2005; Danneneberg, 2009; Frewer et al. 2013; Hess et al. 2016) document the fact that GMOs derived from transgenesis are generally perceived negatively by consumers. Paudel et al. (2023b) highlight some key points from this literature on the perception and acceptability of technologies: (1) there is heterogeneity in behaviour according to socio-demographic dimensions, (2) within GMO foods, consumers are more favourable to those with tangible benefits (nutritional content, environmental benefits, food safety in developing countries), (3) providing positive (favourable) information on the technologies used and their benefits could in some cases improve consumer acceptability, (4) but consumers exposed to negative (unfavourable) information tend to perceive more risks and are less willing to accept these products (bearing in mind that consumers are generally exposed to a continuum of types of information), (5) finally, European consumers reject GMO foods more widely than North American consumers. One of the challenges of the emerging literature on NTGs is to explore these different dimensions, which have been documented for GMOs derived from transgenesis. Other authors, however, feel that a "more nuanced understanding of consumer perceptions, going beyond the knowledge deficit model, is needed" and observe that "cultural worldviews are important" (Yang and Hobbs, 2020) (Canadian study, n=697).

First of all, it is **important to stress that the scientific literature on consumer behaviour towards NTG plants is essentially based on hypothetical products (food, plants). In fact, most of the products concerned are under development (or pre-development) and are not yet available.**

still accessible on the markets (whether for farmers, processors or consumers), at least within the European Union. As a reminder, there are a few exceptions in recent and limited markets, such as soya, apples (Arctic©, USA, Canada), potatoes (Simplot Innate®, USA, Canada) and tomatoes (Sicilian Rouge, Japan) (see section 3.4).

The systematic literature review carried out by the WG (as mentioned in section 7.3) identified 36 scientific contributions dealing with the question of consumers' attitudes to products derived from NTGs. Of these, 19 are common to the literature review conducted by Beghin and Gustafson (2021) on consumer attitudes to and appreciation of food products that have been transformed using new plant engineering techniques (NPETs)[138] including NTGs. Of the 59 articles they identified, at least 37 dealt with CRISPR-Cas9-type gene editing (NTG). The most studied plant food products are food in general (without further precision), apples, potatoes and rice. The consumers most frequently surveyed were North Americans (USA, Canada), Japanese and Italians.

The general finding of Beghin and Gustafson (2021) (shared with other literature reviews; i.e. Strobb et al. 2023; Lindberg et al. 2023; Lemarié and Marette, 2022) is that consumers place less value on NPET products than on their conventional alter egos, even if heterogeneities appear. Attributes geared towards consumer or societal benefits seem to be valued more highly than those geared towards producer benefits (savings/productivity). Furthermore, these products (NPETs) appear to be preferred to transgenic products (GMOs).

These findings can be illustrated by the study by Rousselière and Rousselière (2017). On the basis of Eurobarometer (2010), they observe that while the rejection of biotechnologies is significant, it is heterogeneous between European countries. Furthermore, it appears that to reduce the use of plant protection products, Europeans find vertical transfer technologies (NTGs) more acceptable than horizontal transfer technologies (GMOs derived from transgenesis).

The study conducted by Giacalone and Jaeger (2023) measures the acceptance of several technologies with environmental impacts, among consumers in 4 countries (Australia, India, Singapore, USA, n=2494). Their various analyses led to the identification of three levels of acceptance: (1) High level of acceptance: plants from urban farms, plants packaged with a modified atmosphere; (2) Medium level of acceptance: fish reared in aquaponics, plant-based alternatives to meat and milk, NTG; (3) Low level of acceptance: insects as ingredients, cultivated meat, cultivated fish. 20% of consumers have a high level of acceptance, meaning that 80% have moderate to low levels of acceptance of these new technologies. Moreover, Indians react more positively to these technologies than Americans and Australians.

Baum et al (2023) studied the mechanisms at work in the assessment of NTG products among American consumers (n = 158). Their survey links individual character traits, the perceived risks and benefits of biotechnologies, and perceptions of the technology and the environment with behavioural intention towards CRISPR in food. Their analyses highlight a significant effect of perceived benefits on the intention to adopt NTG foods. The results do not contrast

[138] According to Beghin and Gustafson (2021), the term new plant engineering techniques (NPETs) is fairly broad and includes genome editing, cisgenesis, intragenesis, RNA, etc. The term "new plant engineering techniques" (NPETs) is also used in the context of plant breeding.

pro-technology and pro-environment perceptions. It appears that respondents are more interested in understanding the potential benefits than in deterring the existence of any possible risks.

Lindberg et al (2023) conducted a study of 2000 Americans on the link between the adoption of products derived from NTG plants and confidence in institutions (for the regulation of practices and uses). According to their results, 29% are ready to adopt products derived from NTG plants and have confidence in government regulatory institutions (FDA) and the biotechnology industry. 30% are not ready to adopt products derived from NTG plants and tend to trust consumer and environmental protection groups. Finally, 41% are uncertain about the adoption of these types of products and who they trust in terms of managing the potential development of NTGs. Furthermore, 75% of respondents would like products derived from NTG plants to be labelled, but have little confidence in government agencies to do so. This suggests that US consumer confidence in these types of products (and their labelling) can only be achieved through a tripartite solution involving universities, NGOs and the institutional regulator. According to the authors, this reliance on third parties is linked to the fact that for these food biotechnologies, consumers are faced with uncertainty in terms of risks and unexpected consequences, that they have little knowledge of these technologies and that they feel a limited ability to change the food production system.

- ***The effects of information on consumer preferences***

Initially, it appears that consumer knowledge of NTGs is relatively limited (Baum et al. 2023; Strobb et al. 2023, for example). This initial low level of knowledge of NTGs is in line with the Eurobarometer results for Europe and France. Information and increased knowledge may therefore appear to be a vector which can modify the perception of products derived from these technologies in one direction or another.

A number of articles study the effects of information on consumer preferences. Generally speaking, the information disseminated during surveys consists of explaining what an NTG (genome-edited) product is and how it is not a GMO (genetically modified) product. The results of representative studies from the literature are presented below.

Nales and Fisher (2023) conducted an analysis of focus group data to assess consumer perceptions of genetic technologies in food (Netherlands, Italy, Czech Republic). According to their results, the perception of the naturalness of a process is a very strong factor. The more invasive the technology used, the less natural it is perceived to be, and the more consumers reject it. The introduction of information and discussion between participants reinforced the initial reactions to genetic technologies, except for NTG, which was ultimately perceived more positively than initially. This is associated in particular with the fact that consumers have little, no or poor knowledge of the process. Baum et al (2023) have also emphasised this low level of initial knowledge of NTGs, a point echoed for Europe and France by the results of the Eurobarometer (see Box 2).

Hu et al (2022) conducted an online survey of 1,096 Americans aged 18 and over who were involved in household purchasing decisions. They were divided into four groups

according to the medium used to disseminate information about the technologies (text, computer graphics, video + control group). The groups were made up of between 40% and 45% men, with an average age of 46. The groups are relatively balanced, but not necessarily representative of the American population. The products being investigated are citrus fruits: genetic modification would enable them to be protected against a disease ravaging citrus production (citrus greening). Before receiving information, the participants devalued biotechnology in comparison with conventional products. Individuals receiving information in text form reduced their willingness to pay for the conventional product and increased their willingness to pay for the biotechnology products (with no difference between them). Individuals receiving information in the form of computer graphics or videos had the same reactions: their valuation of NTG products was higher than their valuation of transgenic products.

Paudel et al (2023a, 2023b) also conducted an online survey of 1,573 Americans aged 18 and over who were involved in household purchasing decisions. The sample, 49% of which was made up of men with an average age of 46, was broadly representative of the American population (ethnic origin, income, level of education, etc.). The subject of the survey was soya oil (oil from modified soya containing more oleic acid and being tolerant to herbicides) on the one hand, and apples (modified apples being less sensitive to oxidation) on the other. The groups that received information (detailed definition of biotechnologies and descriptions of their effects in terms of health and the environment) increased their willingness to pay for NTG soya oil, but not for GM soya oil, nor for apples, regardless of the technique used (directed mutagenesis or transgenesis). However, in general, the results of Paudel et al (2023a, 2023b) indicate that the provision of information on the technology and its benefits for health and the environment has no impact on consumers' willingness to consume foods derived from GM plants. In addition, they observe that consumers prefer genetic developments to be carried out by national *start-ups* or universities rather than by multinational companies. Finally, they show that the type of relationship that consumers have with technologies applied to food (technology averse, technology neutral, technology enthusiast) has a significant effect on the perception and acceptability of NTGs. The most averse have a good knowledge of the technologies and reject them. Enthusiasts have confidence in them and are prepared to consume the products resulting from these practices.

Box 3: Effects of misleading information about biotechnology on the evaluation of labels

In a very recent working paper, Lin et al (2023) report on the effects of false information relating to biotechnologies on the evaluation of different labels applied to apples: conventional, GMO (*bioengineered*), certified GMO-free, gene-edited (NTG) and organic farming. Their study was conducted online with 1,270 American consumers (USA) divided into 5 groups: (1) a control group receiving no specific information, (2) a group receiving false information, (3) a group with tools for reading the information before receiving it (*prebunking)*, (4) a group with tools for reading the information after receiving it (*debunking)*, (5) a group with tools for reading the information before and after receiving it. On average, organic and certified non-GMO apples were valued higher than the others (between

3.5 and 4 USD / pound). Conventional apples have a willingness to pay of close to USD 3 per pound. Biotech apples are valued at between 2 and 2.5 USD / pound. Unlike the other studies, NTG apples were valued less highly than transgenic apples, but transgenic apples are referred to here as "bioengineered" apples. Compared with the control group, false information devalues biotech apples. This effect was not improved by ex-post reading tools. However, the ex-ante reading tools virtually cancelled out the effects of the misinformation. The combination of the two reading tools does not have a homogeneous effect between treatments. Thus, the devaluation of biotechnologies is not mitigated by preventive information practices, but can be increased by the dissemination of false information. (It should be noted that at the end of the survey, a debriefing was set up to explain that the information was false and to prevent participants from leaving with false beliefs).

- ***Results obtained on samples of the French population***

Shew et al (2018) questioned 499 French people (as well as 451 Americans, 444 Australians, 458 Belgians and 463 Canadians) in an online survey about a hypothetical glyphosate-resistant rice thanks to a genetic modification brought about by transgenesis or thanks to NTGs (GE by CRISPR-Cas9). 51% of the French people questioned were men, with an average age of 45 (according to the SSI / Dynata survey institute, they are representative of the general population). Among them, 30% would be prepared to consume this rice regardless of the technology used (compared with 46% to 56% for consumers in the other countries surveyed: in ascending order, the United States, Canada, Belgium and Australia); 46% do not want either of these two products and prefer the conventional version (without modification or resistance). It should be noted that 20% are prepared to accept a product obtained using NTG by CRISPR-Cas9, compared with just 3% prepared to accept a product derived from transgenesis. The 30% of the French sample who were prepared to consume the product would do so in return for a price reduction of $2.12 less for the NTG produced by CRISPR-Cas9 and $2.11 less for the product produced by transgenesis, for a *pound of* rice.[139]. In this case, there is no difference between the willingness to pay for the two types of product (the Americans would like a greater reduction; the Canadians and Belgians, less; the Australians are close to the French).

Marette et al (2021a) questioned 162 French people (and 166 Americans) in the laboratory about an apple that does not oxidise when cut. The French sample was representative of the French population (quota method). The American sample is unbalanced, with more women and a higher level of education than the general population. On a basis of 100 for the conventional product, the French reduce their willingness to pay (WTP) to 90-93 for the variety with the non-browning characteristic (this characteristic is valued by the American sample: 109-112). The WTP is reduced to 43-50 when biotechnology is announced (82-83 for the Americans). As far as the French are concerned, on average, genome-edited apples are better accepted than genetically modified apples (but without any really distinctive characteristics). Finally, 43% of the French boycott the product (compared with 20% in the USA). Based on the same sample, Marette et al (2021b) point out that after receiving information on all the technologies, 34% of participants in France and 47% in the United States value the product in question (above 100). This category of consumers may constitute a favourable basis for the emergence of this type of product on the market. However, according to Lemarié and Marette (2022), if there are not enough of them compared with consumers who reject these products, the emergence of the

[139] One imperial pound is equivalent to 0.45 kg.

is becoming less likely. This is all the more true as the proportion of consumers rejecting these products increases the pressure on traceability and labelling requirements and on regulatory mechanisms. In this sense, the breakdown between favourable and unfavourable consumers is an important pivot to identify in order to mobilise the appropriate systems (particularly information systems). However, the relevance of these information tools (including labelling) depends on the ability to distinguish NTG products from other products.

Summary

With regard to consumer behaviour, the literature consulted shows that, even if food products derived from biotechnologies (GMOs and NTGs) are *a priori* less well accepted and appreciated by consumers than conventional products, there is a certain heterogeneity of perceptions between different consumer profiles and between countries, even within the European Union. Although some studies show that consumers with a good knowledge of the technologies are the most averse and tend to reject them, other studies emphasise that the information available on biotechnologies and their differences could change the positions of some consumers from rejection to acceptance of food products derived from them, especially as products derived from NTGs are associated with lower prices. Furthermore, the studies do not allow us to identify categorically whether consumers appreciate NTGs differently depending on the potential benefits (productivity, environment, health) they bring to food products or production processes. However, insofar as NTG-derived products are not currently available to consumers, the decisions and behaviour observed remain declarative (intention rather than action). Finally, no study has assumed that NTG products are untraceable or unlabelled. In this sense, there is still uncertainty as to how consumers would react if all or part of the foodstuffs derived from plants obtained using NTGs were not traced and labelled right through to the final product.

Generally speaking, the acceptability of and willingness to pay for NTG food products places them between GMO products and conventional farming products, which are themselves less well perceived than organic farming products. Further studies, more precise in terms of the characteristics of the products on offer and the information disseminated in particular, would be necessary in order to gain a better understanding of the mechanisms of acceptance and rejection. The question of the intensity of this information could also be raised.

7.4.1.6 Choice of regulation

Bartowski et al. (2018) highlight 4 important characteristics of NTGs that need to be taken into account when discussing regulatory choices: (i) the difficulty of tracing NTGs in the resulting organisms (and products), which raises the question of how controls should be carried out and leads to the opposing view of regulation based on the process versus the product; (ii) the decentralisation of knowledge and uses made possible by easier access to information; (iii) the difficulty of tracing NTGs in the resulting organisms (and products), which raises the question of how controls should be carried out and leads to the opposing view of regulation based on the process versus the product; (iv) the decentralisation of knowledge and uses made possible by easier access to information.

(iii) uncertainties relating to *off-target* alterations, which require a combination of *ex-ante* regulatory procedures, delimiting the framework for the application of NTGs, and *ex-post* procedures, based on rules of liability in the event of unexpected effects; (iv) rapid developments in knowledge and plant breeding technologies, which may rapidly render certain regulations obsolete and make it necessary to put in place appropriate modes of governance.

Kok et al (2019) distinguish between two main types of legislation relating to new plant varieties. In some countries (Europe, Brazil, Australia, etc.), it is the technologies used in the selection process (*process-based selection*) that determine the procedure for authorising the marketing of the new variety. It is therefore the way in which the variety in question is obtained that is considered. In other countries (United States, Canada, etc.), the legislation is product-based selection: it is the specific characteristics of the new variety that determine the authorisation procedure, regardless of how it was developed. For Eckerstorfer et al (2019), the two regulatory frameworks have different properties. Product-based regulation is more flexible because it can be applied to any technology, whereas process-based regulation has to be adjusted each time a new technology is introduced.

Even if, as Lemarié and Marette (2022) note, this distinction is somewhat simplistic, since the existence of a regulatory issue is directly linked to the emergence of a new technology (and therefore to the varietal selection process), it is useful in the case of NTGs because it crosses the issue of traceability and the possibilities of distinguishing between products derived from NTGs and those that are not.

Indeed, if it is not possible to distinguish between NTG and non-NTG products (Bartowski et al. 2019), then this means that some of the current GMO regulations are unsuitable, as the coexistence and labelling rules are based on the possibility of identifying a DNA sequence that is foreign to the controlled species. For various authors (Kok et al. 2021), since it is not possible to distinguish analytically between varieties obtained by new plant breeding techniques and those bred conventionally, only a truly product-oriented approach, assessing each new plant variety on its own merits in terms of modified characteristics and associated risks, can guarantee food and environmental safety (Hartung and Schiemann, 2018).

This difficulty in distinguishing NTG products from conventional varieties raises the question of the risks of contestation and fraud. One consequence of these uncertainties about the NTG or non-NTG characteristics of imported products is highlighted by Gocht et al (2021). These authors hypothesise that this could lead EU players who import products (for animal feed, for example) to shift their demand towards products produced within the EU, rather than internationally. The economic modelling of markets proposed by these authors shows that the development of these innovations could have significant impacts in terms of price rises and increased levels of intensification within the EU.

A final option is to differentiate the rules according to the level of alteration of the initial genome associated with the technology by, for example, establishing exemptions for SDN1 or even SDN2 levels and retaining process-based regulation for SDN-3. Australia has announced that SDN-1 crops will not be subject to the current regulations on

GMOs (see section 4.1). Argentina and Brazil have established a new policy whereby GM crops without transgenes (100% transgene-free crops) may be exempted from the scope of GMOs. In Japan, SDN-2 crops can also be exempted from the scope of GMOs. Considering the various possible options, Van der Berg et al (2020) analyse several scenarios for regulatory change within the EU.

To analyse the impact on international trade, Smith et al (2021) compare scenarios according to whether or not countries adopt NTG technology, distinguishing between countries that are net importers (such as the EU) and countries that are net exporters of plant products (soybeans, for example) (cf. section 7.4.2.3). The authors attempt to anticipate the possible effects of these scenarios on prices, trade and the earnings of producers in the various countries. **The results of these different regulatory scenarios are not presented in the report. The socio-economic issues associated with plants and products obtained using NTGs under different regulatory options (the current GMO regulations, the type 1 NTG regulatory option proposed by the European Commission and a regulatory option proposed by the WG) are analysed in section 7.4.5.**

Summary

The publications analysed highlight four important characteristics of NTGs that must be taken into account when discussing the issues at stake in connection with regulatory choices: (i) the difficulty of tracing NTGs in the resulting organisms (and products) on the basis of current analytical methods, which raises the question of the conditions and procedures for controls to discriminate between products on the markets; (ii) the difficulty of tracing NTGs in the resulting organisms (and products) on the basis of current analytical methods, which raises the question of the conditions and procedures for controls to discriminate between products on the markets.
(ii) the decentralisation of knowledge and uses made possible by easier access to the technology, which could potentially open up the market to new players, but could also increase the risks (e.g. of uncontrolled off-target alterations), if these players have less experience than the traditional players in the breeding market; (iii) uncertainties relating to *off-target* alterations, which require a combination of *ex-ante* regulatory procedures, delimiting the framework for the application of NTGs, and *ex-post* procedures, based on liability and compensation rules in the event of unexpected effects; (iv) rapid developments in knowledge and plant breeding technologies, which may rapidly render certain regulations obsolete and make it necessary to put in place appropriate modes of governance.

A first trade-off discussed in numerous articles concerns the choice between process-based *and* product-based regulations. In the first case, it is the technologies used in the selection process that determine the procedure for authorising the marketing of the new variety. In the second case, the legislation is product-based: the specific characteristics of the new variety determine the authorisation procedure (on a case-by-case basis). The two regulatory frameworks have different properties: product-based regulation is more flexible because it can be applied to any technology, whereas process-based regulation has to be adjusted each time a new technology is introduced.

A second trade-off concerns the possibility of differentiating the rules according to the level of alteration of the initial genome associated with the technology by establishing, for example, exemptions for products obtained by SDN1 or even SDN2 techniques (which could be assimilated to conventional products) and retaining process-based regulations for products derived from SDN3 including transgenes.

A third trade-off concerns the role of *ex ante* regulations (e.g. coexistence rules in the field) and liability rules in the event of *ex post* damage. An important point here, in the event of new varieties derived from NTGs being introduced onto the market, is the interaction between products derived from them and products complying with specifications that exclude these technologies, such as organic farming in particular. This will determine how products derived from NTG varieties are identified (detection and labelling) on the market and how they coexist with products derived from non-NTG varieties (which will influence the costs of segregation, control and preservation of product identity). To date, there is no specific analysis of this point in the economic literature on NTGs, but the parallel with GMOs derived from transgenesis could provide food for thought.

7.4.1.7 Controversies surrounding NTGs and the positions of the players involved

The elements of analysis of the socio-economic issues presented in the previous sections are the subject of a number of scientific controversies highlighted in the various topics covered. This section presents the views and positions of the various types of stakeholder concerned by plants and products derived from NTGs. These arguments "for" or "against" NTGs are linked to the various potential impacts of plants and products derived from NTGs analysed in the previous sections. The analysis of controversies presented in this section is based on scientific articles and hearings of stakeholders concerned by plants and products derived from NTGs.

NTGs are controversial processes from a variety of angles (technical, economic, regulatory, environmental, health, social, political, etc.). What are society's views on NTG? What are the positions, visions and arguments put forward by the various users and audiences concerned: NGOs, associations, industrial players, organic sector players, civil society? **NTGs do not concern a single public, but *a number of publics***. While in some discussions the public is often reduced to the figure of the consumer, it has to be said that NTGs interest and concern a wider and more heterogeneous range of players and social worlds. This diversity of audiences and points of view was taken into account in the referral through an analysis of existing literature, but also through hearings with several stakeholders concerned by NTGs. Table 10 gives an overview of the arguments and points raised at these hearings.

The analysis of controversies, discussed in this section, provides some answers to these questions. Controversies have a major advantage when it comes to science and technology, because they are empirically very rich moments, during which the players mobilise, take a stand, write texts and spell out their arguments. Controversies are therefore an ideal place to observe in order to

examine the links between science and society. The second advantage of studying controversies is that it allows us to grasp their epistemic and political effects. Controversies often lead to the production of new rules, new laws and/or new knowledge.[140]. To put it another way, the analysis of controversies not only enables us to grasp the differences between actors and stakeholders, but also - and above all - to grasp their productivity and their capacity to generate better, more socially robust knowledge.

- ***The arguments for and against NTGs***

Several articles in the literature indicate that NTG proponents develop arguments relating to the nature of the products obtained and the reduced risks compared with GMOs produced by transgenesis, to the issue of food safety and resilience in the face of climate change, and to better economic performance and greater sharing of economic value.

For their supporters, the products obtained by means of NTGs are not GMOs but are more the result of conventional selection or mutations that could have occurred naturally (Bain et al. 2020). In their view, NTGs are different from GMOs because the latter involve "a process that cannot occur naturally because a foreign gene cannot enter the DNA of a plant by its own means" (Bain et al. 2020). Some NTG-derived products would even be indistinguishable from those produced using traditional plant breeding techniques or natural mutations. Genome-editing techniques are more precise, more targeted and faster than techniques for obtaining GMOs (Bain et al. 2020), allowing genome modifications that would lead to few unintended mutations and off-target mutations (Bartowski & Baum, 2019).

With regard to the risks to public health, an argument based on historical use is put forward. Since agriculture developed by modifying the gene pool of wild species through the domestication of cultivated plants, we have been eating food from plants modified by humans for thousands of years. In this respect, the advantage of biotechnologies is that they allow us to be more precise and to modify only one gene at a time, if we wish (Ajoykumar et al. 2020). Since the start of GMO plant production, advocates of these technologies have stressed that they present no more health and environmental risks than conventional agriculture (Anders et al. 2021; Woźniak-Gientka et al. 2022). There is therefore no reason to believe that there are any new risks with genome-editing techniques compared with conventional breeding techniques (Bain et al. 2020).

In the context of climate change (increasing drought) and a growing world population, proponents of NTGs argue that they could secure the future of food security with the rapid development of crop varieties adapted to climatic stresses (Anders et al. 2021). NTGs could simultaneously increase yields while incorporating traits for resistance to pests, disease and the effects of drought and climate change (Bain et al. 2020). The promise of NTGs is to do 'more with less': more soya on less land.

[140] "Public struggles between coalitions and public focus events are necessary to force change in surveillance systems over time, so that they are more responsive to emerging conditions and problems" (Kuzma, 2022).

of land, with fewer inputs, particularly water, fertilisers and pesticides (Bain et al. 2020).

A final argument is aimed at countering the criticisms associated with the GMO sector, which is concentrated in the hands of a few large firms (Monsanto, Bayer, etc.). At least in the case of the CRISPR-Cas9 technique, due to the low cost of applying the technology, its simplicity of use and its greater flexibility, investment by large multinational companies would no longer be as essential (Bartowski & Baum, 2019). According to the FNSEA, there is "*a significant number of seed companies that are in a position to access the technology (...) and not just (...) a certain number of major players who are the only ones able to afford it (...) So there is this aspect of pluralism*" (cf. FNSEA hearing).

NTGs would provide an opportunity for small businesses and public sector scientists to fill a niche left vacant by large companies, developing products with features that are beneficial to farmers, food businesses and consumers, but not necessarily profitable (Bain et al. 2020). The result would be greater and more widely distributed social and economic benefits (Bain et al. 2020). However, these potential benefits of NTGs are the subject of much controversy.

Opponents of gene-editing techniques note that many of the same claims about the benefits of GMOs, such as the promises (to reduce pesticides, provide nutritious food, and help feed the world) that they say have not been kept, are being used again to justify the benefits of NTGs (Bain et al. 2020). In the hearings conducted as part of the assessment, the promise strategy was raised by several players:

> *"We're back to the same promises. The first promises were to feed the world. However, since the development of transgenic GMOs, the number of malnourished people and people with deficiencies has increased (...) The second promise is an improvement in quality and taste (...) We are therefore seeing exactly the same promises about quality, the fight against hunger in the world and a reduction in inputs*" (cf. FNE hearing).
>
> *"The arguments used today are the same as those used before (...) It's to say that we're going to do extraordinary things, that we master the whole genome and that we're going to solve all the problems, that (...) the tomatoes of the future will be tasty, (...) that it was the death of the French seed industry (...) Now we have the information. We can say that twenty years on, what was said twenty years ago was heresy, a lie*" (cf. FNAB hearing).
>
> *"These are big promises. We haven't seen anything to suggest that it will actually happen*" (cf. FCD hearing).
>
> *"We're really in an economy of promises, which can only take us back 30 years to the same promises made about slightly similar varieties, so we need to be cautious*" (cf. Synabio hearing).
>
> *"It's the same type of promises*" (see Confédération Paysanne hearing).
>
> *"I regret that the most ardent promoters of this technology are leading farmers and their collective organisations to believe that NTGs are the alternative to plant protection products and that, as soon as the regulation has been adopted at European level, they will be able to use them.*

> *They're going to have varieties that will enable them to stop using herbicides, especially insecticides and fungicides. This is highly abusive*" (see Semae hearing).

This 'promise economy' can also be observed in other scientific fields, whether in synthetic biology (Mackenzie, 2013; Schyfter and Calvert, 2015), nanotechnology (Selin, 2007, Borup and Konrad, 2004) or geoengineering (Talberg et al. 2018, Stilgoe, 2015). This observation - that the emergence of new fields and new technologies is accompanied by optimistic expectations and promises - is useful to remember here, because it gives us a historical perspective on scientific development (which we do not yet have in the case of NTGs) and qualifies the promises made explicit by calls for greater 'modesty' regarding the possibilities opened up. According to Macnaghten et al (2020), the initial promises made by GMO advocates - which predicted social, environmental and economic benefits for both the countries of the North and small farmers in the countries of the South - have not materialised (see also Lindberg et al (2023), p. 359).

For their opponents, NTGs remain new genetic modification techniques whose risks are not yet fully understood (van der Berg et al. 2021). Unintended DNA modifications and the potential for off-target effects, even horizontal gene transfer (Ajoykumar et al. 2020), could have negative effects on human and environmental health (Bain et al. 2020).

They also note that plant breeding research remains dominated by the private sector, which has its own interests that may differ from those of the public good (Ajoykumar et al. 2020). NGOs critical of GMOs see NTGs not as neutral technologies but as an extension of the power that agricultural biotechnology companies hold over industrial agricultural systems, and therefore over farmers and consumers (Helliwell et al. 2019). In particular, some stakeholders fear a "*further concentration of the seed industry and therefore a supply for farmers, for agricultural sectors (...) that will be reduced (...) The risk with these technologies, as happened with GMOs, is that all the value created by this innovation will be captured by the holders of a few patents. The balance of power can be very unbalanced*" (cf. SEMAE hearing).

A study of the controversies highlights several points: 1) that the scope of the debates on genetics is often relatively narrow: focused on technical aspects, risk and efficacy, it leaves in the shade a whole series of issues, such as intellectual property, market dynamics, the question of justice and equity, and ethical issues; 2) that technological regulation also involves democratic issues and public decision-making. To put it another way, the issue of regulating plants and products obtained by means of NTGs is one that concerns society as a whole, and not just the scientific world.

NGOs and associations also criticise the terminology used (Helliwell et al. 2019). The metaphor of "editing", the inclusion of genome editing in the broader category of New Plant Breeding Techniques (NPBT), and the "precision" language used to describe the practice of genome editing, would sanitise the controversy by using more acceptable language and make the debate unapproachable for a lay audience. Helliwell et al (2019) quote one of the stakeholders interviewed: "The repositioning of new genetic engineering as 'new breeding techniques' (NTG) was the industry's first step in making this new generation of GMOs appear friendly and close to plant breeding...".

classic". The CNAFAL speaks of "*propaganda that consists of fiddling with words*" (cf. CNAFAL hearing). Opponents prefer to talk about "new GMOs" or "GMOs 2.0" (Bain et al. 2020).

Over and above this terminology in relation to technical processes, the potential use of the word 'sustainable' to describe certain NTG-derived plants is also being debated. *The* FNAB believes that "it is *really the systems that are sustainable, not the so-called characteristics that will be sustainable*". The FCD points out: "*The subject of sustainability is of particular concern to us, because it would help to explain the benefits of these varieties to the end consumer (...) this would promote their acceptance*". According to Synabio, "*the sustainable aspect is not as obvious as that (...) it's the system that determines whether you'll be in a sustainable system or not. A sustainable system, yes. A sustainable plant, no*".

A major concern of NGOs opposed to GMOs is that consumers should be able to choose to consume non-GMO products. The challenge is twofold: to ensure traceability (to provide information on the quality, composition and history of a product) and labelling (to provide information on the presence or absence of a certain element). If NTG-derived products are exempted from GMO regulations, there will be no regulatory obligation to introduce traceability for these products and consumers will not be able to select them, according to Helliwell et al (2019). This last point is in line with the concerns of consumers in general (see section 7.4.2.5). In a meta-analysis of public perceptions around the world, Woźniak-Gientka et al. (2022) highlight that despite different attitudes (for or against gene editing), respondents from all regions of the world agreed that labelling of GM or edited products is important and necessary, as consumers want information about the type of genetic technology applied to produce food (cf. Section 7.4.2.5).

A study of the controversies and debates surrounding NTGs, as well as GMOs derived from transgenesis, has shown that the public, as consumers, have a preference for making the issue of genetic modification more visible, so that they can choose whether or not to consume a certain product.

If we ask the various players involved in plants and products obtained using NTGs, their positions become more diverse and complex. The FNAB insists that there should be "compulsory" information and that "*all products (...) should be clearly labelled and identified for us, the farmers, all the way to the consumer*" (cf. FNAB hearing). The CNAFAL also insists on the issues of consumer information, transparency and traceability, which are considered to be reasonable principles. "*The question of legal responsibility is essential. If there is no labelling, can the product be traced and withdrawn? No. (...) If there is no labelling, it is no longer the company's responsibility, which is not neutral"* (cf. CNAFAL hearing). Other players, on the other hand, prefer a system "with no obligation for traceability or labelling", because "*we don't know how to do it (...) We'll have to write 'NGT' everywhere (...) If we had a laboratory, we'd have to analyse all the grains. Obviously, it's a bit complicated*" (see ANIA hearing). An opinion shared by the FNSEA: "*As far as specific labelling is concerned, we think it would be difficult to implement. (...) we don't necessarily manage to find the resources and get people to agree to specific labelling" (FNSEA hearing).* For other players, *"the traceability of NGT1 is not a challenge for the seed industry, because we are in a traced industry. Seeds are labelled*" (see Semae hearing).

The ethical challenge posed by genome editing cannot be summed up by the question of "In addition to the 'consequences' and 'acceptable' side effects, societal issues of intra- and intergenerational equity and justice, and the question of naturalness must also be taken into account (Dabrock, 2009, Bartowski et al. 2018). While these types of questions - and more broadly ELSI-type questions (for ethical, legal and social implications) - are sometimes seen as external to the debate, this separation is often criticised. In particular, the opinion of the INRA-Cirad-IFREMER ethics committee on NTGs (2018) stressed that the notion of risk must be plural, to also include "economic, social and political risks". In this sense, technical assessments must be associated with more general issues (of the intellectual property type, for example), and are not independent of societal choices which, if we listen to the literature cited, should at least be made explicit.

- ***Surveys of the public and stakeholders concerned***

A study carried out by the Royal Society with focus groups (interviews conducted with at least two people present) shows that participants considered genome editing applications to be unacceptable if they created monocultures and if the applications prioritised benefits for certain groups (of individuals or companies) at the expense of society more broadly (van Mil et al. 2017).

Society's point of view on plants and products obtained using NTGs is not only an issue for the public, but also for producers. This is the case, for example, of organic potato producers in Italy (a country that is very anti-GMO) (Pacifico et al. 2016).
Most supporters of organic farming are hostile to genetic modification to produce new varieties and are concerned about possible unintended health effects. Those who argue in favour of deregulation of NTG-derived products generally point to the need for good "communication" with consumers[141].

We could also mention a study that analysed the image of editing among different audiences in the United States (scientists, agents in health and environmental agencies, NGOs, consumer association); they agree on the need for pre-market surveillance and stakeholder engagement, but have different views regarding the novelty of genomic editing, the hopes raised and the regulatory issues (Kuzma et al. 2016). Studies conducted in Japan and Spain show that people with a background in molecular biology or biology have a much more positive perception of GMOs and biotechnologies than non-professionals/specialists (Woźniak-Gientka et al. 2022, see also Marris, 2001).

The main conclusion to be drawn from all these studies is that public attitudes to genetic engineering are not "immutable" or "irrational" (Scott et al. 2016). Public attitudes and responses vary considerably: depending on the country, the questions asked, the types of survey carried out, the profession exercised, etc. Even among 'experts' in the field, views can differ. So it's not just different audiences that need to be taken into account, but also the fact that these different audiences - whether consumers or farmers - are not all the same.

[141] It should be noted that this vision of a consumer as a "passive" receiver of information, a consumer who is "irrational", has been criticised in the literature (particularly in the field of public understanding of science) as a "deficit model", a model that overlooks the values, criticisms, arguments, choices and political, even systemic, questioning of the public.

homogeneous groups. The limitations of this part of the literature on NTGs must also be emphasised: audiences are often described in a hypothetical, reductive and quantitative way, even though surveys have been conducted at least among consumers.

- ***The main voltage lines***

The controversy surrounding NTGs is not simply a question of 'for' versus 'against', but is criss-crossed by several lines of tension. One of these is the tension between different agricultural systems and aims: on the one hand, a vision that sees technological innovation as a guarantee of greater precision, higher yields and greater economic benefits; on the other, a vision that criticises this system, arguing that it does not meet the social and ecological challenges. This is where the differences between large-scale and small-scale, conventional and organic farming come into play (Bartowski et al. 2018). As in the case of GMOs derived from transgenesis, criticism is levelled at a system that is based too much on monoculture and pesticides and is not open to agro-ecological forms (see the literature review in Nawaz and Satterfield, 2022a). For plants modified by NTGs, as for GMOs, one of the salient questions is whether these plants are really necessary, or whether there are other ways (old varieties, agroecology, etc.) of responding to current challenges (climate, ecology, food, etc.). To put it another way, there is a systemic and political critique of NTGs (Heliwell et al. 2019). These lines of tension are also visible when we analyse expectations regarding NTGs. Lindberg et al (2023) use interviews (n=27) and articles published in Euroactiv, a media specialising in European politics (n=53), to analyse the different futures outlined. Positive expectations include: greater competitiveness between players (and less dominance by multinationals), better food quality, fewer negative environmental impacts and greater agricultural productivity. Negative expectations include the continuation of the current system (soil degradation, use of inputs) and the dominance of multinationals (Lindberg et al. 2023).

Criticised are "claims that NTGs will be needed to meet the challenges of agricultural production, arguing that solutions to agricultural problems, such as plant pests, drought and climate change adaptation and mitigation, already come from traditional breeding, organic production and integrated agricultural approaches" (Lindberg et al. (2023), p. 360).

According to de Wit (2020), if the agro-ecological vision and the technicist vision are opposed, a dialogue between the advocates of agro-ecological solutions and the supporters of NTGs would nevertheless be conceivable.

Consequently, for the various publics, the question of the precision of gene editing is less of a priority than for the promoters of this technique (Nawaz et al. 2022). According to perception surveys, individuals seem to be more concerned about the dominant industrial practices and possible alternatives. Furthermore, the various stakeholders concerned by genome editing - whether the public, NGOs, political decision-makers, journalists or farmers (two online surveys: n=109, n=166) - share a concern for the same issues: safety, transparency and sustainability (Will et al. 2022).

Summary

An analysis of the controversies surrounding NTGs shows that there is no unanimity on how to frame the problems to be addressed: because the debate often focuses on technical aspects, risk and efficiency, it leaves in the shade the issues associated with the systemic context, intellectual property, market dynamics, the question of justice and equity, and ethical issues. As a result, one of the visible lines of tension is that between different agricultural systems and aims: on the one hand, a vision that sees technological innovation as a guarantee of greater precision, yield and economic benefits; on the other, a vision that criticises this system, arguing that it does not respond to social and ecological issues, that it is based too much on monoculture and pesticides, and that it mobilises - as was the case at the start of the development of GMOs or synthetic biology - an entire 'economy of promise'. One of the criticisms voiced in some of the hearings (see table 10 in the report) is that NTGs can only resolve certain symptoms of climate change and ecological problems, but are not capable of resolving their root causes. Analysis of the controversies surrounding NTGs also highlights the issue of choice. Whether through traceability and/or labelling, studies show that consumers have a preference for making the issue of genetic modification visible.

The hearings held as part of the processing of this referral show that there are many lines of tension and uncertainty. This is consistent with the results of the literature showing that different publics - be they consumers, farmers or other stakeholders - do not form homogenous groups, and that placing the "public" in the position of a recipient of information runs the risk of overlooking the values, criticisms, arguments, choices and political and even systemic questioning of the publics. Among the questions raised by the stakeholders interviewed were the following: (i) the attribution of costs associated with a possible health problem or contamination and/or downgrading of a batch of organic products due to NTG products, (ii) the implication of the profusion of new terms, such as "NTG", "NGT", "NBT" or genome editing - and the parallel disappearance of terms such as "GMO" - on the accessibility of debates to different audiences, (iii) the potential consequences of the development of NTG-derived plants on market diversification or concentration, (iv) the arrangements for any labelling of NTG products and those for coexistence between different farming systems. If the current regulations are revised, a new controversial issue is likely to emerge, relating to the indicators used to draw the line between GMOs and NTGs (and to determine an 'equivalence' between conventional products and NTG products), and this is likely to become a hotly contested issue.

Key issues	CNAFAL	ANIA	FNAB	FNSEA	Semae	Confédération paysanne	FNE	FCD	Synabio
issues/effects of amending regulation 2001/18	Promise economy (with few examples of success to date); The problem of the economic model (who benefits from the technology?) ; Loss of industrial sovereignty/Loss of freedom for farmers and consumers; The development of herbicide-tolerant plants is not compatible with sustainable development. base seed production on patented techniques owned by the Americans or the Chinese and increase dependence on the seeds needed for political autonomy	Essential deregulation, otherwise significant segregation costs (investment in infrastructure, specific transport lorries, etc.) to enable Impossible for processing plants to keep up with the market because of speed and profitability issues; Need to add value to products such as organic produce to be profitable; The need for innovation to ensure international competitiveness.	Incompatibility between organic farming specifications and the use of NTGs; In the event of contamination, even at very low levels, there is the problem of product downgrading and economic losses suffered solely by farmers in the absence of a compensation fund (application of the polluter-pays principle). The system/economic model behind the use of these technologies is not sustainable. It is not the traits that are sustainable but the farming systems. Loss of consumer confidence in organic production methods.	Importance of taking sustainability into account (DGPR scenarios), but no definition of "sustainability"; Loss of international competitiveness if there are no regulations governing the use of NGTs; Allows the accelerated development of varieties adapted to the needs of French farmers (up to a 2-fold reduction in selection time);	Enable the marketing of improved varieties for characteristics that seed companies are finding it difficult to deal with quickly and effectively through conventional breeding; The impact could be different depending on the plant species (field crops vs. vegetables); Risk of increased concentration, with greater dependence on a small number of patent holders and reduced supply for farmers; Economy of promise in countries where gene editing is authorised with few convincing results; Value creation captured by the major groups, who own the intellectual property.	There are other solutions to these problems; Economy of promises that are difficult to keep (patents are the only objective); Negative impact on biodiversity (reduction in the number of varieties); Incompatibility with organic farming (problem of coexistence); The disappearance of traceability and publication of the processes used to distinguish a GMO from any other (plant) product; Increase concentration (4 companies with a 50% share of the seeds market); No insurance system in place in the event of environmental or health problems.	Via a Promise Economy (aiming to induce a possible technological future via a technological lock); Deregulation, which includes the elimination of traceability and labelling, poses a moral problem (greater freedom of choice for producers and consumers); A shift in the nature/artificial division, which is not the one advocated by FNE; Interventions on the genome and epigenome, which are never mentioned, are artificial and cannot be described as a "natural" evolution of the plant (see the frequent use of the conditional tense in the Commission's arguments).	Problem of coexistence of "NTG type 1" with organic farming and "non-GMO" products Risk of cross-contamination if there is no detection method; Concern / challenge with the definition of "sustainability" in the European Commission's proposal (NTG type 2); Importance of consumer acceptance of plants and products derived from NTGs; A situation similar to that of GMOs derived from transgenesis ("economy of promise"), with many prospects and very few real applications.	Very strong deregulation could be disastrous for the organic sector, as it would be either incompatible or unworkable (lack of traceability, non-mandatory labelling) with organic regulations; Uncertainties about the long-term benefits of NTG-derived plants (irreversibility of changes, lack of choice of seeds, undesired effects, commercial impact and lack of freedom of choice for consumers). The coexistence rules could result in additional costs for the organic sector (need to apply the "polluter pays" principle); The misleading nature of the definition of 'sustainability' in the proposal (NTG type 2).

detection/traceability	Mandatory labelling is essential (the system exists in directive 2001. 18 and should be kept as it is); Traceability is important to reassure consumers and inform them about what they are eating; The development of detection techniques is not a priority for the European Commission (out of €350 million invested by the Commission, only 2% goes into detection), yet they are necessary; Putting the alphanumeric code after the product name won't make labelling much heavier. Seed companies can do this through their patents, contrary to the EC's assertion concerning NTGs (mistrust of Europe and politics); labelling and monitoring should also cover the cosmetics.	Impossible to detect NTG products; Apart from GMOs, traceability to the final product is not appropriate; Traceability would mean doubling France's agricultural and storage facilities.	Detection and traceability are essential to maintain the sustainability of the organic farming sector and guarantee the absence of NTGs and GMOs in organic farming ; Seed companies are able to detect all NTGs (and therefore to trace and label them); Without an obligation on the seed industry to supply detection kits, the door would be wide open to widespread contamination and it would be impossible to track a product in the event of a problem. The need to maintain current regulations for all types of products derived from these technologies.	Detection is difficult because it requires considerable resources (private/public?), Involve high costs; Impossible to isolate NTG flows from other flows (multiplication of silos and production segregation, for example);	The traceability of NGT1 is not a challenge for the seed industry, as the regulatory requirements for seed certification mean that it can be traced; The criteria for equivalence with conventional varieties are not clear in the European Commission's proposed regulations; High traceability costs to be covered by the applicant	A political will to eliminate the traceability of these "new GMOs" (no tenable technical arguments); Existence of detection and identification tools ; Very little funding for detection research in Europe (1.5% of funds allocated to the NTG theme, source: Friends of the Earth); Documentary traceability is possible (as in organic farming); This private detection process must be made public (if a patent is filed, there must be an associated detection technique, otherwise it will be impossible to assert intellectual property rights); As well as removing the traceability of "new GMOs", information on the existence of registered patents is also being removed.	Detection and traceability made possible by the availability of reference material may be based in whole or in part on tests carried out by the holders of patents relating to NGT products; Related techniques and NGT induce numerous detectable genetic modifications that are partly transmitted to varieties; Numerous detection techniques and tools are available; The assertion that modifications down to a threshold of 20 nucleotides "would have no effect" is a "lie of omission" or scientific incompetence.	Need for a strict approval process as for GMOs derived from transgenesis (detection at every stage in the chain); Traceability to ensure non-GMO status of products products can generate exorbitant costs; Current legislation on GMOs is perfectly adequate; The burden of proof lies with the operator who places the NGT/OGM product on the market.	Need for a strict approval process as for GMOs derived from transgenesis (detection at every stage in the chain); Traceability to ensure non-GMO status of products products can generate exorbitant costs; Current legislation on GMOs is perfectly adequate; The burden of proof lies with the operator who places the NGT/OGM product on the market.

Information/perception of stakeholders	A strong commitment to transparency (consumers must be guaranteed information to enable them to make an informed choice); A lack of information can lead to widespread distrust among consumers; In favour of providing a database accessible to all players; Consumers read labels "; We need information on the types of NTG, the percentages contained in the products and the protocols used; Need to know the effects on health (sustainability all right, but there are risks too); NTG=OGM for consumers	Need to communicate to reduce the fears and anxieties of stakeholders (consumers in particular); Need for guidance from the relevant authorities; The need to harmonise and update the European seed catalogue ; It makes sense to include varieties obtained using these technologies in the catalogue.	There are a few seed companies that are committed to providing farmers with information on the techniques they use, but there are very few of them. This can already be seen in the case of vegetable varieties obtained via CMS by cell fusion; Information on the technology used to obtain a plant/seed or product must be compulsory and clearly indicated on the seed bags and not just in a database; Need for clear labelling from farmers to consumers (on the finished product, no QR code);	Information in sufficient catalogues; Farmers trust their suppliers; Identification of the variety when it is included in the catalogue; Specify the technique used; It's not a modification but an acceleration of a naturally possible event.	Notification should be compulsory; The need to harmonise regulations at European level; Positioning/perceptions will differ according to the size of the company ; Everything must be documented at the time of application for registration of the variety (breeding methods, techniques used) and made available to all stakeholders; Need to have information on patents present in varieties so that breeders can eliminate the corresponding traits during the varietal creation process.	These are GMOs; It is impossible for producers to know which GMOs have been authorised, but it is impossible for consumers to know whether or not they are consuming them, especially as there is the possibility of contamination all along the chain (production / processing) and non-declarations of NTGs listed in the catalogue that are impossible to control; Consumers will be forced to eat only what is patented (what is patented is industrial food).	All those involved in the supply chain, right through to consumers, will find themselves handling/consuming products that they do not know are GMO/NTG or not; seed growers have also raised the issue of associated patents. There has been a major democratic deficit on this issue since the CEES was abolished from the HCB.	Stakeholders are not sufficiently informed about the benefits and risks associated with these crops; No opinion on whether these techniques are cheaper and easier to use.	Stakeholders are not sufficiently informed about the benefits and risks associated with these crops; No opinion on whether these techniques are cheaper and easier to use.
General comments	CNAFAL and other consumer associations defend the position that living matter should not be patentable; Neither for nor against, but "needing the most transparent information"; There are other priorities that NTG	Insists that these are useful innovations in the current context; Does not consider plants and products derived from the European Commission's NTG type 1 to be GMOs; Need for	Categorical refusal to use these plants, whatever the technology used, since GMOs are incompatible with the principles of organic production and European organic regulations; Insists that agriculture	The desire to have a range of tools with which to work, the NTG being one tool among others; The use of these techniques should not call into question the plant variety certificate, which the FNSEA supports. attached.	Specifies that it is up to the players to choose (will use the technology if others use it); Need for a better regulatory framework for intellectual property; Explicit request involvement	The question of patents is essential; The only thing that justifies the financial investment in these techniques is the return on the patent investment; A patent on a	Calls for a regulatory status quo in Europe and for the addition of a regulation covering the techniques themselves and not just the products; _ calls for a strengthening of assessment criteria	The trade and distribution sector will adapt in response to consumer feedback; The FCD is not opposed to technical progress (the use of NTGs). but waits	The trade and distribution sector will adapt in response to consumer feedback; The FCD is not opposed to technical progress (the use of NTGs). but waits

	currently The legal liability associated with the use of NTGs must be clearly defined (who insures the risks associated with NTGs?); Risk/benefit: Risk for whom? Benefits for whom and in what timeframe? Privatisation of profits and mutualisation of risks Private investment can also be supplemented by public investment (through public research), which is quite healthy in our system.	communication and education: all the players involved in this field can provide consumers with reassuring, factual and scientific information.	will disappear from the market if plants derived from NTGs are deregulated; The fact remains that the development of these technologies is based on a strategy of promise, as with the first GMOs. This hampers the development of scientifically proven agronomic solutions, such as organic farming.	NTGs should make it possible to increase funding for fundamental research Somewhat in favour of NTG but with concerns about control and traceability costs If it is used in Europe, it must also be used in France (distortion of competition). Variety back at the heart of farming strategies Seed companies are not as profitable as farmers Distinction between varieties obtained by methods giving the same result as conventional breeding and transgenic varieties.	of the European and French public authorities; The regulatory framework of the European Commission's proposal is satisfactory The technology could be better accepted if "the traits targeted are traits that support the agro-ecological transition and adaptation to climate change". The challenges are different for arable and vegetable crops	genetic information or a genetic sequence, it can be used in a huge number of different varieties and species all over the world; NTGs perpetuate the dominant economic systems/models and accentuate the concentration of market players; We will be guinea pigs"; There's a question of scale: we don't develop seeds for local contexts, and that's the only way to get away from pesticides and adapt to climate variations, but it's not profitable in this economic configuration. Preserving genetic diversity is the best way to prepare for the vagaries of climate change. _ Anticipate the legal threats that will weigh on farmers and lead them to purchase NTGs to be sure not to have	risks ; Proposes a reading of the referral within an ethical framework that calls into question the framework of the hearing and the referral; There is no equivalence between the benefits and risks associated with the development of NGTs, according to the various players involved; The current assessment framework does not allow for a holistic approach, for example on the scale of an ecosystem; NBT is not breeding, but a set of uncontrolled genetic and epigenetic modifications.	really demonstrate its usefulness to end consumers.	really demonstrate its usefulness to end consumers.

						by patent holders.			
concrete cases	The case of cotton in the USA, which led to the re-authorisation of Dicamba, a banned product Several cases of attempted marketing abroad show the reluctance of consumers towards this type of product. "Consumers are cautious". In the case of the mushroom that does not turn brown, it is authorised but not marketed (problem of patents and royalties). This problem will be identical for all NTGs. We can only make promises about them; The GABA Tomato was rejected by Japanese consumers.	Acceleration of varietal selection (e.g. to combat beet yellows in the absence of NNI) Varietal improvement on species that have been disinvested in terms of varietal innovation (e.g. buckwheat, peas, etc.). Tomato improvement containing five times more GABA (a hypotensive) beneficial for seniors Improving oil quality from an improved soya variety Wheat improvement to reduce asparagine and therefore the presence of acrylamide when food is cooked.	Plants derived from protoplast fusions (CMS), which are GMOs exempt from the current regulations, which some farmers refuse to use. More details on Produire-bio.org	The case of tomato disease two years ago (classical selection was faster than modern techniques) Interest in the industrial tomato, in the face of climate change, it is a tomato which can also have an interesting aspect with regard to the delta virus which unfortunately will arrive with climate change. The case of the chickpea which did not withstand the floods this spring It's not possible to reuse seeds for tomatoes, which are hybrids, but if we managed to have fixed lines with the same characteristics as hybrids, this would reduce costs for the industry. Potential of NGTs for obtaining multi-resistant varieties more quickly in the strategy framework	Gaba tomato in Japan, a mushroom in the United States that does not turn brown, and a modified soya with a better fatty acid profile to highlight the lack of a harmonised international regulatory framework for these technologies; As far as the CRISPR technique is concerned, the most operational portfolio of patents is currently in the hands of Corteva and the Broad Institute; Monsanto used its control of Round Up Ready and Bt GMO technology to acquire breeding companies.	A patented wheat grown in Argentina that was supposed to be able to cope with anything, but in reality it doesn't work; Herbicide-tolerant oilseed rape produced by Cibus is no longer grown; The potato that doesn't produce acrylamide when you make chips isn't grown, even though there has been a huge amount of investment; Comparison with the USA and cases of farmers being prosecuted for GMO counterfeiting to explain why this market is now largely dominated by large companies marketing GMOs; In Canada and the USA, no more organic rapeseed is grown.	In 2016, Limagrain argued that the probability of "naturally" obtaining a wheat variety resistant to powdery mildew using NTGs is zero; In the USA, where NTGs have been authorised since 2012, there are very few products on the market and none of them address environmental problems such as drought; Transgene is an example of the promise economy: no marketed product and a high level of remuneration for management; Calixt soya: return on investment for this soya did not suit investors; This is the only case of plants obtained by NTG whose claimed characteristic is drought tolerance: no Marketing	Natural hybridisation between a sunflower and an endive to highlight the vagueness of the notion of "gene pool" in the European Commission's proposal.	Natural hybridisation between a sunflower and an endive to highlight the vagueness of the notion of "gene pool" in the European Commission's proposal.

				integrated crop protection			planned; _ See details o f other cases that cast doubt on the commercial value of NTG-derived end products (rapeseed, mushrooms, mustard, etc.) i n the verbatim.		

Table 10: Main points made by stakeholders concerned by plants and products derived from NTGs

7.4.1.8 Governance of NTG controversies

In addition to the analysis of the positioning of stakeholders presented in the section above, the WG considered that the analysis of "economic and social issues" also requires the question of the decision-making processes and the involvement of the various stakeholders to be addressed.

- ***What are the forms and mechanisms of governance and debate?***

Many authors call for public debate and deliberation. Some (Dryzek et al. 2020) propose a "global citizen deliberation", with a hundred or so citizens, on all forms of genome editing, while arguing that this deliberation is necessary for legitimate, robust, coherent and democratic governance.

How can the regulation of genome editing be improved? To this question, the experts questioned by Kuzma et *al* (2016) (n=31) stress the need for broader public participation, stakeholder involvement, and new regimes for intellectual property rights.

So while **there seems to be a consensus on the need for public dialogue,** how should this dialogue be devised, equipped and organised? Some authors suggest opening up the debate by asking questions that are more relevant to the public (Nawaz et al. 2022): instead of relying on the arguments of the proponents of genome editing (in particular the precision and origin of genes) - arguments that do not arouse widespread public interest - and confining the debate to the risks and benefits, these authors suggest including discussions on objectives, systems and alternatives. Some of the players interviewed, for example, stressed the importance of alternatives to NTGs: "*work in the traditional way, you can also do it and do just as well*" (FNAB interview), "*there are alternatives*" (Synabio interview), "*wouldn't it be better to reduce maize consumption and use other crops, such as sorghum*" (CNAFAL interview).

Other authors stress the need to clarify the objectives of these forms of engagement, to question their effectiveness, and to take them into account in political decision-making (Scheufele et al. 2021). They call for "more effective infrastructures (means of communication) for citizen engagement, which go beyond traditional forms of civic participation".

While some authors suggest that we need to communicate more about genome editing, so that the public has more "confidence" in the technology, few studies explain in detail how to communicate. All the more so as some claim that it cannot be "asserted that greater knowledge has a causal influence on positive attitudes" (Calabrese et al. (2021), n=519, United States). One exception is the study by Will et al. (2022), which recommends, among other things, including societal aspects; bringing together different stakeholders; multiplying communication formats, and so on.

European Union vs. United States

In the academic literature, the situation in Europe is often contrasted with that in the United States, the latter having adopted a more liberal and less restrictive policy on NTGs than the former. If we compare Europeans and North Americans, we find different political attitudes and social perceptions of NTGs

(Lassoued et al. 2021). A comparative study (based on two questionnaires: n=201, n=173) shows that the EU is socially and politically more cautious about the application of new genetic technologies than the rest of the world (Lassoued et al. 2021). We can also refer to the work of Winickoff et al (2005) on the WTO debates, which shows that trade conflicts and differences in perception are linked to different choices in terms of defining the rules and the framework for what is implemented as expertise and in terms of organising regulatory decision-making.

In Europe, for some, it is "scientifically necessary and politically possible to reinterpret **the precautionary principle** and modify EU regulations on plant gene editing", particularly in view of climate change (Garland, 2021). Stakeholders such as the European Plant Science Organisation, scientists, industry groups and the US government have criticised the CJEU's 2018 decision. For others, on the contrary, the precautionary principle remains valid (Hamburger, 2018).

In the United States, the position of the US Department of Agriculture (which is responsible for regulating plants obtained using NTGs and GMOs derived from transgenesis) is not unanimous and is the subject of controversy: the experts questioned (n=31) want mandatory pre-market regulation, deplore the fact that decisions are not taken in an open and transparent way and say they are "dissatisfied with the current system" (Kuzma et al. 2016). The position of the public in the United States (representative survey, n=2000) is mixed: most (41%) say they are unsure about adopting genome editing (compared with 29% who are opposed and 29% who are in favour) and who to trust, and most Americans (75%) are in favour of labelling (Lindberg et al. 2023b).

This observation is echoed in another study (n=45), which discusses the growing protests in the United States, with some experts (but also industrialists) calling for new forms of regulation, greater transparency and public involvement (Selfa et al. 2021). The authors show that definition (equivalence between NTGs and GMOs), labelling and regulation are lines of tension between players. They end on a pessimistic note, arguing that in the face of a government that has historically favoured the agri-biotech industry, players such as NGOs, start-ups and traders will be no match: "It is unlikely that the economic, discursive and political power wielded by the major agri-biotech companies will be seriously disrupted".

Within the EU, positions vary. Between 8 and 10 countries can be described as "very restrictive", while between 8 and 10 others (notably northern countries such as Sweden and Finland) are rather "permissive" with regard to GMOs (Erikkson et al. 2017).

For EU agricultural policy, the **coexistence of farming systems** (with and without GMOs) is a fundamental principle. On the one hand, this principle can be a means of avoiding conflict, as it allows two agricultural systems to exist. On the other hand, however, it has also exacerbated certain conflicts by reinforcing the asymmetries between industrialised agriculture and alternative farming practices. "*The fact that the Commission does not foresee coexistence rules a priori could complicate the work of the various operators, wherever they are in the product development chain. There will also be costs. (...) In any case, these costs will be passed on to the consumer at some point*", says the FCD (see FCD hearing). For the anti-GMO movement, coexistence is illusory and is not a long-term option, as it will lead to the disappearance of agriculture without GMOs.

GMOs and will favour the dominant model of industrialised agriculture while consolidating the processes of market concentration and monopolisation (Friedrich et al. 2019). According to the FNAB, "*authorising these new GMOs to be placed on the market without any detection tests or controls means disseminating all GMOs in agriculture. It is therefore the death (...) of all other forms of agriculture, whether GMO-free or organic (...) there is no compatibility between organic farming and NGTs*" (see FNAB hearing). For Synabio, "*if we disrupt the regulations on GMOs (...) we prevent the organic sector from continuing to work properly*" (cf. Synabio hearing).

- ***Acting in an uncertain world***

The emergence and application of new technologies, such as NTGs, require coordination and collective organisation between the various players involved (Nkott and Temple, 2021).

Hamburger (2018) lists the **various stakeholders and interests to be taken into account**: the rights and interests of consumers, human health and food safety, environmental protection, the coherence of the regulatory framework and ethical or religious convictions, the interests of industry, farmers and public opinion. As these interests differ from country to country, the role of the legislator is to identify them and strike an appropriate balance between them (Hamburger, 2018).

However, given the large number of stakeholders and priorities involved, it is difficult to imagine a single best solution, let alone a group of stakeholders who should take the decisions (Wirz et al. 2020). For example, for some (associations, NGOs, consumer groups) labels guarantee the right to know and to choose, whereas they give too negative an image for consumers and represent a controversy to be avoided for others (particularly private players). Genome editing is described in many articles as a "*wicked problem*".

Beyond a technical and technocratic debate, the example of the introduction of rice in Madagascar (methodology: 38 interviews, multi-stakeholder forum, survey with 148 producers) shows that acceptability requires regulatory structures, knowledge, assessments (of the effects on biodiversity and soil), and a biosafety system (Nkott and Temple, 2021). There is no single controversy surrounding NTGs, but a number of different issues are being discussed, including regulation, intellectual property rights, environmental aspects, health aspects and adaptation to climate change (Will et al. 2022). This argument is reminiscent of the discussions by Levidow et al (1997) on the existence of different framings (each with its own implicit social model) of risk in biotechnology and those by Marris and Calvert (2020) on the fact that uncertainty in synthetic biology is often reduced to the question of risk, and that risk, in turn, is assumed to be quantifiable and manageable.

There is therefore no single way of involving the public (Scheufele et al. 2021). The question of NTG governance can also be posed in terms of "imagination". If we analyse the public comments submitted to the FDA's *Genome Editing in New Plant Varieties Used for Food* dossier, we can discern three imaginations: plants derived from NTGs are not GMOs, they can generate a new green revolution, and they can democratise agricultural biotechnologies (Bain et al. 2020). However, these imaginations can be criticised and give rise to counter-imaginaries. For example, the term

"The term 'democratisation' does not necessarily refer to access to knowledge or the right to seeds, but more often to the low cost of the technology and the absence of regulation (de Wit, 2020).

Some advocate, for example, drawing on the notion of "**responsible research and innovation**" in order to bring together the players concerned by the regulation of NTGs (Agapito- Tenfen et al. 2018; see also Müller et al. 2022) - the idea of responsible research and innovation is also being mobilised in other fields, such as synthetic biology (see Brian, 2015; Douglas and Stemerding, 2012) and in arenas such as the OECD or the European Commission (see Frahm et al. 2022). Consequently, the question arises of the acceptability, sustainability and societal desirability of the innovation process and not to assume that there are "singular answers to scientific and societal questions" (Agapito-Tenfen et al. 2018). Some authors propose five essential characteristics for promoting more socially responsible forms of governance: openness, recognition of underlying values, involvement of a multiplicity of stakeholders, consideration of alternatives (Hartley et al. 2016). The "debate on agricultural biotechnology is not just a technical debate about physical risks: it involves other ethical and social concerns" write Hartley et al. (2016).

Similarly, Gordon et al (2021), discussing the US context, propose 6 principles for better governance: prevention of tangible societal risks and benefits; robust and inclusive societal engagement; effective, science-based government regulation; voluntary best practices to complement regulatory oversight; transparency about GM products in the environment; and inclusive access to technologies and resources. Still in the United States, some advocate "a coalition and certification process for biotech crop developers based on transparent information and accountable, community-led governance" (Kuzma and Greiger, 2020).

Summary

The question of governance in the face of these controversies also arises. While there seems to be a consensus in the literature on the need for public dialogue, the ways in which this dialogue can be organised are less explicit. The common denominator is that the debate requires coordination and collective organisation between the various players involved: the rights and interests of consumers, human health and food safety, environmental protection, the coherence of the regulatory framework and ethical convictions, the interests of industry, farmers and public opinion.

The literature also shows that the contrast between the United States and Europe is less clear-cut than it first appears. In the United States, there are growing protests, and a majority of the experts consulted want compulsory pre-market regulation and are calling for greater transparency and public involvement. In Europe, based on the precautionary principle and the principle of coexistence, the notion of "responsible research and innovation" is also being mobilised. There are calls for greater transparency, accessibility and openness in the governance of science. Genome editing does not pose a problem

not only technical feasibility, but also social desirability, ethical acceptability and the democratic model.

In pushing for a change in the regulation of plants obtained by NTG, some players are also aiming to avoid or put an end to past conflicts, particularly those surrounding transgenic plants. NTG promoters put forward a number of arguments: segregation between products without NTGs and products with NTGs would represent a considerable cost and logistical burden; without deregulation, the gap between countries will widen, leading to a lack of competitiveness; NTGs represent considerable potential in terms of technical innovation. However, this ambition for closure would come at the price of ignoring the arguments of consumers, organic players and the associations and NGOs concerned. Academic literature shows that the majority of consumers prefer products that are not genetically transformed.

7.4.2 Regulatory scenarios for plants and products obtained using certain NTGs and associated socio-economic issues

The question of possible changes to GMO regulations, and whether or not varieties derived from transgenesis and those derived from site-directed mutagenesis should be considered in the same way, can be approached from different angles. Firstly, it can be analysed from the point of view of the impact it could have on the incentives for industry players to develop and use varieties derived from site-directed mutagenesis, on the choices given to consumers, and more generally on the advantages and disadvantages, particularly economic, that the various types of player may find.

But over and above the short-term effects of the possible options, changes in regulations also raise questions about the longer-term dynamics of the agricultural and food system, and the role, for example, that genetic engineering-based varietal innovation should play in it, in relation to changes in farming practices in an agro-ecological model for European agriculture, the need to rethink patent and licensing regulations in the light of the development of directed mutagenesis technology, and the role of public research bodies in guaranteeing varietal innovation that meets the challenges of sustainability.

These issues are important but go beyond the scope of this referral. Nevertheless, they deserve to be analysed and discussed in depth in future work, especially as they lie at the root of many controversies (see section 7.2.4.7).

This section is therefore limited to examining "feasible" scenarios in the short term, with the emphasis on an analysis of possible economic impacts. Nevertheless, it has attempted to link it to the controversies identified in other sections of this report, and in so doing to place it in relation to a number of longer-term issues.

The 3 scenarios considered here range from the Status Quo (scenario 1: current GMO regulations) to a variant of the Status Quo (scenario 2: adaptation of the risk assessment process).

to a scenario of revision of the current regulations **(** scenario 3), and therefore from a situation in which the probability of the development of varietal innovations resulting from site-directed mutagenesis technology is low, to a situation in which it would be significantly higher.

7.4.2.1 Scenario 1: "Status quo: unmodified GMO regulations".

Directed mutagenesis has two major characteristics: (i) it could enable new varieties to be developed at lower R&D costs than varieties derived from transgenesis, and (ii) in some cases, there are no analytical methods available to differentiate them from varieties obtained using conventional breeding methods.

The question is therefore to what extent these two characteristics could lead to different economic impacts from those observed for GMOs produced by transgenesis, if the regulations were not changed and if all varieties produced by site-directed mutagenesis came under the current GMO regulations (Figure 47).

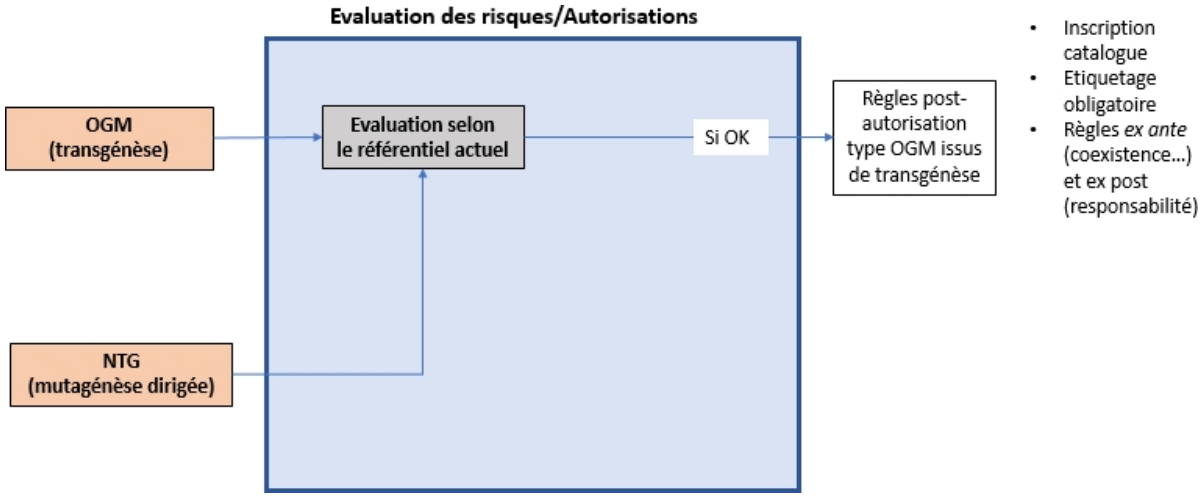


Figure 47. Status Quo: unchanged GMO regulations for NTGs

The development of site-directed mutagenesis will depend on the potential for value creation associated with the development and use of the resulting varieties; the way in which this value is distributed, which determines the commitment of the various players to this technology; and the commercial and legal uncertainties associated with the operation of the market and changes in regulations within and outside the EU.

- **Incentives for upstream players to develop seeds derived from site-directed mutagenesis**

The marketing of varieties derived from site-directed mutagenesis for production in Europe will depend on the economic incentives for breeders to carry out R&D using this technology. These incentives will depend on a trade-off between (i) the lower R&D costs compared with transgenesis and (ii) the potential value of these varieties derived from site-directed mutagenesis, i.e. the willingness of breeders to pay for their varieties.

This, in turn, will depend on the potential productivity gains they bring about at farm level and the willingness to pay of the entire chain of players, right through to consumers.

The hypothesis of a drop in R&D costs is put forward by a large part of the literature, without it being possible to assess the precise amplitude and concrete impact. The data vary considerably from one source to another. Nevertheless, studies converge in pointing to a significant shortening of the duration of R&D phases and an increase in the success rate in the development of new varieties. That said, if regulations remain unchanged, other factors will have an impact on the likelihood of the development of varieties derived from site-directed mutagenesis.

As far as producers are concerned, if varieties derived from site-directed mutagenesis lead to productivity gains (higher yields, lower inputs), it will be the price of seed that will determine whether they are worth adopting. In the case of GMOs derived from transgenesis, a higher price for seeds than for conventional seeds has been observed in the countries where they have been developed, allowing a significant proportion of the value to be passed on to players upstream in agriculture (see **Appendix 14**). However, these price levels seem to have led to a certain increase in producers' incomes (a precondition for their interest in adopting GM varieties derived from transgenesis).

It can be assumed that, in a similar way, the price of seeds of varieties derived from site-directed mutagenesis would be higher than that of conventional seeds, with the sharing of profits associated with their use depending on the concentration of upstream markets and the rules governing patents and the granting of licences.

- **Coexistence and traceability**

With unchanged regulations, the costs associated with marketing authorisations, from risk assessment to the inclusion of varieties in the catalogue, should not change. At producer level, if the same regulations apply, the costs of segregation in the field (distances between crops, isolation strips, etc.) and coexistence in the supply chain (separate management of product flows to avoid cross-contamination) should not vary from what they would be with GMOs produced by transgenesis.

One major uncertainty concerns product traceability. The difficulty of distinguishing, on the basis of analytical methods, between varieties derived from site-directed mutagenesis and conventional (non-NTG) varieties will raise the question of how to control the seeds used, since downstream operators will want to give consumers guarantees on the absence of products derived from NTG products *via* labelling. Guaranteeing consumers that products are not derived from varieties obtained by site-directed mutagenesis may have an upward impact on the price of these products. This is because it will increase the requirements for documentary traceability and impose tighter monitoring arrangements and contractual commitments, which are generally put in place as part of the
"certification".

The absence of standardised analytical methods for detecting NTGs could therefore complicate product identification and control and render the current liability rules inoperative, for example in the event of contamination between a field cultivated with a variety derived from NTGs and a field cultivated with a non-NTG variety. Without the possibility of *ex-post* control, any market segregation policy would have little credibility, as it would not be possible to guarantee that a variety resulting from site-directed mutagenesis would not be present on the market.

market, or that products derived from varieties obtained by site-directed mutagenesis, which are already authorised outside the EU, will not enter the EU. The difficulty of distinguishing, on the basis of analytical methods, between varieties obtained through site-directed mutagenesis and products derived from them, and conventional varieties and products, can be a source of disputes in commercial relations.

With regard to non-GMO sectors, and particularly organic farming, the presence on the market of varieties derived from site-directed mutagenesis and products derived from them could render the rules of coexistence null and void, even if varieties derived from site-directed mutagenesis do not develop on European soil. It will be difficult to guarantee the non-GMO nature of imported products, even if the rule is to ban products derived from varieties derived from site-directed mutagenesis in imported organic products.

- **The end market**

At end-market level, we know that consumers penalise technologies based on genome modification, which are considered to be 'unnatural', by being less willing to pay (or even rejecting) the products in question. This is particularly true if the traits selected are only intended to improve production efficiency, without adding functionalities of potential interest to consumers (taste, nutritional quality, etc.). Under these conditions, products derived from varieties obtained by site-directed mutagenesis, like those derived from transgenic varieties, could only enter the market at a lower price than conventional products. In this hypothesis, the likelihood of the development of site-directed mutagenesis, with unchanged regulations, would be further reduced.

Could the selection of traits of value to consumers make it possible to develop varieties derived from site-directed mutagenesis? If, on the one hand, R&D costs are reduced through the use of this technique and, on the other hand, innovations lead to traits that can be valued by consumers, this could facilitate the development of this technology. It should be noted, however, that in the case of GMOs derived from transgenesis, no innovation has led to the marketing of products positioned at higher prices than conventional products, by taking advantage of consumers' possible willingness to pay higher prices for certain characteristics. In other words, no trait has been able to compensate for the initial devaluation of GMOs resulting from transgenesis by consumers, in a way that is compatible with the development costs of these GMOs and the size of the markets required to cover them (see Appendix 14). Directed mutagenesis, by enabling R&D investment to be made profitable on smaller markets, could facilitate this development path. But with unchanged regulations (and therefore with the costs incurred by these regulations), this presupposes the creation of traits that generate significant increases in consumers' willingness to pay, which does not seem to be demonstrated by the available studies.

We can therefore assume that lower R&D costs will not be enough to guarantee the development of varieties derived from site-directed mutagenesis. In the presence of high regulatory costs and a devaluation of products by consumers, varieties derived from site-directed mutagenesis would either have to generate significant productivity gains, or the developers of these varieties would have to bear the coexistence costs borne by the industry, by setting very low seed prices. This is clearly not a likely scenario.

- **International trade and commerce**

In the EU, transgenic GMOs have mainly entered the market through imports of products intended for animal feed. One of the reasons for this is the lack of labelling requirements for end products of animal origin. A similar development could occur in the case of products derived from varieties obtained by directed mutagenesis.

However, as indicated above, the current lack of analytical methods for identifying GMOs derived from site-directed mutagenesis is likely to call into question the possibility of marketing products derived from them in segregated markets. This comment applies to intra-EU trade, but probably even more so to international trade, given the development of cultivation of varieties derived from site-directed mutagenesis outside the EU and the limited possibilities for documentary control outside the EU by European authorities.

Apart from these regulatory aspects, there is also the question of the competitiveness of European agricultural production in relation to that of the EU's trading partners who have accepted the cultivation of varieties derived from site-directed mutagenesis. Similarly, there is the question of the effects of regulatory choices on the incentives to maintain and develop public and private research forces in Europe in these fields.

- **Sustainability issues**

In this context, what role could be played by innovations aimed at meeting environmental challenges, and mitigating or adapting to climate change, for which there are not necessarily market incentives for their emergence (no productivity gains (or reduction in production risks) for producers, or additional willingness to pay on the part of consumers)? And what room is there for innovation in species other than the major global crops on which transgenic GMOs have been developed? A necessary condition for the emergence of innovations
"However, it can be assumed that the challenges of product segregation, coexistence with sectors seeking to promote the non-NTG nature of their production, traceability and labelling, etc., will not be overcome. But we can assume that the challenges of product segregation, coexistence with sectors seeking to promote the non-NTG nature of their production, and the traceability and labelling of NTG products will make their development difficult.

- **Controversies surrounding GMO regulations**

The question of maintaining GMO regulation for plants and products derived from NTGs (Statu Quo) is therefore not just a technical issue, but also an economic, social, regulatory, ethical and political one. On the one hand, the Statu Quo would have a number of merits compared with the major principles and political guidelines, such as the precautionary principle, coexistence and segregation. In this sense, the Status Quo is not necessarily a brake on innovation, but can be seen as an incentive to innovate differently (and elsewhere). Research into old varieties (e.g. drought-resistant), strengthening the role of agro-ecology, finding natural alternatives to pesticides and insecticides, rebalancing the balance of power between conventional and organic farming, taking consumers more seriously by giving them more decision-making power over their food, making better use of ancestral know-how and the relationship between agriculture and the environment.

humans and the living world: the Status Quo could bring about positive changes at all these levels.

The Status Quo can therefore be interpreted as a recognition of the history of controversies surrounding biotechnologies, particularly those surrounding GMOs. Given that the majority of consumers ultimately prefer GMO-free products, that the negative environmental externalities generated by the agro-industry are not negligible, and that NTGs can only solve certain symptoms of climate change and ecological problems, but not their root causes, the Statu Quo could be interpreted as a recognition of the history of controversies surrounding biotechnology, particularly those surrounding GMOs.
The Statu Quo can also be used to "appease" current and future controversies, and can act as an incentive to explore alternative technical, economic and social avenues. However, while the Statu Quo, in this reading, will be a means of avoiding certain controversies - and of ensuring a broader and more socio-political framing of the NTG issue - many uncertainties will remain. What technical resources will be available to detect and differentiate plants derived from NTGs? What regulatory, human and infra-structural resources will be needed to ensure that different farming systems can 'coexist'? If certain players or countries develop NTGs, what will be the (negative) impact at European and/or French level?

As you can see, while the status quo may ease some tensions, it will exasperate others. For industrial players, the need to segregate products without NTG and products with NTG would represent a considerable cost and logistical burden. At the scientific level, there is a risk of a widening gap between countries, and even between public and private players. And at the political level, the status quo would be tantamount to disavowing certain stakeholders and lobbies who are particularly keen to develop these innovations.

7.4.2.2 Scenario 2: "adapting the risk assessment process" (Status Quo variant)

A second option (cf. Figure 48) would be, while maintaining the existing regulations, to differentiate, in the risk assessment process itself, between seeds produced by directed mutagenesis and transgenesis technologies. This differentiation would consist in distinguishing, within the NTGs resulting from directed mutagenesis, seeds which would be considered in the same way as GMOs resulting from transgenesis, and would therefore undergo a "complete" risk assessment, and those which could undergo a lighter assessment process, because they are considered, on the basis of criteria defined a priori, to present lower levels of risk. In the second case, authorisation costs would be significantly reduced.

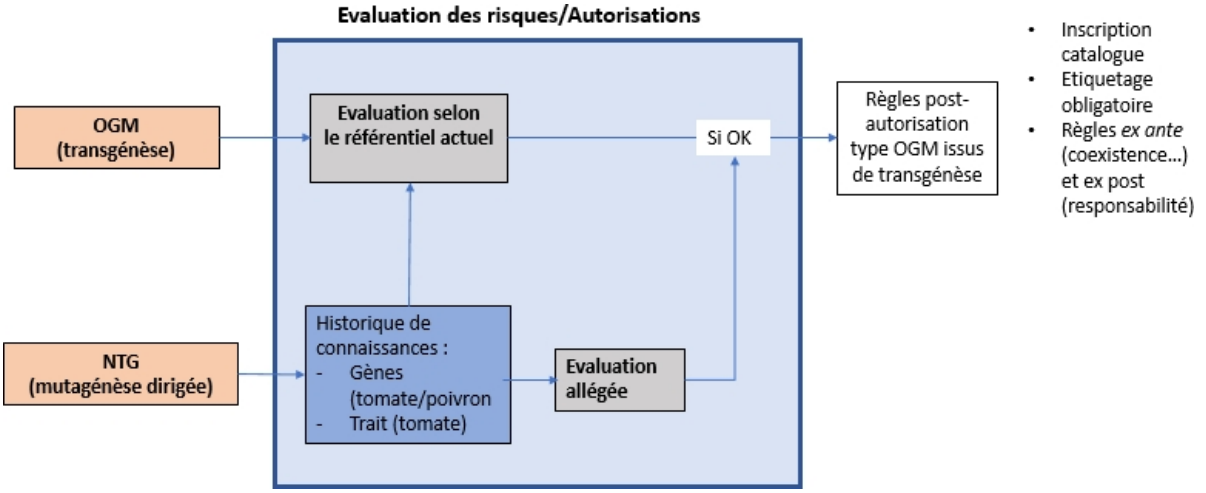


Figure 48. Status Quo, with modified risk assessment

In this scenario, all the elements described in the "Status Quo" scenario would be maintained, with two differences.

Firstly, lower authorisation costs could increase the likelihood of developing varieties derived from site-directed mutagenesis in Europe. For this to happen, it would have to be sufficient, combined with lower R&D costs and any productivity gains, to offset the costs of coexistence and traceability, which would remain unchanged compared with the status quo.

In this hypothesis, this scenario would amplify some of the advantages and disadvantages noted in the case of the Status Quo. On the one hand, increasing the probability of the development of plants obtained using NTGs would make it possible to take better advantage of the potential benefits of the traits selected (productivity gains, in particular). On the other hand, by increasing the number of varieties derived from directed mutagenesis on the market, this scenario would reinforce the negative consequences for the non-NTG sectors.

The second point concerns the criteria used to distinguish, among seeds derived from site-directed mutagenesis, between those that would be subject to a risk assessment process identical to that for GMOs derived from transgenesis, and others that would benefit from a lighter assessment. A distinction of this kind exists in many countries, but the arrangements vary.

The choice of these criteria, which is a matter for the risk assessors, is not neutral in terms of the possible impacts of the scenario. Indeed, it may affect the choices made by breeders and seed companies who, anticipating lower authorisation costs, will tend to favour innovations that comply with these criteria. The types of innovation favoured may therefore differ according to the criteria adopted.

- **Controversies surrounding the adaptation of the risk assessment process**

There are at least three potential problems with this scenario. Firstly, there is the question of the potential impact of new varieties obtained using NTGs on non-NTG sectors, particularly the organic sector. While, on paper, the risk is low and the negative impact is unlikely, there is no such thing as zero risk. Secondly, defining a characteristic as "sustainable" poses a problem. For some, sustainability is an important, positive element that needs to be displayed and promoted. For others, a "sustainable trait" is not something to be taken for granted.

This is not a realistic unit, as the entire system - and over time - must be considered if we are to talk about "sustainability" (cf. section 7.4.2.7). Thirdly, a new line of tension is likely to emerge: how to distinguish between different degrees of risk, and how therefore to draw the line between GMOs produced by transgenesis and plants obtained by means of NTGs? The existence of this boundary - and of the indicators used to draw it - is likely to become an arena of fierce contestation.

7.4.2.3 Scenario 3: "regulatory change".

In this (these) scenario(s), seeds derived from site-directed mutagenesis which meet the criteria defined a priori as presenting lower levels of risk may, following a reduced assessment (scenario 3a) or without assessment (scenario 3b), be subject to the same regulatory framework applicable to seeds derived from conventional breeding. They are then not subject to the rules of segregation and coexistence, nor to compulsory labelling on the final market.

Two variants are possible. In the first case (see Figure 49), varieties resulting from site-directed mutagenesis that meet the criteria defined in the previous scenario are subjected to a simplified assessment and, if this proves positive, they are considered as conventional seeds. In this scenario, a risk assessment and authorisation phase is therefore maintained. In the second case (see Figure 50), varieties derived from site-directed mutagenesis that meet the predefined criteria are exempt from a risk assessment and authorisation procedure, and are therefore treated directly as conventional varieties.

Compared with the previous scenarios, this one would of course be more favourable to the development of NTGs, as the lower costs of segregation and coexistence (borne by the GMO industry in the current configuration) would be combined with lower R&D and authorisation costs, with variant 2 amplifying these effects compared with variant 1.

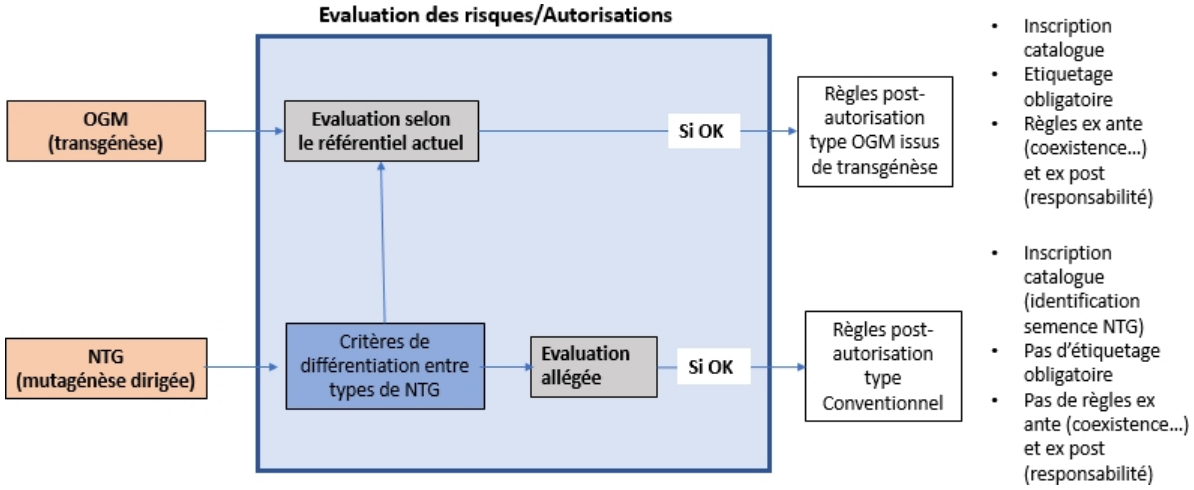


Figure 49. Scenario 3a: "Regulatory change

- **Incentives for upstream players to develop seeds derived from site-directed mutagenesis**

If the technology of site-directed mutagenesis makes it possible to create value (via productivity gains at agricultural level by increasing yields or reducing post-harvest losses, for example), then the commitment of each player - breeder, seed grower, producer - to the development and use of seeds resulting from site-directed mutagenesis implies that they benefit from a share of this value, or that at the very least they gain at least as much as in the alternative option (not developing and not using seeds resulting from site-directed mutagenesis).

If there is a potential for creating value associated with the technology of directed mutagenesis, and outside a situation of very high dependence[142]we can assume that each of these players will benefit from a share of the value created, at the very least so that each player has an interest in the development and use of varieties derived from directed mutagenesis. The way in which this is shared will depend on the balance of power that is expressed through the valuation of patents and property rights and the price of seeds. As in the case of GMOs derived from transgenesis, the price of seeds could be higher than the price of conventional seeds, transferring part of the value associated with productivity gains to players upstream in agriculture, and all the more so as the degree of concentration at this upstream level is high.

From this point of view, the reduction in R&D costs made possible by the technology of directed mutagenesis, on the one hand, and the reduction in authorisation costs, on the other, would make it possible to reduce, compared with GMOs produced by transgenesis, the size of the markets that need to be reached to make the investment required to develop new varieties profitable. This could open up competition upstream by allowing the entry of smaller operators, or even public players, offering varieties derived from directed mutagenesis for a wider range of species and traits. Although studies at this stage show the presence of smaller operators on the market for NTGs derived from site-directed mutagenesis, including those from public research, the high degree of concentration among players in varietal innovation and seed production suggests that these players will retain a dominant position in the development of varieties derived from site-directed mutagenesis.

An important issue is the regulation of patents and licensing procedures (breeder exemption principle, farmer's privilege, etc.). Their possible adaptation in the case of varieties derived from directed mutagenesis will influence the way in which value is shared. Furthermore, the development of varieties derived from site-directed mutagenesis could accelerate the pace of innovation and facilitate the stacking of traits, which would contribute to the creation of "patent bushes". In this case, the development of a new variety from a patented variety would require the negotiation of several licences, which would necessarily affect the distribution of value and the industrial strategies of upstream agricultural companies.

- **Coexistence and traceability**

Since they would be considered as conventional seeds, seeds obtained using NTGs, and the products derived from them, would not be subject to the coexistence and traceability rules that apply to GMOs derived from transgenesis.

[142] This is of course no longer true if one of the players has no alternative to the transaction. If situations of abuse of a dominant position arise, it is up to the competition authorities to characterise them and intervene if necessary.

The questions raised here relate more to the non-NTG sectors, and in particular organic farming, with regard to the risks of cross-contamination in the field (gene flow from NTG crop plots to non-NTG plots), or mixtures between seeds and products obtained using NGT and non-NTG along the logistics chains (silos, processing sites, transport, etc.).

The first step would be to include a reference in the national and European catalogues stating that the varieties in question are the result of site-directed mutagenesis, so that this information can be made public, particularly for producers who do not want to use seeds derived from this technology. Seed labelling, mentioning the technology used, would be an essential requirement for traceability.

Furthermore, unlike in the case of GMOs derived from transgenesis, the adventitious presence of seeds or traces of products derived from directed mutagenesis technology in conventional and organic products would not necessarily result in the product being downgraded, as long as the seeds or products in question were considered to be equivalent to conventional products (and not varieties derived from transgenesis).

However, this eventuality would weaken the credibility of the non-NTG or organic signal, since it is based on a commitment to consumers that there will be no traces of products resulting from directed mutagenesis. It is this effect that could be the most damaging for the conventional and organic sectors. To guard against this reputational effect, which would penalise the organic label, the sectors in question would have to strengthen their segregation and traceability systems, which could ultimately affect the costs of preserving product identity and lead to higher prices.

It is likely that this tension between sectors using varieties derived from site-directed mutagenesis and those that do not will depend on the product sectors, and in particular on two factors: the spatial organisation of production and the interweaving of the two types of sector within the territory; and the extent to which the market is open to imports of organic products from third countries (and potentially containing products derived from site-directed mutagenesis).

- **The end market**

How might the development of technology based on site-directed mutagenesis and the distribution of the resulting seeds affect the segmentation of the end market? This will depend on the type of traits selected, on the one hand, and consumer acceptability and willingness to pay for these traits, on the other.

If the traits selected are aimed solely at productivity gains, without functionalities that can be valued by consumers, and if consumers know that the products are derived from a technology that they devalue in comparison with conventional varietal selection practices, then the products in question can only enter the market at a lower price than the conventional product (this is a way of sharing the value created by directed mutagenesis technologies with consumers).

The question is how much lower this price has to be for the product to be preferred, by a sufficient fraction of consumers, to the non-NTG product. Studies suggest that there is considerable heterogeneity between consumers in terms of the acceptability of NTGs derived from directed mutagenesis, but also a lesser devaluation of this technology compared with GMOs derived from transgenesis. This will have to be confirmed on the basis of evaluations based on actual purchase data. But in this case, the discount compared with the conventional product would be smaller than in the case of these GMOs (the discount is so large in the case of

GMOs derived from transgenesis have not developed in Europe), reinforcing the likelihood that NTGs derived from site-directed mutagenesis will develop.

If the products in question are direct substitutes for conventional products, it is possible that through this mechanism the former could take market share from the latter, eventually replacing them completely. In this case, the product resulting from directed mutagenesis would become the market standard, which could be accompanied by a rise in its price.

If the traits selected form part of differentiation strategies, by highlighting functionalities that can potentially be used by consumers, the development of varieties derived from site-directed mutagenesis may lead to the creation of segmented or even niche markets. Given the lower R&D costs, these segmented markets could develop for smaller price differentials and market sizes than in the case of GMOs derived from transgenesis. The lower price differential required to ensure the profitability of R&D investments would make it easier to implement such strategies.

These different market positioning options will depend to a large extent on the information available to consumers regarding the characteristics of the products (labelling of products derived from site-directed mutagenesis is not mandatory in this scenario), on the attention they pay to this subject (they seem to be less concerned than in the case of GMOs derived from transgenesis), and more generally on changes in consumer perceptions and public opinion in general if the controversies over varieties derived from site-directed mutagenesis (are these varieties identical or not to conventional varieties?) develop in the public debate (cf. sections 7.4.2.5 and 7.4.2.7).) become part of the public debate (see sections 7.4.2.5 and 7.4.2.7).

- **International trade and commerce**

This scenario is similar to the regulations adopted in a large number of non-European countries, which exempt from the regulation of GMOs derived from transgenesis some of the varieties derived from directed mutagenesis. It would result in a degree of convergence between EU regulations and those adopted at international level, making trade in these types of products easier.

However, there would still be difficulties linked to the fact that the criteria for distinguishing between varieties resulting from directed mutagenesis, which can be assimilated to GMOs resulting from transgenesis, and those considered to be conventional seeds, vary from country to country. The definition of each product category (conventional versus GMO) would remain heterogeneous, maintaining real complexities in trade between exporting and importing countries.

Assuming that varieties derived from site-directed mutagenesis lead to productivity gains (increased yields, less variability, etc.), their use could help to maintain the competitiveness of European agriculture. In addition, the possibility of developing directed mutagenesis technologies would have an impact on the flow of funding dedicated to research into these technologies, and could mitigate the risks of relocation of some European research and laboratories.

- **Sustainability issues**

The question of the contribution of directed mutagenesis technology to the challenges of sustainability arises at several levels.

This scenario could create the market incentives that would make it possible to develop favourable characteristics in terms of sustainability (environmental and/or health impacts), as long as they were associated with economic advantages at production level, or with additional willingness to pay on the part of certain consumers (those who want to respond to environmental issues).

However, this would be more difficult for traits that respond to environmental issues without such market incentives. One possibility suggested by the WG would be to entrust the development and marketing of varieties resulting from site-directed mutagenesis with traits of general interest (in particular resistance to water stress, resistance to bio-aggressors, nutrient use efficiency) entirely to public institutions (or to affiliated or contracted firms). This option nevertheless raises two questions: (i) its compatibility with current national, European and international regulations, and (ii) the support of public opinion and NGOs.

This example shows that sustainability issues raise the broader question of long-term developments in the face of climate and environmental challenges, and the way in which current choices, in this case regulation, affect future options.

On the one hand, there is the prevailing idea that technological developments, and directed mutagenesis technology in particular, can help to meet the challenges of climate change and environmental issues; not encouraging their development today would limit the range of levers for action tomorrow, leading to a possible deadlock, for example because of a loss of research skills or technological independence in the field.

On the other hand, there is the prevailing idea that the response to climate and environmental issues requires a profound redesign of agricultural and food systems, with the answers to be found more in changing production methods (agro-ecology) than in genetic engineering technologies. The adoption of NTGs derived from site-directed mutagenesis would detract from this redesign of production systems (for example, by creating difficulties for the organic sector), a redesign that would become increasingly difficult as the use of site-directed mutagenesis technology develops.

- **Controversy surrounding changes to regulations**

On the one hand, amending the regulations would mean taking on board the arguments put forward by part of the scientific community and some of the stakeholders concerned by plants and products derived from NTGs. By removing plants and products derived from NTGs from the scope of GMO regulations, some of these stakeholders hope to avoid the controversies and conflicts of the past (Macnaghten, 2020). The word "GMO" would be used less and more recent technical terms (such as NTG, NBT, mutagenesis, CRISPR) would pose fewer problems; technical innovation would no longer be limited by overly restrictive regulation; consumers' lack of appetite for products containing GMOs would no longer be a problem; and outbursts and critical stances towards GMOs (GMO mowing) would be avoided. In other words, for NTG promoters, a change in the regulations would make it possible to "close" the controversial history of GMOs. The potential gains put forward are numerous: productivity gains, environmental benefits, lower authorisation costs, greater competitiveness, alignment of European regulations with those of countries such as the United States, etc.

On the other hand, trying to put an end to the controversial history of GMOs by excluding plants and products derived from NTGs from current regulations would come at a price. Neither the opinion of consumers, nor that of the players (in the organic sector in particular), nor that of the associations and NGOs concerned would have been taken into account. For the organic sector, the challenge will be to avoid contamination and downgrading. This is a technical issue (how do you detect/guarantee the organic nature of a product?), an economic issue (who will pay the costs? will it be the 'death' of organic, as some of the players interviewed put it?) and a political issue (will the conventional sector be in a position of domination over organic?). For consumers and the associations and NGOs concerned, there is, among other things, the problem of representativeness and their place in the science-society debate. These players may feel excluded from the debate: the profusion of new terms (NTG, etc.) and the disappearance of others (GMOs) make the debate inaccessible and reduce the possibility of having a say in agricultural systems.

What if the promises made don't materialise? Who is responsible if a batch of organic produce is contaminated? Is deregulation irreversible? In the longer term, will we see an increase and diversification of private players, or, on the contrary, a concentration? Can we guarantee that a 'sustainable' trait will translate into a sustainable system? And how 'sustainable' will this trait be over time? All these questions show that many uncertainties remain in the case of a change in the regulations governing plants and products derived from NTGs (just as they do in the case of the status quo).

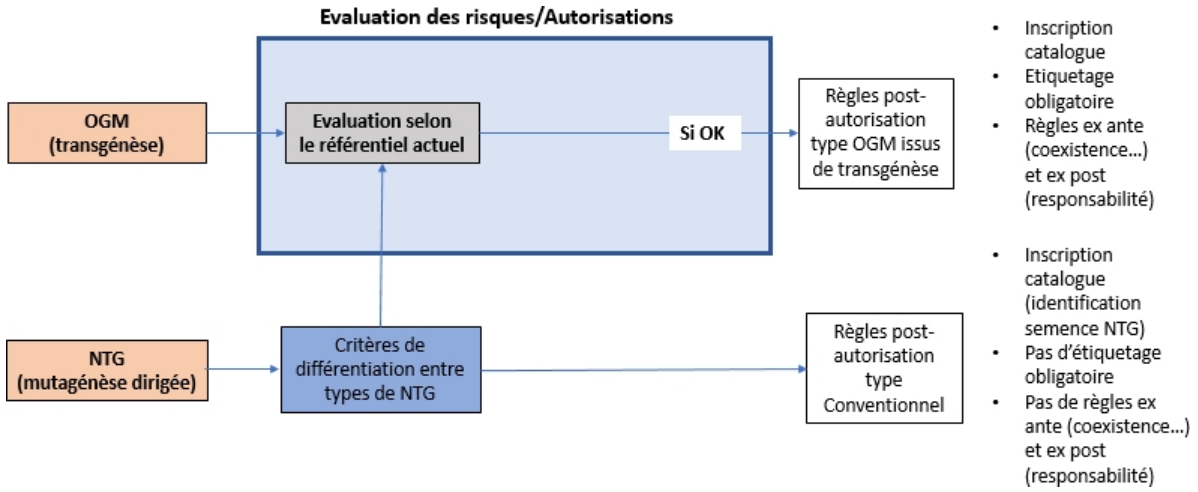


Figure 50: Scenario 3b: "Change in regulations, without risk assessment for some varieties derived from site-directed mutagenesis".

7.4.2.4 Advantages and disadvantages of "Status Quo" versus "regulatory change".

All in all, the different scenarios examined fall on an increasing gradient of market openness to varieties derived from the technology of site-directed mutagenesis. The advantages and disadvantages of the two extreme scenarios are summarised below.

- **Status quo (scenario 1)**

Advantages :

- Status quo on risks (precautionary principle).
- The principle of freedom of choice is retained, both for producers (principle of coexistence) and consumers (labelling).
- Protection of non-NTG sectors, if the economic and regulatory context is sufficient to limit the development of NTGs.
- This is in line with public opinion, with most members of the public, consumers, NGOs and associations opposed to the development of NTGs.

Disadvantages :

- Not being able to take advantage of the potential benefits of traits selected by site-directed mutagenesis technology, either in terms of productivity gains (yields, resilience, and ultimately lower final prices) or environmental benefits (climate, biodiversity).
- If, despite the regulatory status quo, varieties derived from site-directed mutagenesis develop, then the segregation and control procedures will be very costly and/or not very credible, which would greatly weaken the principle of coexistence and the labelling rules.
- Possible impact on the competitive differential between European agriculture and that of other producer countries (which use NTGs).
- Possible effects of the relocation of research forces outside the EU on these technologies and on the competitiveness of European laboratories.
- Heterogeneity between European regulations and those of other major producing countries, with effects on the operation of international markets.

- Amendment of regulation 2001/18 **(scenario 3)**

Advantages :

- Possibility of taking advantage of the potential benefits of traits selected by site-directed mutagenesis technology, either in terms of productivity gains (yields, resilience, and ultimately lower final prices) or environmental benefits (under certain conditions).
- Lower authorisation and coexistence costs for sectors using varieties derived from site-directed mutagenesis.
- Possible favourable impact on the competitiveness differential between European agriculture and that of other producer countries (which use NTGs).
- Reinforces the research strengths of European laboratories in these technologies.
- Less heterogeneity between European regulations and those of other major producing countries.

Disadvantages :

- No regulatory system for coexistence and compulsory labelling of the presence of varieties derived from site-directed mutagenesis, which means that the burden of proof is shifted (that the product is not derived from varieties obtained by mutagenesis).

directed) to non-NTG channels, with possible effects on costs and the credibility of these channels' commitments.
- The principle of freedom of choice for consumers is weakened if they want to know about products using directed mutagenesis technologies.
- Difficulties linked to discrepancies with public opinion, with most members of the public and consumers rather reticent about genome modification technologies.

Discussion of the scenarios analysed

Changes to the regulations would have an impact at several levels. This section focused in particular on the potential economic impacts. The WG believes that identifying economic impacts is both crucial and, at the same time, complex and difficult (empirical scientific studies are very rare, and academic discussions are more often based on hypothetical cases and projections than on actual surveys). The economic impact is all the more important to examine in depth, as it has several dimensions: price, impact on sales and production costs, the issue of patents, etc. At the same time, there are questions about how NTG products will (or will not) be traced, labelled, registered and made public on the market.

Regulatory change would also have more systemic effects. The coexistence of different agricultural and food systems, the place of the agro-ecological model, the positioning of public research players in the ecosystem of players involved in NTGs: regulation provides a regulatory and safety framework around technical processes, just as it will have wider consequences on models of agriculture, forms of economy and society. In short, regulatory change is both a technical and a political problem.

The concept of *responsible research and innovation* (see section 7.4.2.8.) makes it possible to think about both. We might mention here the Norwegian *Research Council*, which is encouraging the adoption of a framework for responsible governance in order to "Looking forward, thinking through, inviting along, and working together". For some authors (MacNaghten et al. 2020), the Norwegian model is interesting on several levels: Norway has a regulatory framework based on a *tiered assessment, which seeks to take into account* the arguments of both supporters and opponents of NTGs. This model goes beyond a focus on safety issues to look at broader socio-economic, ecological and ethical considerations, thus making it possible, according to the authors, to "break the current rigidity" of the debate on the GMO directive.[143.]

Wider considerations include the place of the consumer in the governance of NTGs and ethical issues. "We

[143.] The authors explain: "The Norwegian model could serve as an example to the EU and make an important contribution to breaking the deadlock, insofar as it seriously tackles the arguments of both proponents and opponents (...).) The advantages of such a multi-layered system are considerable in that it offers, in principle, a means of linking risk assessment to benefit assessment, of relaxing the current regulatory regime only in the context of an agreement on societal benefits, sustainability and ethics, and finally a model designed to harness the potential of genetic technologies while addressing significant societal concerns and unease".

argue that a regulatory framework for such a controversial and consequential technology, which will be effective and profitable in the long term, must take into account consumer and producer preferences, ethical considerations and the characteristics of the transactions involved" conclude Bartowski et al. (2018).

Responsible governance requires multiple perspectives to be taken into account, beyond technical expertise on the subject (Scheufele et al. 2021). Such governance requires the adoption of a broader definition of risk, so as not to reduce the issue of risk to a technical one, but to include broader political and social aspects. For some authors, such responsible governance - open to a multitude of players and arguments and not reducing risk to technical risk - will ultimately make it possible to implement participatory democracy around NTGs (Friedrich et al. 2019). The WG believes that expert appraisal of NTGs is all the more robust if it is **interdisciplinary and plural, and if it analyses NTGs as socio-technical objects.**

8 Conclusions of the working group

The new genomic techniques (NTG), developed mainly after the entry into force of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, enable modifications to be made to the plant genome at specific sites chosen by the breeder. In some cases, known as directed (or targeted) mutagenesis, a limited number of base pairs can be modified, leading some stakeholders to consider these modifications as similar to those potentially obtained by conventional breeding. In addition, some plant varieties obtained using NTGs are already available on the market in non-EU countries and could appear on the European market in the short term. This raises the question of European regulations for assessing the health and environmental safety of these plants and their possible adaptation, as well as the socio-economic issues that may be associated with them, particularly in view of the international context and the lack of specific assessment of these plants in some countries.

Among the NTGs, the CRISPR-Cas system, which is less expensive and simpler to implement, is more widely used than the other NTGs listed. This technique can be used for directed mutagenesis, cisgenesis and transgenesis. As the use of NTGs for transgenesis is outside the scope of this referral (no adaptation of the regulations is planned for these plants, for which Directive 2001/18/EC remains applicable), and as cisgenesis still appears to be relatively little used, **this collective expertise report focuses on plants resulting from directed mutagenesis obtained using the CRISPR-Cas system**.

The first objective of this work was therefore to determine whether the current regulations concerning the assessment of health and environmental risks of genetically modified plants could be applied to plants resulting from site-directed mutagenesis obtained using the CRISPR-Cas system, or whether they needed to be adapted or modified. To this end, the working group first conducted a systematic analysis of the literature on the undesired effects on the plant genome associated with the use of the CRISPR-Cas system, in order to identify any risks that might be associated with it and to propose specific requirements for the molecular characterisation of plants obtained using the CRISPR-Cas system. The working group then looked at the literature, in particular specific cases of plants modified by site-directed mutagenesis, to determine the possible health and environmental risks associated with these plants, and then, on the basis of the risks thus defined, to propose specific assessment methods. The second objective of this work, pursued in parallel with the first, was to carry out an analysis of the potential socio-economic implications in France of a change or otherwise in the regulations concerning plants obtained using NTGs. To do this, the working group identified the various sectors of activity and players potentially concerned by NTG-derived plants and products by describing four agricultural sectors (tomato, soft wheat, carrot and vine) representing various possible applications of NTGs and different technical and economic situations. The socio-economic issues associated with NTGs for these different sectors and French players were then analysed by means of a

systematic literature review. This literature review was supplemented by an analysis of the positions of the stakeholders, based on the existing literature on controversies relating to NTG-derived plants and on hearings with stakeholders. On this basis, the working group analysed the potential socio-economic implications of changing or not changing the regulations concerning plants obtained using NTGs, according to various possible scenarios.

An analysis of the scientific literature shows that the CRISPR-Cas system can be used for a **wide range of applications**. On the one hand, it can be used on a very wide variety of species and, on the other, it can be used to modify a large number of plant traits, including plant composition (applications aimed directly at modifying plant composition account for more than a quarter of the applications identified). In particular, the WG notes that the modification of species hitherto unaffected by transgenesis could lead to new risks for the environment, by encouraging the **spread of modified genes or plants**, and by modifying the **interactions between animals and these plants**. Furthermore, in the event of a change in plant composition, whether desired or unexpected, the WG considers that a **change in the toxicity, allergenicity or nutritional characteristics** of the plant is possible. More generally, the WG notes the possibility, following any modification, of **pleiotropic effects** leading to a change in the plant's properties.

The WG considers that the **current framework for the assessment of genetically modified plants allows certain risks to be taken into account that remain relevant for plants derived from site-directed mutagenesis, but that other requirements are generally not directly transposable or relevant for the assessment of plants derived from site-directed mutagenesis.** This is the case in particular for the requirements concerning the risks associated with proteins newly expressed by the modified plant, which are generally not relevant in the case of plants derived from site-directed mutagenesis. This is also the case for the requirements relating to gene transfer from the modified plant to micro-organisms. In addition, the WG points out that **technical difficulties** could arise in carrying out certain studies required for the assessment of genetically modified plants, in particular toxicological and nutritional studies.

Furthermore, while **certain modifications to the plant genome obtained using CRISPR-Cas may be similar to those obtained using other selection methods, particularly conventional methods**, **other modifications can only be obtained using NTGs**. These include, for example, modifications targeting several genes at once (multiplexing) or targeting areas of the genome that are not easily accessible. In the case of multiplexing, as in the case of modifications targeting transcription factors, the probability of the appearance of pleiotropic effects or unexpected effects on plant composition is increased. Finally, the use of the CRISPR-Cas system may enable the *de novo* domestication of wild species for which there is no history of safe consumption.

The scientific literature also indicates that **the use of the CRISPR-Cas system can unexpectedly cause unwanted modifications to the genome**, particularly at sites other than the targeted sequence. These modifications are known as off-target modifications,

can be limited if the guide RNA used to target the genome sequence to be modified is designed in such a way as to maintain a sufficient number (more than four) of mismatches with any region of the genome other than the targeted region, thereby hindering the binding of the guide RNA to these regions.

Concerning the identification of health and environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system, the WG concludes that **some of the known risks already associated with genetically modified plants remain relevant for plants obtained using CRISPR-Cas, but that new risks have been identified.** These new risks could emerge as a result of (i) obtaining **genotypes that cannot be obtained using other selection techniques**, (ii) the **wide diversity of species and traits that could potentially be modified using CRISPR-Cas**, compared with what has been identified for plants derived from transgenesis (modification of more invasive species, or easier modification of composition, for example) and (iii) the **potential overexposure that would be linked to the significant increase in the area under cultivation of varieties with the same modified trait.**

The WG notes, however, that in some cases the **CRISPR-Cas** system **may be used to reproduce known mutations**, either because they have already been obtained by other systems, or because they are intended to replicate a known allele in another variety or in a closely related species. In such cases, where the safety of the plant has already been demonstrated, the WG considers the level of risk to be less of a concern and therefore justifiable for a simplified risk assessment.

Consequently, given the diversity of situations, the WG recommends that, following their molecular characterisation, an assessment of the risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system should be carried out on a case-by-case basis. This assessment should take into account the purpose and consequences of the genetic modification on the agronomic, phenotypic and compositional characteristics of the genetically modified plant, as well as immunological, toxicological and nutritional assessments.

With regard to molecular characterisation, the WG recommends that the **target zones be sequenced, that the resulting modifications be characterised and their genetic stability demonstrated, and that an appropriate detection method be provided by the petitioner**. The WG also recommends that, where possible, the breeder should use **guide RNAs with more than 4 mismatches with non-target areas of the genome, and that any unwanted effects on the genome should be investigated using the most efficient method possible.** The method chosen will depend on the availability of the complete genome sequence of the modified species and the technical possibilities for resequencing the genome of the modified plant.

Finally, for the assessment of the risks associated with the use of plants derived from site-directed mutagenesis using the CRISPR-Cas system, the WG recommends in particular:

- to assess, under **current** GM plants **regulations**, plants for which **the absence of foreign genetic material (including the CRISPR-Cas system) in the genome cannot be demonstrated**;
- to assess plants with a **proven history of knowledge** using a **simplified reference framework** limited to a comparative study of composition. The latter should demonstrate that the genetic modifications carried out are functionally similar at molecular level to modifications obtained by other techniques and already authorised on the market or naturally present in another species, without any specific health or environmental risk having been described, and that the genetic modifications carried out lead to a known phenotype whose health and environmental safety has been demonstrated;
- assess **other plants that do not have** a history of knowledge, using a **reference system adapted** from that currently used for genetically modified plants, with the exception of requirements relating to the expression of a new protein and gene transfer to micro-organisms, but supplemented by specific requirements relating to the species or modified trait.

Lastly, given the lack of data on the medium- and long-term environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system, the WG recommends that a **post-authorisation environmental risk monitoring plan be set up by a body independent of the petitioner, regardless of the assessment framework used**. This overall monitoring plan should take into account the **cumulative impact of** cultivating different varieties resulting from site-directed mutagenesis with the same modified trait, as well as the **impact of marketing plants resulting from site-directed mutagenesis on cultivation practices**.

- **Conclusions on the agricultural sectors potentially impacted by NTG-derived plants**

A description of the agricultural sectors potentially impacted by the NTG-derived plants selected for the study (tomato, common wheat, carrot and vine), through the value chain, has made it possible to identify the different types of players and to perceive certain issues for these sectors arising from the introduction of NTGs in France or elsewhere (European Union or the rest of the world). **However, given the absence of NTG-derived plants currently being cultivated and/or marketed (and of their derived products) in France and Europe, it has not been possible to carry out any impact analysis on the sectors.**

Studies of these sectors have highlighted the dynamism of variety creation in France. However, this dynamism is not observed in the rest of the value chain. For example, in recent years, tomato production has tended to fall in France, soft wheat production has remained static, grape production has fluctuated with no clear trend, and carrot production has increased. These different trends can be explained by the production systems (which can be affected to varying degrees by weather conditions, disease, etc.) in which these crops are grown, but also by the strategic choices made by producers, prices, competition and integration into international trade. **The impact of current regulations or changes to them could vary depending on the specific features of each sector. It will depend on**

in particular the technical and economic situation of the sector (varietal development, productivity, etc.) and its integration into international trade.

Some sectors, where domestic consumption is highly dependent on imports, could be tempted, in order to become more competitive, to produce plants obtained using NTGs (tomato and carrot). However, the introduction of NTG-derived plants in France or elsewhere could affect the sectors differently, because of the specific features of their integration into international trade. Sectors such as carrots, which are essentially involved in intra-branch trade and import almost exclusively from the European Union, could be less affected by the introduction of NTG-derived plants and products into countries outside the European Union, unlike sectors whose imports come mainly from countries outside the European Union, such as the tomato sector.

In the specific case of the common wheat and vine sectors, which are well integrated into international trade and account for a significant proportion of France's trade balance, NTG-derived plants could also be of interest. If these plants are introduced into the European Union or France's other trading partners, these sectors may be tempted to use them to maintain or even gain market share.

However, despite the interest that plants obtained using NTGs can present through the various characteristics highlighted in the potential applications, the adoption of these innovations in the various sectors could require changes in the specifications, particularly for organic farming. This raises potential difficulties associated with the coexistence of the NTG, conventional and organic sectors.

- **Conclusions on the socio-economic issues associated with NTG plants and products**

The WG identifies two important characteristics of NTGs that need to be taken into account, both with a view to assessing their possible impact on the sectors and in the discussions prior to making regulatory choices concerning them:

(i) Firstly, NTGs could make it possible **to develop plant varieties likely to reach the end market at a lower cost and in a shorter time than plants derived from transgenesis**, because of the precision in targeting the traits to be developed and a greater probability of success in the upstream R&D phases. This reduction in R&D costs should then be weighed against the costs incurred by any regulatory requirements, in order to anticipate the choices made by economic players and their consequences for the development of NTG-derived plants on the market.

(ii) Secondly, unlike plants derived from transgenesis, **varieties derived from site-directed mutagenesis are in some cases difficult to distinguish, on the basis of current analytical detection methods, from varieties derived from conventional breeding techniques.** This characteristic raises questions about the traceability, labelling and control of plants and products derived from NTGs.

Current GMO regulations, combined with consumer reluctance, have resulted in very little development of genetically modified plants in Europe, either in production or in the use of products derived from these plants. They have mainly entered the European market through imported animal feed. **With unchanged regulations, unless there is a very significant drop in R&D costs and/or a commitment from the public authorities to make NTGs particularly attractive, it is therefore likely that their development on European soil will be limited, as was** the case for plants derived from transgenesis. On the one hand, this limitation would satisfy a large part of public opinion and a fraction of consumers who are reticent about the use of genetic engineering in the food sector. It would also satisfy non-GMO sectors whose specifications exclude the use of this type of technology. On the other hand, this limitation would mean that France/EU would be giving up the right to take advantage of this technology to create varietal innovations likely to contribute to productivity gains or improved product characteristics, or to provide a response to certain environmental issues and adaptation to climate change (varieties adapted to drought). Furthermore, even if NTG-derived plants were not developed in Europe, the current difficulties in detecting NTG-derived products using standardised analytical methods would make it difficult to control imported products, given the widespread use of this technology outside Europe, and could cause tensions in trade with countries exporting to Europe.

With regard to the possible economic impacts of different regulatory scenarios, a change in regulations based on a distinction between plants derived from site-directed mutagenesis, which would be subject to regulatory measures similar to those for plants derived from conventional breeding, and those which would continue to be subject to the current regulations on GMOs, **could in particular lead to different impacts depending on whether the varietal innovation is in one or the other situation.**

The first point concerns the criteria on which this distinction would be made. **These criteria could play an important role if they are not too restrictive for biotechnology companies. They would facilitate access to the market for varietal innovations for plants** covered by regulatory systems similar to those for conventionally bred plants**, and would limit the development of innovations** covered by current regulations**.** By choosing these criteria, the public decision-maker can steer the dynamics of innovation in a direction expected by the community. It should be noted that in terms of risk assessment, the WG's proposal, explained in the first part of this conclusion, is to maintain a risk assessment, albeit a simplified one, for varieties similar to those of conventionally bred plants, in order to obtain marketing authorisation. The WG recommends a case-by-case approach, without exempting any type of NTG from a risk assessment. In addition, by requiring the introduction of a system for monitoring environmental impact, this proposal aims to ensure that regulatory choices can be reversed in the event of unanticipated negative effects on the environment.

A second point concerns the effects on the industry of **a change in regulations** aimed at considering plants derived from site-directed mutagenesis as conventional varieties. In the context of the regulation of conventional varieties, this would **exempt the sectors concerned from the rules of segregation in the field, coexistence and labelling, thus creating a context favourable to their development on European soil.** This regulatory approach would reinforce the effects of lower R&D costs made possible by directed mutagenesis technology. On the one hand, considering plants derived from NTGs as conventional varieties **would make it possible to use this technology, in addition to other policy levers, for varietal innovations of agronomic and/or environmental interest**. It would also allow a certain degree of harmonisation with regulations in place outside Europe, which would limit the points of tension on imports and contribute to the involvement of European companies in NTG export markets. On the other hand, such a change in **GMO regulations could have a major impact on non-NTG sectors such as the organic sector.**

The various points highlighted above have led the WG to propose the following recommendations:

- **Adapting the regulatory framework for patenting, licensing and intellectual property rights in relation to NTG-derived plants.**

The development of varieties derived from site-directed mutagenesis could accelerate the pace of innovation and facilitate the stacking of traits, which would contribute to the creation of "patent bushes". In this case, the development of a new variety from a patented variety would require the negotiation of several licences, which would necessarily affect the distribution of value in terms of gains/benefits linked to its use and the industrial strategies of upstream agricultural companies. **The proliferation of patents on plant varieties could therefore have a major negative impact on the ability of small and medium-sized companies in the plant breeding sector to innovate, for example by reducing access to the pool of quality germplasm.**

Faced with these issues raised by the development of NTGs, several solutions have been proposed in the literature, ranging from specific forms of patent to a more far-reaching reform of the regulatory system. This is a major issue to be considered in conjunction with possible changes to GMO regulations, and **the current regulatory framework for intellectual property rights needs to be adapted if the aim is to enable the dynamics of varietal innovation by limiting imbalances between players in terms of value sharing.**

- **Monitor the effects of the development of NTG-derived plants on the market power and degree of concentration of biotechnology and plant breeding companies.**

The development of plants derived from transgenesis has been associated, at international level, with a major concentration process that has strengthened the market power of biotechnology and varietal innovation players. The question of the extent to which the characteristics of directed mutagenesis technology (precision in the selection of

The question remains open as to whether this process of concentration in the plant breeding and seed sector (e.g. desired characteristics, lower development costs, ease of use, etc.) could be amplified or whether, on the contrary, it would help to reduce the barriers to entry into these markets and encourage the involvement of small and medium-sized biotech companies, or even public research players.

Nevertheless, it is clear that the impact of the development of NTG-derived plants on the concentration of the plant breeding and seed sector is a major issue, and one in respect of which the public authorities should be vigilant in the event of any changes to GMO regulations, and be alert to any abuses of dominant market positions.

- **To avoid penalising non-NTG sectors.**

Any changes to the regulations must take account of their possible effects on non-NTG agricultural sectors, and in particular on organic farming.

In the case of varieties derived from directed mutagenesis that could come under current GMO regulations, the current GMO coexistence and labelling rules would apply and would, in principle, guarantee the protection of these non-GMO sectors (organic or conventional). In fact, these rules make the GMO sectors bear the burden of the economic losses incurred by the non-GMO sectors in the event of contamination by GMO products. However, **the difficulty of tracing varieties resulting from directed mutagenesis using standardised analytical methods raises the question of how possible cases of cross-contamination should be identified and the associated liability rules applied. Solutions should be proposed here.**

In the event of organic crops being contaminated by NTG-derived crops covered by regulatory provisions similar to those for conventionally bred plants, organic products would not necessarily be downgraded. However, this situation could affect the reputation and ability to meet the commitments made to consumers by the organic and, more generally, non-NTG sectors, since they would not be able to guarantee the absence of contamination by NTG-derived varieties. This risk would require the non-NTG sectors (whether organic or not) to strengthen their documentary traceability systems, which could contribute to an increase in costs for these sectors, potentially putting the organic sectors in difficulty.

- **Meeting consumer expectations for information.**

One of the expectations of consumers is to be informed about the nature of the products they are offered, particularly in terms of the technologies used for varietal selection. This concern should be taken into account, also with a view to increasing the overall transparency of these products.

Products derived from NTG plants, which would come under current GMO regulations, would still h a v e to be labelled and would be subject to the following conditions

would apply to these products as well as to those derived from transgenic varieties. Here again, the difficulty would be to use standardised analytical detection methods to guarantee the non-NTG nature of products presented as such to consumers. Requiring the applicant, when applying for marketing authorisation for a variety derived from NTGs, to provide a detection method to enable traceability could help to overcome these difficulties. However, it is to be expected that this requirement would act as a greater disincentive to the development of NTG-derived products if they were covered by current GMO regulations.

With regard to products derived from plants obtained using NTGs, which would come under regulatory arrangements similar to those for plants derived from conventional breeding, the labelling obligation would be more problematic. Sectors (particularly organic) wishing to highlight the non-NTG nature of their products could develop specific labelling on a voluntary basis. **However, as mentioned above, this provision could require a strengthening of documentary traceability, which is already in place in sectors with labels, and would most certainly result in an increase in product monitoring costs for both the sectors and the control authorities, all the more so in the absence of standardised analytical detection methods. Seed labelling, mentioning the technology used, would be an essential requirement for traceability.**

- **Guarantee the involvement of public research in the development of varietal innovations designed to meet the challenges of the common good.**

While certain characteristics of varieties derived from NTGs (increased yields, allergen-free products, different sensory and nutritional qualities, etc.) may encourage players in the sectors to develop them, this is not necessarily the case for certain innovations which, although they respond to environmental and climatic issues, generate neither productivity gains nor growth in demand (additional willingness to pay on the part of consumers for these characteristics, etc.). **In this context, taking into account the health, environmental and social concerns that these innovations are likely to introduce, public intervention, and especially support for public research, would be decisive in guaranteeing the capacity to develop innovations with a view to greater sustainability of the European agricultural and food system.**

- **Take account of the controversies that raise questions about the long-term direction of the agricultural and food system.**

Over and above the short-term advantages and disadvantages of the possible regulatory options, regulatory developments raise other crucial questions, which are summarised below:

- **The question of the place of varietal innovation based on genetic engineering in** changes to **farming** practices **to implement the agro-ecological transition in European agriculture;**

- **the need to rethink patent and licensing regulations in the light of the development of directed mutagenesis technology;**
- **or the question of the role of public research players in guaranteeing varietal innovations that meet the challenges of sustainability**.

These questions, which are only touched on in this report, deserve to be analysed in depth in subsequent studies, especially as they are the source of much controversy.

The WG's analysis of these controversies has identified several points of tension. The technology of directed mutagenesis creates **a new node in the controversies, namely that of the existence, or not, of a boundary between so-called "GMO" and "NTG" technologies**, and that of the indicators used to draw this boundary and determine a possible "equivalence" between conventional products and products derived from directed mutagenesis (NTG). **The debates on regulatory developments raise potential problems of "path dependence", i.e. decisions taken today could limit the scope for manoeuvre in the future**. On the one hand, today's decision not to use the technology of directed mutagenesis may be seen as limiting the scope for action in the event of difficulty in meeting future climate and environmental challenges by changing agricultural practices and production methods alone. On the other hand, the use of directed mutagenesis technology can be seen as opposing the necessary evolution of the current agricultural and food system towards a more sustainable agro-ecological model. **The role of technology, and in this case genetic engineering, in establishing an agro-ecological model for European agriculture** is at the heart of these debates.

In this context, **the question of how to ensure that opposing viewpoints and their foundations are expressed in public debate on a scientific basis, and how to overcome them, is crucial.** While there seems to be a consensus on the need for public dialogue, it is less clear how this dialogue should be organised and conducted if it is to be fruitful and contribute to overcoming these oppositions. The study of the conditions and procedures for the governance of these controversies was beyond the scope of this referral. Here again, further work should be done.

Given the technical, economic and social uncertainties identified in this report and the controversies raised by the development of NTG-derived plants, the WG recommends that **a system be set up to monitor NTG plants and products derived from them**. This system should make it possible to ensure the traceability and control of these plants and products and to inform the public about their characteristics. In addition to a case-by-case assessment of the specific risks (see decision tree), the WG considers **that an overall monitoring plan should be applied to each marketing authorisation (MA) decision in order to gather the necessary information which, compiled by sector, would make it possible to assess the socio-economic impacts of the development of plants obtained using NTGs**. This post-authorisation monitoring plan should make it possible to gather environmental and socio-economic information on

in situ impacts of authorised NTG-derived plants. From a socio-economic point of view, it should help to monitor the effects of the development of NTG-derived plants, particularly on the market power and degree of concentration of biotechnology and plant breeding companies, while being alert to any abuses of dominant market positions. **The definition and implementation of such a global plan should involve all stakeholders in a transparent and democratic framework.**

The WG concludes by emphasising that its work has highlighted the major socio-economic issues involved in the existence of plants and products derived from NTGs. These issues show that decisions on the development and management of future varietal innovations obtained using NTGs are societal choices that cannot be based solely on scientific and socio-economic arguments. The WG considers that these societal choices should be subject to structured and democratic governance.

9 Bibliography

9.1 Publications

Acha, Giovana, Ricardo Vergara, Marisol Muñoz, Roxana Mora, Carlos Aguirre, Manuel Muñoz, Julio Kalazich, and Humberto Prieto. 2021. "A Traceable DNA-Replicon Derived Vector to Speed Up Gene Editing in Potato: Interrupting Genes Related to Undesirable Postharvest Tuber Traits as an Example". *Plants (Basel, Switzerland)* 10 (9): 1882. https://doi.org/10.3390/plants10091882.

Adachi, Kohei, Aya Hirose, Yuhei Kanazashi, Miki Hibara, Toshiyuki Hirata, Masafumi Mikami, Masaki Endo, et al. 2021. "Site-Directed Mutagenesis by Biolistic Transformation Efficiently Generates Inheritable Mutations in a Targeted Locus in Soybean Somatic Embryos and Transgene-Free Descendants in the T1 Generation". *Transgenic Research* 30 (1): 77-89. https://doi.org/10.1007/s11248-020-00229-4.

Agapito-Tenfen, Sarah Z., Arinze S. Okoli, Michael J. Bernstein, Odd-Gunnar Wikmark, and Anne I. Myhr. 2018. "Revisiting Risk Governance of GM Plants: The Need to Consider New and Emerging Gene-Editing Techniques." *Frontiers in Plant Science* 9: 1874. https://doi.org/10.3389/fpls.2018.01874.

Aesaert, Stijn, Lennert Impens, Griet Coussens, Els Van Lerberge, Rudy Vanderhaeghen, Laurence Desmet, Yasmine Vanhevel, et al. 2022. "Optimized Transformation and Gene Editing of the B104 Public Maize Inbred by Improved Tissue Culture and Use of Morphogenic Regulators". *Frontiers in Plant Science* 13 (April): 883847. https://doi.org/10.3389/fpls.2022.883847.

Ajoykumar, K. N., G. Singh, and A. M. Shackira. 2020. "Socio-Ethical Aspect of Genetically Modified Organisms: A Critical Analysis. In *Policy Issues in Genetically Modified Crops: A Global Perspective*, 421-50. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85127117116&doi=10.1016%2fB978-0-12-820780-2.00019-4&partnerID=40&md5=9f0db49a13b896ccedc11b6e90327c5d.

Anders, S., W. Cowling, A. Pareek, K. J. Gupta, S. L. Singla-Pareek, and C. H. Foyer. 2021. "Gaining Acceptance of Novel Plant Breeding Technologies. *Trends in Plant Science* 26 (6): 575-87. https://doi.org/10.1016/j.tplants.2021.03.004.

Anses. 2023. Avis relatif à l'analyse scientifique de l'annexe I de la proposition de règlement de la Commission européenne du 5 juillet 2023 relative aux nouvelles techniques génomiques (NTG) - Examen des critères d'équivalence proposés pour définir les plantes NTG de catégorie 1 (autosaisine n° 2023-AUTO-0189). Maisons-Alfort: Anses, 34 p.

Areal, F. J., L. Riesgo, and E. Rodríguez-Cerezo. 2013. "Economic and agronomic impact of commercialized GM crops: A meta-analysis". *Journal of Agricultural Science* 151 (1): 7-33. https://doi.org/10.1017/S0021859612000111.

Arndell, T., N. Sharma, P. Langridge, U. Baumann, N. S. Watson-Haigh, and R. Whitford. 2019. "gRNA Validation for Wheat Genome Editing with the CRISPR-Cas9 System". *BMC Biotechnology* 19 (1): 71. https://doi.org/10.1186/s12896-019-0565-z.

Badhan, S., A. S. Ball, and N. Mantri. 2021. "First Report of CRISPR/Cas9 Mediated DNA-Free Editing of 4CL and RVE7 Genes in Chickpea Protoplasts". *International Journal of Molecular Sciences* 22 (1): 396. https://doi.org/10.3390/ijms22010396.

Bain, C., S. Lindberg, and T. Selfa. 2020. "Emerging sociotechnical imaginaries for gene edited crops for foods in the United States: implications for governance." *Agriculture and Human Values* 37 (2): 265-79. https://doi.org/10.1007/s10460-019-09980-9.

Bartkowski, B., and C. M. Baum. 2019. "Dealing with rejection: An application of the exit-voice framework to genome-edited food". *Frontiers in Bioengineering and Biotechnology* 7 (MAR). https://doi.org/10.3389/fbioe.2019.00057.

Bartkowski, B., I. Theesfeld, F. Pirscher, and J. Timaeus. 2018. "Snipping around for food: Economic, ethical and policy implications of CRISPR/Cas genome editing". *Geoforum* 96: 172-80. https://doi.org/10.1016/j.geoforum.2018.07.017.

Bearth, A., G. Kaptan, and S. H. Kessler. H. Kessler. 2022. "Genome-edited versus genetically-modified tomatoes: an experiment on people's perceptions and acceptance of food biotechnology in the UK and Switzerland." *Agriculture and Human Values* 39 (3): 1117-31. https://doi.org/10.1007/s10460-022-10311-8.

Bechtold, S. 2018. "Beyond risk considerations: Where and how can a debate about non-safety related issues of genome editing in agriculture take place?" *Frontiers in Plant Science* 871. https://doi.org/10.3389/fpls.2018.01724.

Beghin, J. C., and C. R. Gustafson. 2021. "Consumer valuation of and attitudes towards novel foods produced with new plant engineering techniques: A review". *Sustainability (Switzerland)* 13 (20). https://doi.org/10.3390/su132011348.

Bellec-Gauche, Agnès, Yuna Chiffoleau, and Camille Maffezzoli. 2015. "Case Study: Multidimensional Comparison of Local and Global Fresh Tomato Supply Chains in France (Task 3.5)." *Institut National de La Recherche Agronomique*.

Berg, J. P. van der, L. M. S. Bouwman, E. Battaglia, and G. A. Kleter. 2021. "Future-proofing EU legislation for genome-edited plants: Dutch stakeholders' views on possible ways forward". *Agronomy* 11 (7). https://doi.org/10.3390/agronomy11071331.

Bonny, Sylvie. 2017. "Corporate concentration and technological change in the global seed industry". *Sustainability* 9 (9): 1632.

Borup, Mads, and Kornelia Konrad. 2004. "Expectations in Nanotechnology and in Energy-Foresight in the Sea of Expectations".

Brian, Jenny Dyck. 2015. "Special perspectives section: Responsible research and innovation for synthetic biology". *Journal of Responsible Innovation* 2 (1): 78-80.

Brinegar, Katelyn, Ali K. Yetisen, Sun Choi, Emily Vallillo, Guillermo U. Ruiz-Esparza, Anand M. Prabhakar, Ali Khademhosseini, and Seok-Hyun Yun. 2017. "The commercialization of genome-editing technologies". *Critical Reviews in Biotechnology* 37 (7): 924-32. https://doi.org/10.1080/07388551.2016.1271768.

Bullock, D. W., W. W. Wilson, and J. Neadeau. 2021. "Gene Editing Versus Genetic Modification in the Research and Development of New Crop Traits: An Economic Comparison. *American Journal of Agricultural Economics* 103 (5): 1700-1719. https://doi.org/10.1111/ajae.12201.

Butler, Nathaniel M., Nicholas J. Baltes, Daniel F. Voytas, and David S. Douches. 2016. "Geminivirus-Mediated Genome Editing in Potato (Solanum tuberosum L.) Using Sequence-SpecificNucleases". *Frontiers in Plant Science* 7. https://www.frontiersin.org/articles/10.3389/fpls.2016.01045.

Calabrese, Christopher, Jieyu Ding Featherstone, Matthew Robbins, and George A Barnett. 2021. "Examining the relationship between gene editing knowledge, value predispositions,

and general science attitudes among US farmers, scientists, policymakers, and the general public". *Journal of Science Communication* 20 (2): A02.

Castagné, Paul, Armelle Guingand, Alexandra Moderc, and Sarah Monard. 2018. "Engineering the bacterial genome using the CRISPR/Cas12a tool". *medicine/sciences* 34 (5): 399-400. https://doi.org/10.1051/medsci/20183405009.

Catacora-Vargas, Georgina, Rosa Binimelis, Anne I Myhr, and Brian Wynne. 2018. "Socio-economic research on genetically modified crops: A study of the literature". *Agriculture and Human Values* 35: 489-513.

Joint Research Centre (European Commission), Claudia Parisi, and Emilio Rodríguez-Cerezo. 2021. *Current and Future Market Applications of New Genomic Techniques*. LU: Publications Office of the European Union. https://data.europa.eu/doi/10.2760/02472.

Cheng, Hongtao, Mengyu Hao, Bingli Ding, Desheng Mei, Wenxiang Wang, Hui Wang, Rijin Zhou, Jia Liu, Chao Li, and Qiong Hu. 2021. "Base Editing with High Efficiency in Allotetraploid Oilseed Rape by A3A-PBE System". *Plant Biotechnology Journal* 19 (1): 87-97. https://doi.org/10.1111/pbi.13444.

Chu, Philomena, and Sarah Zanon Agapito-Tenfen. 2022. "Unintended Genomic Outcomes in Current and Next Generation GM Techniques: A Systematic Review." *Plants* 11 (21): 2997. https://doi.org/10.3390/plants11212997.

Dabrock, Peter. 2009. "Playing God? Synthetic biology as a theological and ethical challenge". *Systems and synthetic biology* 3: 47-54.

Dannenberg, Astrid. 2009. "The dispersion and development of consumer preferences for genetically modified food-a meta-analysis". *Ecological Economics* 68 (8-9): 2182-92.

Deconinck, Koen. 2019. "New evidence on concentration in seed markets". *Global Food Security* 23: 135-38.

Demont, Matty, and Yann Devos. 2008. "Regulating coexistence of GM and non-GM crops without jeopardizing economic incentives. *Trends in Biotechnology* 26 (7): 353-58.

Demont, Matty, Koen Dillen, Wim Daems, Christophe Sausse, Eric Tollens, and Erik Mathijs. 2009. "On the proportionality of EU spatial ex ante coexistence regulations. *Food Policy* 34 (6): 508-18. https://doi.org/10.1016/j.foodpol.2009.04.003.

Deng, Lei, Hang Wang, Chuanlong Sun, Qian Li, Hongling Jiang, Minmin Du, Chang-Bao Li, and Chuanyou Li. 2018. "Efficient generation of pink-fruited tomatoes using CRISPR/Cas9 system". *Journal of Genetics and Genomics* 45 (1): 51-54. https://doi.org/10.1016/j.jgg.2017.10.002.

Détain, Alexandre, Pankaj Bhowmik, Nathalie Leborgne-Castel, and Sergio Ochatt. 2022. "Latest biotechnology tools and targets for improving abiotic stress tolerance in protein legumes". *Environmental and Experimental Botany* 197 (May): 104824. https://doi.org/10.1016/j.envexpbot.2022.104824.

Douglas, Conor MW, and Dirk Stemerding. 2013. "Governing synthetic biology for global health through responsible research and innovation". *Systems and Synthetic Biology* 7: 139-50.

Dramburg, Stephanie, Christiane Hilger, Alexandra F. Santos, Leticia de Las Vecillas, Rob C. Aalberse, Nathalie Acevedo, Lorenz Aglas, et al. 2023. "EAACI Molecular Allergology User's Guide 2.0. *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology* 34 Suppl 28 (March): e13854. https://doi.org/10.1111/pai.13854.

Drapal, Margit, Eugenia M. A. Enfissi, Juliana Almeida, Elzbieta Rapacz, Marilise Nogueira, and Paul D. Fraser. 2023. "The Potential of Metabolomics in Assessing Global Compositional Changes Resulting from the Application of CRISPR/Cas9 Technologies". *Transgenic Research* 32 (4): 265-78. https://doi.org/10.1007/s11248-023-00347-9.

Dryzek, John S, Dianne Nicol, Simon Niemeyer, Sonya Pemberton, Nicole Curato, André Bächtiger, Philip Batterham, Bjørn Bedsted, Simon Burall, and Michael Burgess. 2020. "Global citizen deliberation on genome editing". *Science* 369 (6510): 1435-37.

Duensing, Nina, Thorben Sprink, Wayne A. Parrott, Maria Fedorova, Martin A. Lema, Jeffrey D. Wolt, and Detlef Bartsch. 2018. "Novel Features and Considerations for ERA and Regulation of Crops Produced by Genome Editing". *Frontiers in Bioengineering and Biotechnology* 6: 79. https://doi.org/10.3389/fbioe.2018.00079.

Eckerstorfer, Michael F., Marion Dolezel, Margret Engelhard, Valeria Giovannelli, Marcin Grabowski, Andreas Heissenberger, Matteo Lener, et al. 2023. "Recommendations for the Assessment of Potential Environmental Effects of Genome-Editing Applications in Plants in the EU". *Plants (Basel, Switzerland)* 12 (9): 1764. https://doi.org/10.3390/plants12091764.

Eckerstorfer, Michael F., Marion Dolezel, Andreas Heissenberger, Marianne Miklau, Wolfram Reichenbecher, Ricarda A. Steinbrecher, and Friedrich Waßmann. 2019. "An EU Perspective on Biosafety Considerations for Plants Developed by Genome Editing and Other New Genetic Modification Techniques (nGMs)." *Frontiers in Bioengineering and Biotechnology* 7: 31. https://doi.org/10.3389/fbioe.2019.00031.

Eckerstorfer, Michael F., Marcin Grabowski, Matteo Lener, Margret Engelhard, Samson Simon, Marion Dolezel, Andreas Heissenberger, and Christoph Lüthi. 2021. "Biosafety of Genome Editing Applications in Plant Breeding: Considerations for a Focused Case-Specific Risk Assessment in the EU". *Biotech (Basel (Switzerland))* 10 (3): 10. https://doi.org/10.3390/biotech10030010.

EFSA. 2009. Response to public consultation on Statistical considerations for the safety evaluation of GMOs, on request of EFSA. EFSA Journal 2009; 340 [37pp].

---. 2012. "Compendium of Botanicals Reported to Contain Naturally Occuring Substances of Possible Concern for Human Health When Used in Food and Food Supplements". *EFSA Journal* 10 (5): 2663. https://doi.org/10.2903/j.efsa.2012.2663.

---. 2019. "Human Dietary Exposure Assessment to Newly Expressed Proteins in GM Foods". *EFSA Journal* 17 (7): e05802. https://doi.org/10.2903/j.efsa.2019.5802.---. 2021. "Overview of EFSA and European National Authorities' Scientific Opinions on the Risk Assessment of Plants Developed through New Genomic Techniques". *EFSA Journal. European Food Safety Authority* 19 (4): e06314. https://doi.org/10.2903/j.efsa.2021.6314.

EFSA GMO Panel. 2010. "Guidance on the Environmental Risk Assessment of Genetically Modified Plants. *EFSA Journal* 8 (11): 1879. https://doi.org/10.2903/j.efsa.2010.1879.

---. 2011a. "Guidance for Risk Assessment of Food and Feed from Genetically Modified Plants". *EFSA Journal* 9 (5): 2150. https://doi.org/10.2903/j.efsa.2011.2150.

---. 2011b. "Guidance on Selection of Comparators for the Risk Assessment of Genetically Modified Plants and Derived Food and Feed". *EFSA Journal* 9 (5): 2149. https://doi.org/10.2903/j.efsa.2011.2149.

---. 2011c. "Guidance on the Post-Market Environmental Monitoring (PMEM) of Genetically Modified Plants". *EFSA Journal* 9 (8): 2316. https://doi.org/10.2903/j.efsa.2011.2316.

---. 2012. "Scientific Opinion Addressing the Safety Assessment of Plants Developed Using Zinc Finger Nuclease 3 and Other Site-Directed Nucleases with Similar Function". *EFSA Journal* 10 (10): 2943. https://doi.org/10.2903/j.efsa.2012.2943.

---. 2015. "Guidance on the Agronomic and Phenotypic Characterisation of Genetically Modified Plants". *EFSA Journal* 13 (6): 4128. https://doi.org/10.2903/j.efsa.2015.4128.

---. 2017. "Guidance on Allergenicity Assessment of Genetically Modified Plants". *EFSA Journal* 15 (6): e04862. https://doi.org/10.2903/j.efsa.2017.4862.

---. 2020. "Applicability of the EFSA Opinion on Site-Directed Nucleases Type 3 for the Safety Assessment of Plants Developed Using Site-Directed Nucleases Type 1 and 2 and Oligonucleotide-Directed Mutagenesis". *EFSA Journal. European Food Safety Authority* 18 (11): e06299. https://doi.org/10.2903/j.efsa.2020.6299.

---. 2021. "Evaluation of existing guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified plants obtained through synthetic biology". *EFSA Journal* 19 (2). https://doi.org/10.2903/j.efsa.2021.6301.

---. 2023. "Animal Dietary Exposure in the Risk Assessment of Feed Derived from Genetically Modified Plants". *EFSA Journal* 21 (1): e07732. https://doi.org/10.2903/j.efsa.2023.7732.

Egelie, K. J., G. D. Graff, S. P. Strand, and B. Johansen. 2016. "The emerging patent landscape of CRISPR-Cas gene editing technology". *Nature Biotechnology* 34 (10): 1025-31. https://doi.org/10.1038/nbt.3692.

El-Brolosy, Mohamed A., and Didier Y. R. Stainier. 2017. "Genetic Compensation: A Phenomenon in Search of Mechanisms". *PLOS Genetics* 13 (7): e1006780. https://doi.org/10.1371/journal.pgen.1006780.

Finger, R., N. E. Benni, T. Kaphengst, C. Evans, S. Herbert, B. Lehmann, S. Morse, and N. Stupak. 2011. "A meta analysis on farm-level costs and benefits of GM crops". *Sustainability* 3 (5): 743-62. https://doi.org/10.3390/su3050743.

Fischer, K., E. Ekener-Petersen, L. Rydhmer, and K. Edvardsson Björnberg. 2015. "Social impacts of GM crops in agriculture: A systematic literature review". *Sustainability (Switzerland)* 7 (7): 8598-8620. https://doi.org/10.3390/su7078598.

Flint, Shelby A., Ruth G. Shaw, and Nicholas R. Jordan. 2021. "Effects of Selection Regime on Invasive Characteristics in an Emerging Biomass Crop, Switchgrass (Panicum Virgatum L.)." *Sustainability* 13 (9): 5045. https://doi.org/10.3390/su13095045.

Frewer, Lynn J, Ivo A van der Lans, Arnout RH Fischer, Machiel J Reinders, Davide Menozzi, Xiaoyong Zhang, Isabelle van den Berg, and Karin L Zimmermann. 2013. "Public perceptions of agri-food applications of genetic modification-a systematic review and meta-analysis". *Trends in Food Science & Technology* 30 (2): 142-52.

Friedrich, B., S. Hackfort, M. Boyer, and D. Gottschlich. 2019. "Conflicts over GMOs and their contribution to food democracy." *Politics and Governance* 7 (4): 165-77. https://doi.org/10.17645/pag.v7i4.2082.

Fulton, Murray, and Konstantinos Giannakas. 2004. "Inserting GM products into the food chain: The market and welfare effects of different labeling and regulatory regimes. *American Journal of Agricultural Economics*, 42-60.

Gaj, Thomas, Charles A. Gersbach, and Carlos F. Barbas. 2013. "ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering." *Trends in Biotechnology* 31 (7): 397-405. https://doi.org/10.1016/j.tibtech.2013.04.004.

Garland, S. 2021. "EU policy must change to reflect the potential of gene editing for addressing climatechange". *Global Food Security* 28. https://doi.org/10.1016/j.gfs.2021.100496.

Girard, Fabien, and Christine Noiville. 2014. "Industrial property and plant biotechnologies: the Nova Atlantis. A propos de la recommandation du Haut Conseil des Biotechnologies". *International Review of Economic Law* 28 (1): 59-109.

Gocht, A., N. Consmüller, F. Thom, and H. Grethe. 2021. "Economic and environmental consequences of the ECJ genome editing judgment in agriculture". *Agronomy* 11 (6). https://doi.org/10.3390/agronomy11061212.

Gordon, D. R., G. Jaffe, M. Doane, A. Glaser, T. M. Gremillion, and M. D. Ho. 2021. "Responsible governance of gene editing in agriculture and the environment". *Nature Biotechnology* 39 (9): 1055-57. https://doi.org/10.1038/s41587-021-01023-1.

Hahn, Florian, and Vladimir Nekrasov. 2019. "CRISPR/Cas Precision: Do We Need to Worry about off-Targeting in Plants?" *Plant Cell Reports* 38 (4): 437-41. https://doi.org/10.1007/s00299-018-2355-9.

Hamburger, D. J. S. 2018. "Normative criteria and their inclusion in a regulatory framework for new plant varieties derived from genome editing". *Frontiers in Bioengineering and Biotechnology* 6 (DEC). https://doi.org/10.3389/fbioe.2018.00176.

Hartley, S., F. Gillund, L. van Hove, and F. Wickson. 2016. "Essential Features of Responsible Governance of Agricultural Biotechnology". *PLoS Biology* 14 (5). https://doi.org/10.1371/journal.pbio.1002453.

Hartman, Jeffrey C., Jesse B. Nippert, Rebecca A. Orozco, and Clint J. Springer. 2011. "Potential ecological impacts of switchgrass (Panicum virgatum L.) biofuel cultivation in the Central Great Plains, USA. *Biomass and Bioenergy*, PROCEEDINGS OF A WORKSHOP OF IEA BIOENERGY TASK 31 ON 'SUSTAINABLE FORESTRY SYSTEMS FOR BIOENERGY: INTEGRATION, INNOVATION AND INFORMATION', 35 (8): 3415-21. https://doi.org/10.1016/j.biombioe.2011.04.055.

Hartung, Frank, and Joachim Schiemann. 2014. "Precise plant breeding using new genome editing techniques: opportunities, safety and regulation in the EU". *The Plant Journal* 78 (5): 742-52.

Helliwell, R., S. Hartley, and W. Pearce. 2019. "NGO perspectives on the social and ethical dimensions of plant genome-editing". *Agriculture and Human Values* 36 (4): 779-91. https://doi.org/10.1007/s10460-019-09956-9.

Hess, Sebastian, Carl Johan Lagerkvist, William Redekop, and Ashkan Pakseresht. 2016. "Consumers' evaluation of biotechnologically modified food products: new evidence from a meta-survey. *European Review of Agricultural Economics* 43 (5): 703-36.

Hillary, V. Edwin, and S. Antony Ceasar. 2023. "A Review on the Mechanism and Applications of CRISPR/Cas9/Cas12/Cas13/Cas14 Proteins Utilized for Genome Engineering." *Molecular Biotechnology* 65 (3): 311-25. https://doi.org/10.1007/s12033-022-00567-0.

Hu, Yang, Lisa A House, and Zhifeng Gao. 2022. "How do consumers respond to labels for crispr (gene-editing)?" *Food Policy* 112: 102366.

Hurley, Terrance M. 2016. "Shock and awe pest management: time for change". *Choices* 31 (4): 1-8.

Jacobs, Thomas B., Ning Zhang, Dhruv Patel, and Gregory B. Martin. 2017. "Generation of a Collection of Mutant Tomato Lines Using Pooled CRISPR Libraries." *Plant Physiology* 174 (4): 2023-37. https://doi.org/10.1104/pp.17.00489.

Janik, Edyta, Marcin Niemcewicz, Michal Ceremuga, Lukasz Krzowski, Joanna Saluk-Bijak, and Michal Bijak. 2020. "Various Aspects of a Gene Editing System-CRISPR-Cas9". *International Journal of Molecular Sciences* 21 (24): 9604. https://doi.org/10.3390/ijms21249604.

Jedličková, Veronika, Kateřina Mácová, Marie Štefková, Jan Butula, Jana Staveníková, Marek Sedláček, and Hélène S. Robert. 2022. "Hairy root transformation system as a tool for CRISPR/Cas9-directed genome editing in oilseed rape (Brassica napus)". *Frontiers in Plant Science* 13. https://www.frontiersin.org/articles/10.3389/fpls.2022.919290.

Jin, Yan, Dušan Drabik, Nico Heerink, and Justus Wesseler. 2019. "Getting an imported GM crop approved in China". *Trends in biotechnology* 37 (6): 566-69.

Jorasch, P. 2020. "Potential, Challenges, and Threats for the Application of New Breeding Techniques by the Private Plant Breeding Sector in the EU." *Frontiers in Plant Science* 11. https://doi.org/10.3389/fpls.2020.582011.

Jordan, N. R., J. Kuzma, D. K. Ray, K. Foot, M. Snider, K. Miller, E. Wilensky-Lanford, and G. Amarteifio. 2022. "Should Gene Editing Be Used to Develop Crops for Continuous-Living-Cover Agriculture? A Multi-Sector Stakeholder Assessment Using a Cooperative Governance Approach". *Frontiers in Bioengineering and Biotechnology* 10. https://doi.org/10.3389/fbioe.2022.843093.

Kalaitzandonakes, Nicholas, Jayson Lusk, and Alexandre Magnier. 2018. "The price of non-genetically modified (non-GM) food". *Food Policy* 78 (July): 38-50. https://doi.org/10.1016/j.foodpol.2018.02.005.

Kaufmann, Kerstin, Alice Pajoro, and Gerco C. Angenent. 2010. "Regulation of Transcription in Plants: Mechanisms Controlling Developmental Switches". *Nature Reviews Genetics* 11 (12): 830-42. https://doi.org/10.1038/nrg2885.

Kawall, K., J. Cotter, and C. Then. 2020. "Broadening the GMO risk assessment in the EU for genome editing technologies in agriculture". *Environmental Sciences Europe* 32 (106). https://doi.org/10.1186/s12302-020-00361-2.

Kawall, Katharina. 2021. "The Generic Risks and the Potential of SDN-1 Applications in Crop Plants". *Plants (Basel, Switzerland)* 10 (11): 2259. https://doi.org/10.3390/plants10112259.

Kloppenburg, Jack. 2018. "Re-purposing the master's tools: the open source seed initiative and the struggle for seed sovereignty". In *Food and Culture*, 414-38. Routledge.

Klümper, W., and M. Qaim. 2014. "A meta-analysis of the impacts of genetically modified crops". *PLoS ONE* 9 (11). https://doi.org/10.1371/journal.pone.0111629.

Kock, Michael A. 2021. "Open Intellectual Property Models for Plant Innovations in the Context of New Breeding Technologies". *Agronomy* 11 (6): 1218.

Kock, Michael A, and Floris ten Have. 2016. "The 'International Licensing Platform-Vegetables': A prototype of a patent clearing house in the life science industry". *Journal of Intellectual Property Law & Practice* 11 (7): 496-515.

Kok, E. J., D. C. M. Glandorf, T. W. Prins, and R. G. F. Visser. 2019. "Food and environmental safety assessment of new plant varieties after the European Court decision: process-triggered or product-based?" *Trends in Food Science & Technology* 88: 24-32. https://doi.org/10.1016/j.tifs.2019.03.007.

Kotschi, Johannes, and Bernd Horneburg. 2018. "The Open Source Seed Licence: A novel approach to safeguarding access to plant germplasm". *PLoS Biology* 16 (10): e3000023.

Kuzma, J., and K. Grieger. 2020. "Community-led governance for gene-edited crops". *Science (Washington)* 370 (6519): 916-18. https://doi.org/10.1126/science.abd1512.

Kuzma, J., A. Kokotovich, and A. Kuzhabekova. 2016. "Attitudes towards governance of gene editing". *Asian Biotechnology and Development Review* 18 (1): 69-92.

Lackner, Martin, Nelly Helmbrecht, Svante Pääbo, and Stephan Riesenberg. 2023. "Detection of unintended on-target effects in CRISPR genome editing by DNA donors carrying diagnostic substitutions". *Nucleic Acids Research* 51 (5): e26. https://doi.org/10.1093/nar/gkac1254.

Lassoued, R., D. M. Macall, H. Hesseln, P. W. B. Phillips, and S. J. Smyth. 2019. "Benefits of genome-edited crops: expert opinion". *Transgenic Research* 28 (2): 247-56. https://doi.org/10.1007/s11248-019-00118-5.

Lassoued, R., P. W. B. Phillips, D. M. Macall, H. Hesseln, and S. J. Smyth. 2021. "Expert opinions on the regulation of plant genome editing". *Plant Biotechnology Journal* 19 (6): 1104-9. https://doi.org/10.1111/pbi.13597.

Lassoued, R., P. W. B. Phillips, S. J. Smyth, and H. Hesseln. 2019. "Estimating the cost of regulating genome edited crops: expert judgment and overconfidence". *GM Crops and Food: Biotechnology in Agriculture and the Food Chain* 10 (1): 44-62. https://doi.org/10.1080/21645698.2019.1612689.

Le Corre, Valérie, Mathieu Siol, Yves Vigouroux, Maud I. Tenaillon, and Christophe Délye. 2020. "Adaptive introgression from maize has facilitated the establishment of teosinte as a noxious weed in Europe". *Proceedings of the National Academy of Sciences* 117 (41): 25618-27. https://doi.org/10.1073/pnas.2006633117.

Lemarié, S., and S. Marette. Marette. 2022. "The socio-economic factors affecting the emergence and impacts of new genomic techniques in agriculture: A scoping review." *Trends in Food Science and Technology* 129: 38-48. https://doi.org/10.1016/j.tifs.2022.07.013.

Levidow, Les, Susan Carr, David Wield, and Rene Von Schomberg. 1997. "European biotechnology regulation: framing the risk assessment of a herbicide-tolerant crop. *Science, Technology, & Human Values* 22 (4): 472-505.

Li, Jun, Huawei Zhang, Xiaomin Si, Youhui Tian, Kunling Chen, Jinxing Liu, Huabang Chen, and Caixia Gao. 2017. "Generation of Thermosensitive Male-Sterile Maize by Targeted Knockout of the ZmTMS5 Gene". *Journal of Genetics and Genomics* 44 (9): 465-68. https://doi.org/10.1016/j.jgg.2017.02.002.

Li, Ruiling, Alex Maioli, Zhe Yan, Yuling Bai, Danila Valentino, Anna Maria Milani, Valerio Pompili, et al. 2022. "CRISPR/Cas9-Based Knock-Out of the PMR4 Gene Reduces Susceptibility to Late Blight in Two Tomato Cultivars". *International Journal of Molecular Sciences* 23 (23): 14542. https://doi.org/10.3390/ijms232314542.

Li, Shaofang, Lang Liu, Wenxian Sun, Xueping Zhou, and Huanbin Zhou. 2022. "A large-scale genome and transcriptome sequencing analysis reveals the mutation landscapes induced by high-activity adenine base editors in plants." *Genome Biology* 23 (1): 51. https://doi.org/10.1186/s13059-022-02618-w.

Lin, Lin, David L Ortega, and Jiayu Sun. 2023. "The effectiveness of misinformation corrective strategies and implications for consumers' food preferences and policy attitudes".

Lindberg, S., C. Bain, and T. Selfa. 2023. "Regulating gene editing in agriculture and food in the European Union: Disentangling expectations and path dependencies" 63 (2): 348-69. https://doi.org/10.1111/soru.12429.

Liu, Xiaojing, Jiangtao Yang, Yaya Song, Xiaochun Zhang, Xujing Wang, and Zhixing Wang. 2022. "Effects of sgRNA length and number on gene editing efficiency and predicted mutations generated in rice". *The Crop Journal* 10 (2): 577-81. https://doi.org/10.1016/j.cj.2021.05.015.

Liu, Yang, Paul Merrick, Zhengzhi Zhang, Chonghui Ji, Bing Yang, and Shui-zhang Fei. 2018. "Targeted Mutagenesis in Tetraploid Switchgrass (Panicum Virgatum L.) Using CRISPR/Cas9". *Plant Biotechnology Journal* 16 (2): 381-93. https://doi.org/10.1111/pbi.12778.

Livingston, Mike, Jorge Fernandez-Cornejo, Jesse Unger, Craig Osteen, David Schimmelpfennig, Timothy Park, and Dayton M Lambert. 1952. "The economics of glyphosate resistance management in corn and soybean production". *Economic Research Report No. ERR-184, US Department of Agriculture*.

Lu, Yuming, and Jian-Kang Zhu. 2017. "Precise Editing of a Target Base in the Rice Genome Using a Modified CRISPR/Cas9 System". *Molecular Plant* 10 (3): 523-25. https://doi.org/10.1016/j.molp.2016.11.013.

Luby, Claire H, Jack Kloppenburg, Thomas E Michaels, and Irwin L Goldman. 2015. "Enhancing freedom to operate for plant breeders and farmers through open source plant breeding". *Crop Science* 55 (6): 2481-88.

Lucht, J. M. 2015. "Public acceptance of plant biotechnology and GM crops". *Viruses* 7 (8): 4254-81. https://doi.org/10.3390/v7082819.

Lusk, Jayson L, Mustafa Jamal, Lauren Kurlander, Maud Roucan, and Lesley Taulman. 2005. "A meta-analysis of genetically modified food valuation studies. *Journal of agricultural and resource economics*, 28-44.

Maaß, O., N. Consmüller, and H. Kehlenbeck. 2019. "Socioeconomic impact of genome editing on agricultural value chains: the case of fungal-resistant and coeliac-safe wheat." *Sustainability* 11 (22). https://doi.org/10.3390/su11226421.

Mackenzie, Adrian. 2013. "Realizing the promise of biotechnology: Infrastructural-icons in synthetic biology". *Futures* 48: 5-12.

Macnaghten, P., and M. G. J. L. Habets. 2020. "Breaking the impasse: Towards a forward-looking governance framework for gene editing with plants. *Plants People Planet* 2 (4): 353-65. https://doi.org/10.1002/ppp3.10107.

Marette, S., J. Beghin, A. C. Disdier, and E. Mojduszka. 2021. "Can foods produced with new plant engineering techniques succeed in the marketplace? A case study of apples". *Applied Economic Perspectives and Policy*. https://doi.org/10.1002/aepp.13208.

Marette, S., A. C. Disdier, and J. C. Beghin. 2021. "A comparison of EU and US consumers' willingness to pay for gene-edited food: evidence from apples". *Appetite* 159. https://doi.org/10.1016/j.appet.2020.105064.

Marette, S., A. C. Disdier, A. Bodnar, and J. Beghin. 2022. "New plant engineering techniques, R&D investment and international trade". *Journal of Agricultural Economics*. https://doi.org/10.1111/1477-9552.12516.

Marris, Claire. 2001. "Public views on GMOs: deconstructing the myths. *EMBO reports* 2 (7): 545-48.

Marris, Claire, and Jane Calvert. 2020. "Science and technology studies in policy: the UK synthetic biology roadmap". *Science, Technology, & Human Values* 45 (1): 34-61.

Martínez-Reyna, J. M., and K. P. Vogel. 2002. "Incompatibility Systems in Switchgrass. *Crop Science* 42 (6): 1800-1805. https://doi.org/10.2135/cropsci2002.1800.

Mil, Anita van, Henrietta Hopkins, and Suzannah Kinsella. 2017. "Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society". *Findings Report*.

Modrzejewski, Dominik, Frank Hartung, Heike Lehnert, Thorben Sprink, Christian Kohl, Jens Keilwagen, and Ralf Wilhelm. 2020. "Which Factors Affect the Occurrence of Off-Target Effects Caused by the Use of CRISPR/Cas: A Systematic Review in Plants." *Frontiers in Plant Science* 11. https://www.frontiersin.org/articles/10.3389/fpls.2020.574959.

Modrzejewski, Dominik, Frank Hartung, Thorben Sprink, Dörthe Krause, Christian Kohl, and Ralf Wilhelm. 2019. "What is the available evidence for the range of applications of genome-editing as a new tool for plant trait modification and the potential occurrence of associated off- target effects: a systematic map." *Environmental Evidence* 8 (1): 27. https://doi.org/10.1186/s13750-019-0171-5.

Montenegro de Wit, Maywa. 2019. "Beating the bounds: How does 'open source'become a seed commons?" *The Journal of Peasant Studies* 46 (1): 44-79.

Mortensen, David A., and Richard G. Smith. 2020. "Confronting Barriers to Cropping System Diversification." *Frontiers in Sustainable Food Systems* 4 (November). https://doi.org/10.3389/fsufs.2020.564197.

Narushima, Jumpei, Shinya Kimata, Yuh Shiwa, Takahiro Gondo, Satoshi Akimoto, Keisuke Soga, Satoko Yoshiba, Kosuke Nakamura, Norihito Shibata, and Kazunari Kondo. 2022. "Unbiased Prediction of Off-Target Sites in Genome-Edited Rice Using SITE-Seq Analysis on a Web-Based Platform". *Genes to Cells* 27 (12): 706-18. https://doi.org/10.1111/gtc.12985.

Nawaz, S., and T. Satterfield. 2022a. "Climate solution or corporate co-optation? US and Canadian publics' views on agricultural gene editing". *PLoS ONE* 17 (3 March). https://doi.org/10.1371/journal.pone.0265635.

---. 2022b. "On the nature of naturalness? Theorizing 'nature' for the study of public perceptions of novel genomic technologies in agriculture and conservation". *Environmental Science and Policy* 136: 291-303. https://doi.org/10.1016/j.envsci.2022.06.008.

Nawaz, S., T. Satterfield, and R. Phurisamban. 2022. "Does "Precision" Matter? A Q Study of Public Interpretations of Gene Editing in Agriculture". *Science Technology and Human Values*. https://doi.org/10.1177/01622439221112460.

Noleppa, Steffen, and Matti Cartsburg. 2021. "The socio-economic and environmental values of plant breeding in the EU and for selected EU member states". *An Ex-Post Evaluation and Ex-Ante Assessment Considering the "Farm to Fork" and "Biodiversity" Strategies*.

Nonaka, Satoko, Chikako Arai, Mariko Takayama, Chiaki Matsukura, and Hiroshi Ezura. 2017. "Efficient Increase of ɣ-Aminobutyric Acid (GABA) Content in Tomato Fruits by Targeted Mutagenesis". *Scientific Reports* 7 (1): 7057. https://doi.org/10.1038/s41598-017-06400-y.

OECD. 2008. *Test No. 407: Repeated Dose Oral Toxicity - 28 Days in Rodents*. Paris: Organisation for Economic Co-operation and Development. https://www.oecd-ilibrary.org/environment/essai-n-407-toxicite-orale-a-doses-repetees-pendant-28-jours-sur-les-rongeurs_9789264070691-en.

---. 2018. *Trial 408: Repeated-dose oral toxicity - rodents: 90 days*. Paris: Organisation for Economic Co-operation and Development. https://www.oecd-ilibrary.org/environment/test-n-408-toxicite-orale-a-doses-repetees-rodents-90-days_9789264070714-en.

Paudel, Bindu, Deepthi E Kolady, David Just, and Evert Van der Sluis. n.d. "Determinants of consumer acceptance of gene-edited foods and its implications for innovators and policymakers". *Agribusiness*.

Paudel, Bindu, Deepthi Kolady, David Just, and Mariam Ishaq. 2023. "Effect of information and innovator reputation on consumers' willingness to pay for genome-edited foods". *Food Quality and Preference* 107: 104825.

Pellegrino, Elisa, Stefano Bedini, Marco Nuti, and Laura Ercoli. 2018. "Impact of genetically engineered maize on agronomic, environmental and toxicological traits: a meta-analysis of 21 years of field data". *Scientific reports* 8 (1): 3113.

Pompili, Valerio, Lorenza Dalla Costa, Stefano Piazza, Massimo Pindo, and Mickael Malnoy. 2020. "Reduced Fire Blight Susceptibility in Apple Cultivars Using a High-Efficiency CRISPR/Cas9-FLP/FRT-Based Gene Editing System." *Plant Biotechnology Journal* 18 (3): 845-58. https://doi.org/10.1111/pbi.13253.

Porter, Michael E. 1985. "Competitive strategy: Creating and sustaining superior performance. *The free, New York*.

Purnhagen, K. P., and J. H. H. Wesseler. 2019. "Maximum vs minimum harmonization: what to expect from the institutional and legal battles in the EU on gene editing technologies". *Pest Management Science* 75 (9): 2310-15. https://doi.org/10.1002/ps.5367.

Qaim, Matin. 2009. "The economics of genetically modified crops. *Annu. Rev. Resour. Econ.* 1 (1): 665-94.

Qiu, Jie, Yongjun Zhou, Lingfeng Mao, Chuyu Ye, Weidi Wang, Jianping Zhang, Yongyi Yu, et al. 2017. "Genomic Variation Associated with Local Adaptation of Weedy Rice during De-Domestication". *Nature Communications* 8 (1): 15323. https://doi.org/10.1038/ncomms15323.

Rehman, Maqsood, Jennifer L. Hansen, Carol A. Mallory-Smith, and Robert S. Zemetra. 2017. "Impact of Transgene Genome Location on Gene Migration from Herbicide-Resistant Wheat (Triticum Aestivum L.) to Jointed Goatgrass (Aegilops Cylindrica Host)". *Pest Management Science* 73 (8): 1593-97. https://doi.org/10.1002/ps.4490.

Ren, Qiurong, Simon Sretenovic, Guanqing Liu, Zhaohui Zhong, Jiaheng Wang, Lan Huang, Xu Tang, et al. 2021. "Improved Plant Cytosine Base Editors with High Editing Activity, Purity, and Specificity". *Plant Biotechnology Journal* 19 (10): 2052-68. https://doi.org/10.1111/pbi.13635.

Ribarits, Alexandra, Michael Eckerstorfer, Samson Simon, and Walter Stepanek. 2021. "Genome-edited plants: Opportunities and challenges for an anticipatory detection and identification framework". *Foods* 10 (2): 430.

Ricroch, A. E., and M. C. Hénard-Damave. 2016. "Next biotech plants: new traits, crops, developers and technologies for addressing global challenges". *Critical Reviews in Biotechnology* 36 (4): 675-90. https://doi.org/10.3109/07388551.2015.1004521.

Rousselière, Damien, and Samira Rousselière. 2017. "Is biotechnology (more) acceptable when it enables a reduction in phytosanitary treatments? A European comparison of the

acceptability of transgenesis and cisgenesis". *PLOS ONE* 12 (9): e0183213. https://doi.org/10.1371/journal.pone.0183213.

Sánchez-León, Susana, Javier Gil-Humanes, Carmen V. Ozuna, María J. Giménez, Carolina Sousa, Daniel F. Voytas, and Francisco Barro. 2018. "Low-Gluten, Nontransgenic Wheat Engineered with CRISPR/Cas9". *Plant Biotechnology Journal* 16 (4): 902-10. https://doi.org/10.1111/pbi.12837.

Schafer, Meredith G., Andrew A. Ross, Jason P. Londo, Connie A. Burdick, E. Henry Lee, Steven E. Travers, Peter K. Van de Water, and Cynthia L. Sagers. 2011. "The Establishment of Genetically Engineered Canola Populations in the U.S." *PLOS ONE* 6 (10): e25736. https://doi.org/10.1371/journal.pone.0025736.

Scheufele, Dietram A, Nicole M Krause, Isabelle Freiling, and Dominique Brossard. 2021. "What we know about effective public engagement on CRISPR and beyond". *Proceedings of the national academy of sciences* 118 (22): e2004835117.

Schmitz, Ulf. 2004. "Frost resistance of tomato seeds and the degree of naturalisation of Lycopersicon esculentum Mill. in Central Europe". *Flora - Morphology, Distribution, Functional Ecology of Plants* 199 (6): 476-80. https://doi.org/10.1078/0367-2530-00176.

Schulze, Juerg, Tina Frauenknecht, Peter Brodmann, and Claudia Bagutti. 2014. "Unexpected Diversity of Feral Genetically Modified Oilseed Rape (Brassica Napus L.) Despite a Cultivation and Import Ban in Switzerland." *PLOS ONE* 9 (12): e114477. https://doi.org/10.1371/journal.pone.0114477.

Schyfter, Pablo, and Jane Calvert. 2015. "Intentions, expectations and institutions: engineering the future of synthetic biology in the USA and the UK". *Science as Culture* 24 (4): 359-83.

Selfa, T., S. Lindberg, and C. Bain. 2021. "Governing gene editing in agriculture and food in the United States: Tensions, contestations, and realignments." *Elementa* 9 (1). https://doi.org/10.1525/elementa.2020.00153.

Selin, Cynthia. 2007. "Expectations and the Emergence of Nanotechnology. *Science, Technology, & Human Values* 32 (2): 196-220.

Shea, Beverley J., Barnaby C. Reeves, George Wells, Micere Thuku, Candyce Hamel, Julian Moran, David Moher, et al. 2017. "AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both". *BMJ* 358 (September): j4008. https://doi.org/10.1136/bmj.j4008.

Shew, A. M., L. L. Nalley, H. A. Snell, R. M. Nayga Jr. and B. L. Dixon. 2018. "CRISPR versus GMOs: public acceptance and valuation". *Global Food Security* 19: 71-80. https://doi.org/10.1016/j.gfs.2018.10.005.

Shi, Guanming, Jean-Paul Chavas, and Kyle W Stiegert. 2009. "Pricing of herbicide-tolerant soybean seeds: a market-structure approach".

Shillito, Raymond D., Sherry Whitt, Margit Ross, Farhad Ghavami, David De Vleesschauwer, Katelijn D'Halluin, Annelies Van Hoecke, and Frank Meulewaeter. 2021. "Detection of Genome Edits in Plants-from Editing to Seed". *In Vitro Cellular & Developmental Biology - Plant* 57
(4): 595-608. https://doi.org/10.1007/s11627-021-10214-z.

Shimatani, Zenpei, Sachiko Kashojiya, Mariko Takayama, Rie Terada, Takayuki Arazoe, Hisaki Ishii, Hiroshi Teramura, et al. 2017. "Targeted Base Editing in Rice and Tomato Using a CRISPR-Cas9 Cytidine Deaminase Fusion". *Nature Biotechnology* 35 (5): 441-43. https://doi.org/10.1038/nbt.3833.

Shin, Na-Ri, Yun-Hee Shin, Han-Seul Kim, and Young-Doo Park. 2022. "Function Analysis of the PR55/B Gene Related to Self-Incompatibility in Chinese Cabbage Using CRISPR/Cas9." *International Journal of Molecular Sciences* 23 (9): 5062. https://doi.org/10.3390/ijms23095062.

Shin, Yun-Hee, and Young-Doo Park. 2022. "CRISPR/Cas9-Mediated Mutagenesis of BrLEAFY Delays the Bolting Time in Chinese Cabbage (Brassica Rapa L. Ssp. Pekinensis)." *International Journal of Molecular Sciences* 24 (1): 541. https://doi.org/10.3390/ijms24010541.

Smith, Vincent, Justus HH Wesseler, and David Zilberman. 2021. "New plant breeding technologies: An assessment of the political economy of the regulatory environment and implications for sustainability". *Sustainability* 13 (7): 3687.

Stilgoe, Jack. 2015. *Experiment Earth: Responsible innovation in geoengineering*. Routledge.

Sturme, Mark H. J., Jan Pieter van der Berg, Lianne M. S. Bouwman, Adinda De Schrijver, Ruud A. de Maagd, Gijs A. Kleter, and Evy Battaglia-de Wilde. 2022. "Occurrence and Nature of Off-Target Modifications by CRISPR-Cas Genome Editing in Plants". *ACS Agricultural Science & Technology* 2 (2): 192-201. https://doi.org/10.1021/acsagscitech.1c00270.

Sumpter, Bethany. 2020. "The Growing monopoly in the corn seed industry: is it time for the government to interfere?" *Tex. A&M L. Rev.* 8: 633.

Talberg, Anita, Sebastian Thomas, Peter Christoff, and David Karoly. 2018. "How geoengineering scenarios frame assumptions and create expectations". *Sustainability Science* 13: 1093-1104.

Tan, Jiantao, Dongchang Zeng, Yanchang Zhao, Yaxi Wang, Taoli Liu, Shuangchun Li, Yang Xue, et al. 2022. "PhieABEs: A PAM-Less/Free High-Efficiency Adenine Base Editor Toolbox with Wide Target Scope in Plants". *Plant Biotechnology Journal* 20 (5): 934-43. https://doi.org/10.1111/pbi.13774.

Temple, Ludovic, Frédéric Lançon, Florence Palpacuer, and Gilles Paché. 2011. "Actualisation du concept de filière dans l'agriculture et l'agroalimentaire". *Economies et Sociétés. Série AG Systèmes agroalimentaires*, nº 33: 1785-97.

Torshizi, Mohammad, and Jennifer Clapp. 2021. "Price effects of common ownership in the seed sector". *The Antitrust Bulletin* 66 (1): 39-67.

Touzdjian Pinheiro Kohlrausch Távora, Fabiano, Francisco de Assis Dos Santos Diniz, Camila de Moraes Rêgo-Machado, Natália Chagas Freitas, Fabrício Barbosa Monteiro Arraes, Eduardo Chumbinho de Andrade, Leila Lourenço Furtado, et al. 2022. "CRISPR/Cas- and Topical RNAi-Based Technologies for Crop Management and Improvement: Reviewing the Risk Assessment and Challenges Towards a More Sustainable Agriculture". *Frontiers in Bioengineering and Biotechnology* 10: 913728. https://doi.org/10.3389/fbioe.2022.913728.

Tran, Mil Thi, Duong Thi Hai Doan, Jihae Kim, Young Jong Song, Yeon Woo Sung, Swati Das, Eun-Jung Kim, et al. 2021. "CRISPR/Cas9-Based Precise Excision of SlHyPRP1 Domain(s) to Obtain Salt Stress-Tolerant Tomato." *Plant Cell Reports* 40 (6): 999-1011. https://doi.org/10.1007/s00299-020-02622-z.

Tremblay, Jacques P. 2015. "CRISPR, a system for correcting or modifying the expression of genes responsible for hereditary diseases". *medicine/sciences* 31 (11): 1014-22. https://doi.org/10.1051/medsci/20153111016.

Troadec, Marie-Bérengère, Jean-Christophe Pagès, and the Scientific Committee of the High Council for biotechnology, France. 2019. "Where Are We with Unintended Effects in Genome.

Editing Applications from DNA to Phenotype: Focus on Plant Applications". *Transgenic Research* 28 (Suppl 2): 125-33. https://doi.org/10.1007/s11248-019-00146-1.

Trtikova, Miluse, Andre Lohn, Rosa Binimelis, Ignacio Chapela, Bernadette Oehen, Niklaus Zemp, Alex Widmer, and Angelika Hilbeck. 2017. "Teosinte in Europe - Searching for the Origin of a Novel Weed". *Scientific Reports* 7 (1): 1560. https://doi.org/10.1038/s41598-017-01478- w.

Van Deynze, Braeden, Scott M Swinton, and David A Hennessy. 2022. "Are glyphosate-resistant weeds a threat to conservation agriculture? Evidence from tillage practices in soybeans". *American Journal of Agricultural Economics* 104 (2): 645-72.

Van Overwalle, Geertrui. 2009. *Gene patents and collaborative licensing models: patent pools, clearinghouses, open source models and liability regimes*. Cambridge University Press.

Veillet, Florian, Laura Perrot, Laura Chauvin, Marie-Paule Kermarrec, Anouchka Guyon-Debast, Jean-Eric Chauvin, Fabien Nogué, and Marianne Mazier. 2019. "Transgene-Free Genome Editing in Tomato and Potato Plants Using Agrobacterium-Mediated Delivery of a CRISPR/Cas9 Cytidine Base Editor". *International Journal of Molecular Sciences* 20 (2): 402. https://doi.org/10.3390/ijms20020402.

Venezia, Matthew, and Kate M Creasey Krainer. 2021. "Current advancements and limitations of gene editing in orphan crops". *Frontiers in Plant Science* 12: 742932.

Waltz, Emily. 2021. "GABA-Enriched Tomato Is First CRISPR-Edited Food to Enter Market". *Nature Biotechnology* 40 (1): 9-11. https://doi.org/10.1038/d41587-021-00026-2.

Wan, Lili, Zhuanrong Wang, Mi Tang, Dengfeng Hong, Yuhong Sun, Jian Ren, Na Zhang, and Hongxia Zeng. 2021. "CRISPR-Cas9 gene editing for fruit and vegetable crops: strategies and prospects". *Horticulturae* 7 (7): 193.

Wang, Xianhang, Mingxing Tu, Dejun Wang, Jianwei Liu, Yajuan Li, Zhi Li, Yuejin Wang, and Xiping Wang. 2018. "CRISPR/Cas9-Mediated Efficient Targeted Mutagenesis in Grape in the First Generation". *Plant Biotechnology Journal* 16 (4): 844-55. https://doi.org/10.1111/pbi.12832.

Wang, Xianhang, Mingxing Tu, Ya Wang, Wuchen Yin, Yu Zhang, Hongsong Wu, Yincong Gu, Zhi Li, Zhumei Xi, and Xiping Wang. 2021. "Whole-genome sequencing reveals rare off-target mutations in CRISPR/Cas9-edited grapevine". *Horticulture Research* 8 (January): 114. https://doi.org/10.1038/s41438-021-00549-4.

Wesseler, J., H. Politiek, and D. Zilberman. 2019. "The economics of regulating new plant breeding technologies - implications for the bioeconomy illustrated by a survey among Dutch plant breeders." *Frontiers in Plant Science* 10 (December). https://doi.org/10.3389/fpls.2019.01597.

Whelan, A. I., P. Gutti, and M. A. Lema. 2020. "Gene Editing Regulation and Innovation Economics." *Frontiers in Bioengineering and Biotechnology* 8. https://doi.org/10.3389/fbioe.2020.00303.

Will, S., N. Vangheluwe, D. Krause, A. R. H. Fischer, P. Jorasch, C. Kohl, A. Nair, A. K. Nanda, and R. Wilhelm. 2022. "Communicating about plant breeding and genome editing in plants: Assessment of European stakeholders, sources, channels and content". *Food and Energy Security*. https://doi.org/10.1002/fes3.415.

Winickoff, David, Sheila Jasanoff, Lawrence Busch, and Robin Grove-White. 2005. "Adjudicating the GM food wars: science, risk, and democracy in world trade law. *Yale J. Int'l L.* 30: 81.

Wirz, C. D., D. A. Scheufele, and D. Brossard. 2020. "Societal Debates About Emerging Genetic Technologies: Toward a Science of Public Engagement. *Environmental Communication* 14
(7): 859-64. https://doi.org/10.1080/17524032.2020.1811478.

Wit, M. M. de. 2020. "Democratizing CRISPR? Stories, practices, and politics of science and governance on the agricultural gene editing frontier". *Elementa: Science of the Anthropocene* 8 (9). https://doi.org/10.1525/elementa.405.

Woźniak, E., E. Waszkowska, T. Zimny, S. Sowa, and T. Twardowski. 2019. "The Rapeseed Potential in Poland and Germany in the Context of Production, Legislation, and Intellectual Property Rights". *Frontiers in Plant Science* 10. https://doi.org/10.3389/fpls.2019.01423.

Wu, Yuechao, Qiurong Ren, Zhaohui Zhong, Guanqing Liu, Yangshuo Han, Yu Bao, Li Liu, et al. 2022. "Genome-Wide Analyses of PAM-Relaxed Cas9 Genome Editors Reveal Substantial off-Target Effects by ABE8e in Rice." *Plant Biotechnology Journal* 20 (9): 1670-82. https://doi.org/10.1111/pbi.13838.

Yan, Daqi, Bin Ren, Lang Liu, Fang Yan, Shaofang Li, Guirong Wang, Wenxian Sun, Xueping Zhou, and Huanbin Zhou. 2021. "High-efficiency and multiplex adenine base editing in plants using new TadA variants". *Molecular Plant* 14 (5): 722-31. https://doi.org/10.1016/j.molp.2021.02.007.

Yang, Y., and J. E. Hobbs. 2020. "How Do Cultural Worldviews Shape Food Technology Perceptions? Evidence from a Discrete Choice Experiment. *Journal of Agricultural Economics* 71 (2): 465-92. https://doi.org/10.1111/1477-9552.12364.

Yang, Yang, Kaiyu Zhu, Huailin Li, Shaoqing Han, Qingwei Meng, Shahid Ullah Khan, Chuchuan Fan, Kabin Xie, and Yongming Zhou. 2018. "Precise Editing of CLAVATA Genes in Brassica Napus L. Regulates Multilocular Silique Development." *Plant Biotechnology Journal* 16 (7): 1322-35. https://doi.org/10.1111/pbi.12872.

You, Jun, Donghua Li, Li Yang, Senouwa Segla Koffi Dossou, Rong Zhou, Yanxin Zhang, and Linhai Wang. 2022. "CRISPR/Cas9-Mediated Efficient Targeted Mutagenesis in Sesame (Sesamum indicum L .)". *Frontiers in Plant Science* 13. https://www.frontiersin.org/articles/10.3389/fpls.2022.935825.

Zaman, Qamar U., Ali Raza, Rafaqat Ali Gill, Muhammad Azhar Hussain, Hua Feng Wang, and Rajeev K. Varshney. 2023. "New Possibilities for Trait Improvement via Mobile CRISPR-RNA. *Trends in Biotechnology* 41 (11): 1335-38. https://doi.org/10.1016/j.tibtech.2023.05.001.

Zhang, Yingxiao, Yuechao Wu, Gen Li, Aileen Qi, Yong Zhang, Tao Zhang, and Yiping Qi. 2023. "Genome-Wide Investigation of Multiplexed CRISPR-Cas12a-Mediated Editing in Rice". *The Plant Genome* 16 (2): e20266. https://doi.org/10.1002/tpg2.20266.

Zhao, Hui, and Jeffrey D. Wolt. 2017. "Risk Associated with Off-Target Plant Genome Editing and Methods for Its Limitation." *Emerging Topics in Life Sciences* 1 (2): 231-40. https://doi.org/10.1042/ETLS20170037.

Zhou, Zheng, Hexin Tan, Qing Li, Junfeng Chen, Shouhong Gao, Yun Wang, Wansheng Chen, and Lei Zhang. 2018. "CRISPR/Cas9-mediated efficient targeted mutagenesis of RAS in Salvia miltiorrhiza". *Phytochemistry* 148 (April): 63-70. https://doi.org/10.1016/j.phytochem.2018.01.015.

Zong, Yuan, Yijing Liu, Chenxiao Xue, Boshu Li, Xiangyang Li, Yanpeng Wang, Ji Li, et al. 2022. "An Engineered Prime Editor with Enhanced Editing Efficiency in Plants". *Nature Biotechnology* 40 (9): 1394-1402. https://doi.org/10.1038/s41587-022-01254-w.

9.2 Standards

AFNOR. 2003. NF X 50-110 *Qualité en expertise - Prescriptions générales de compétence pour une expertise.* AFNOR (classification index X 50-110).

9.3 Legislation and regulations

Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on Applications for Authorisation of Genetically Modified Food and Feed in Accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and Amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006 Text with EEA Relevance. 2013. OJ L. Vol. 157. http://data.europa.eu/eli/reg_impl/2013/503/oj/eng.

Council Directive 2002/53/EC of 13 June 2002 on the Common Catalogue of Varieties of Agricultural Plant Species. 2002. OJ L. Vol. 193. http://data.europa.eu/eli/dir/2002/53/oj/eng.

Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Statement. 2001. OJ L. Vol. 106. http://data.europa.eu/eli/dir/2001/18/oj/fra.

Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (Text with EEA relevance). 2003. OJ L. Vol. 268. http://data.europa.eu/eli/reg/2003/1829/oj/fra.

APPENDICES

Appendix 1: Referral letter

2021-SA-0019

GOUVERNEMENT
Liberté
Égalité
Fraternité

Paris, le 28 JAN. 2021

Ministère de la transition écologique et solidaire

Direction générale de la prévention des risques
Service des risques liés à l'environnement, des déchets et des pollutions diffuses
Sous-direction santé-environnement, produits chimiques, agriculture
Bureau des biotechnologies et de l'agriculture

Dossier suivi par : Charles BOURGEOIS
Tél : 01 40 81 71 56
Mél : charles.bourgeois@developpement-durable.gouv.fr

Ministère de l'agriculture et de l'alimentation

Direction générale de l'alimentation
Service des actions sanitaires en production primaire
Sous-direction de la qualité, de la santé et de la protection des végétaux
Bureau des semences et de la protection intégrée des cultures

Dossier suivi par : Anne GREVET
Tél. : 01 49 55 58 25
Mél : anne.grevet@agriculture.gouv.fr

Le Directeur général de la prévention des risques

Le Directeur général de l'alimentation

à

Monsieur le Directeur général de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail

14 rue Pierre et Marie Curie
94701 MAISONS-ALFORT CEDEX

Objet : Saisine : Travaux de fond sur les méthodes d'évaluation des risques liés à l'utilisation des OGM en alimentation animale et humaine (« METHEVALOGM ») – Action 2

Éléments de contexte :

Les NBT, ou « New Breeding Techniques », constituent un ensemble hétérogène de techniques de modification du génome, mettant en œuvre différents processus : mutations, insertions, ou délétions de gènes notamment.

Certaines de ces techniques visent à modifier de façon précise et ciblée une séquence du génome, offrant un champ d'application très large, y compris dans le domaine de la sélection variétale. Ces techniques, et notamment celles basées sur le système Crispr-Cas, se développent très rapidement, et certaines variétés végétales obtenues à l'aide de NBT sont d'ores et déjà mise sur le marché dans certains pays, notamment aux Etats-Unis et au Canada.

En Europe, l'arrêt rendu par la Cour de Justice de l'Union Européenne (CJUE) le 25 juillet 2018 est venu préciser que tout produit issu d'une technique de mutagenèse est un OGM et que seuls sont exemptés du champ de la réglementation sur les OGM « les organismes obtenus au moyen de techniques/méthodes de mutagenèse qui ont été traditionnellement utilisées pour diverses applications et dont la sécurité est avérée depuis longtemps ». Cette définition implique, de fait, que les nouvelles techniques de mutagénèse sont soumises à la réglementation sur les OGM, et que l'utilisation de ces techniques doit donc respecter le cadre réglementaire tel qu'il a été conçu pour les OGM issus de transgénèse, notamment en matière d'évaluation des risques, de procédure d'autorisation, de traçabilité ou de contrôle.

Le Conseil d'Etat a, dans sa décision du 7 février 2020, traduit au niveau national l'arrêt de la CJUE.

Dans ce contexte, le Conseil de l'Union européenne a demandé à la Commission européenne de remettre, d'ici au 30 avril 2021, une étude à la lumière de l'arrêt de la Cour de justice concernant le statut des nouvelles techniques génomiques dans le droit de l'Union, et une proposition, le cas échéant pour tenir compte des résultats de l'étude.

En parallèle, la Commission européenne a donné plusieurs mandats à l'EFSA, concernant notamment les nouvelles techniques de modification ciblée du génome et la biologie de synthèse. Ces travaux ont pour objectif d'évaluer l'adéquation des documents guides actuels de l'EFSA, conçus pour évaluer les OGM issus de transgénèse, à l'évaluation des risques des organismes obtenus à l'aide de ces nouvelles technologies.

Following these referrals, EFSA adopted a number of opinions, including :

- on new techniques for targeted genome modification, on 25 October 2012 (for techniques "SDN-3") and 14 October 2020 (for "SON-1", "SDN-2" and "ODM" techniques);
- With regard to organisms derived from synthetic biology, EFSA has divided the European Commission's mandate into six work packages (WP), which will give rise to six opinions; only the opinion on micro-organisms (WP1) was adopted on 28 October 2020, with the opinion on plants (WP2) due to be adopted shortly.

In view of these various contextual factors, it would seem necessary for the Anses to initiate an in-depth discussion without delay on the methods for assessing the risks associated with the use of these new genome modification techniques.

Referral :

In its work programme for 2021, Anses presents the "METHEVALOGM" project, consisting of in-depth work on risk assessment methods related to the use of GMOs in animal feed and food. Action 2 of this project aims to initiate methodological reflection on the safety assessment of plants derived from NBT (New Breeding Techniques), in particular CRISPR-cas9 and related techniques.

Anses has been asked to launch action 2 of the METHEVALOGM project, the results of which will provide scientific support to the French authorities in future discussions at European level. Priority will be given to assessing the health safety of plants obtained from CRIPSR-Cas9 and related techniques, focusing initially on the applications most likely to lead to commercial varieties in the short term. The aim will be to identify the potential risks associated specifically with these techniques, in comparison with the risks associated with other genetic modification techniques already in common use, and if necessary to define the necessary adaptations to the methodology for assessing the safety of plants derived from these techniques.

In a second phase, we expect to see information on plants that could be developed in the longer term, including complex combinations of traits or traits that are entirely new to the variety or species.

Timetable:

In view of the discussions already underway at European level, we would be grateful if you could launch work on action 2 of the METHEVALOGM project without delay.

The action will last 18 months from the date of referral. However, in view of the forthcoming European deadlines (European Commission study on the legal status of NBT), an initial progress report, in the form of a discussion meeting for example, will be presented in May 2021.

Recipients of the e-mail reply:

DGAL addressees: institutional box of the trade office (bsoic.sdgsDv.dqaIDaariculture.qouv fr), project manager responsible for the dossier (anne.qrevettŒaoriculture qouv.fr) and institutional box for referrals- anses doaltŒaüriculture.qouv fr

To: DPGR: Head of the Biotechnologies and Agriculture Office (alianore.descourstOdeveloopement-durable.qouv.fr), Head of the Biotechnologies Unit, responsible for the dossier (charles bouraeois@developement-durable aouv.fr)

Our departments will be happy to provide you with any further information you may require.

Please acknowledge receipt of this request.

The Director General for Food

BRUNO FERREIRA ID,°,*% ,/' Signature numérique by BRUNO FERREIRA ID

Bruno FERREIRA

The direct ur gê^*^^!
de la prévenhondes

Cédric BOURILLET

Appendix 2: List of plants resulting from directed mutagenesis using the CRISPR-Cas system identified by the WG and likely to reach the market

Annex 2 is available on the Anses website.

https://www.anses.fr/fr/system/files/BIORISK2021SA0019Ra-Anx2-4-7.xlsx

Appendix 3: Research methodology for the systematic literature review on the undesired effects of the CRISPR-Cas system on the tomato genome

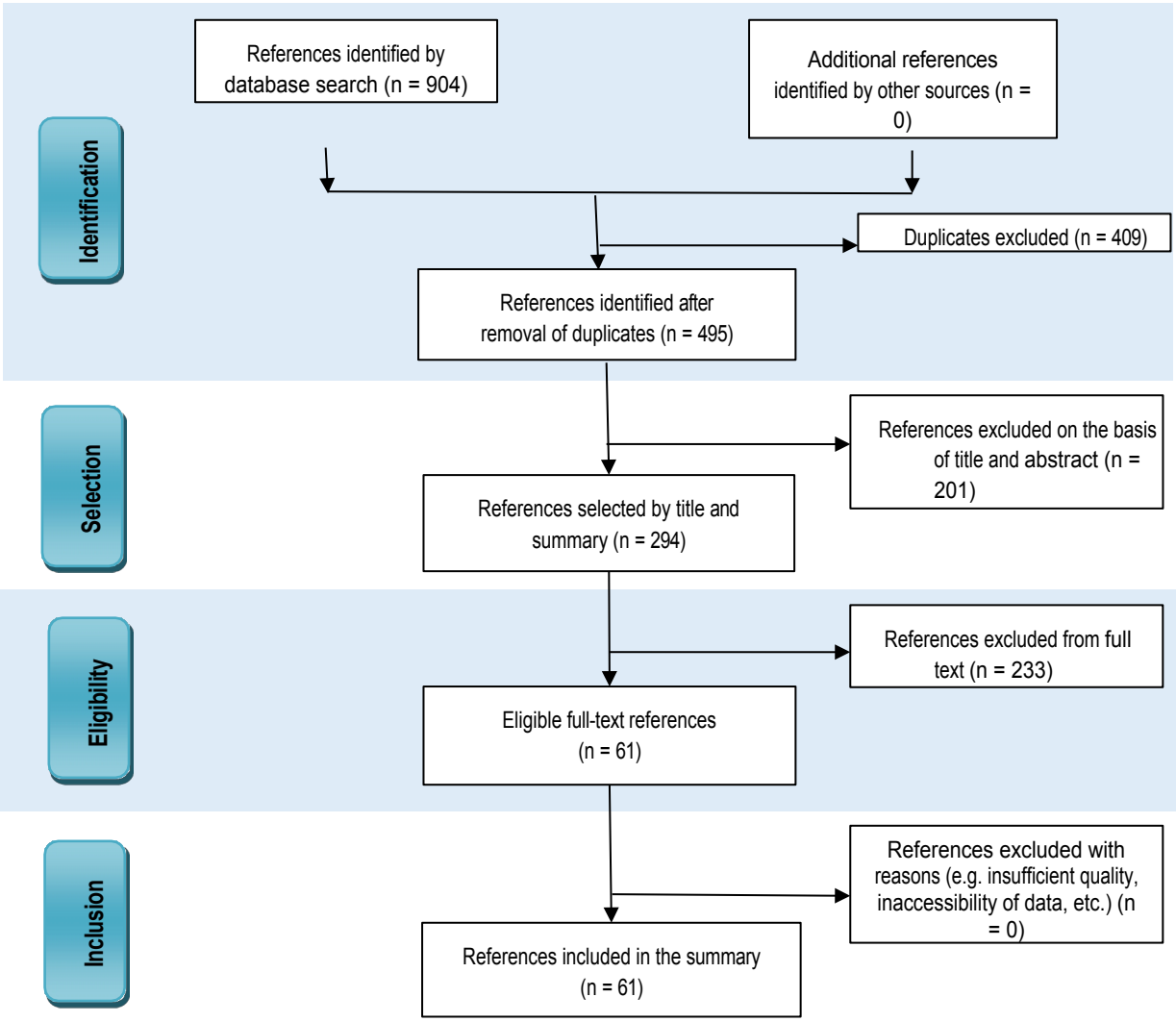
1. PICO STRUCTURE

Themes	Keywords from thesaurus
Population (or subjects studied)	Tomato
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Tomato not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. Ex: mortality, health effects, psychosocial effects, perceptions, economic results)	Unintended effects on and off target
Temporality (Research periods)	∞ - 15/12/2022

2. BIBLIOGRAPHIC SEARCH STRATEGY

Database	Date	Request	Number of references
Scopus	15/12/2022	(tomato OR lycopersicum) AND CRISPR Keywords searched in the titles, abstracts and keywords Articles in English or French	448
PubMed	15/12/2022	(tomato OR lycopersicum) AND CRISPR Keywords searched in all fields Articles in English or French	336
CAB Abstracts	15/12/2022	(tomato OR lycopersicum) AND CRISPR Keywords searched in all fields Articles in English or French	120

3. FLOW CHART (PRISMA)



Appendix 4: Table extracting the data contained in the articles selected for the systematic literature review on the undesired effects of the CRISPR-Cas system on the tomato genome

Annex 4 is available on the Anses website.

https://www.anses.fr/fr/system/files/BIORISK2021SA0019Ra-Anx2-4-7.xlsx

Appendix 5: Research methodology for the systematic literature review on the undesired effects of the CRISPR-Cas system on the genome of all plants for which applications have been documented

1. PICO STRUCTURE

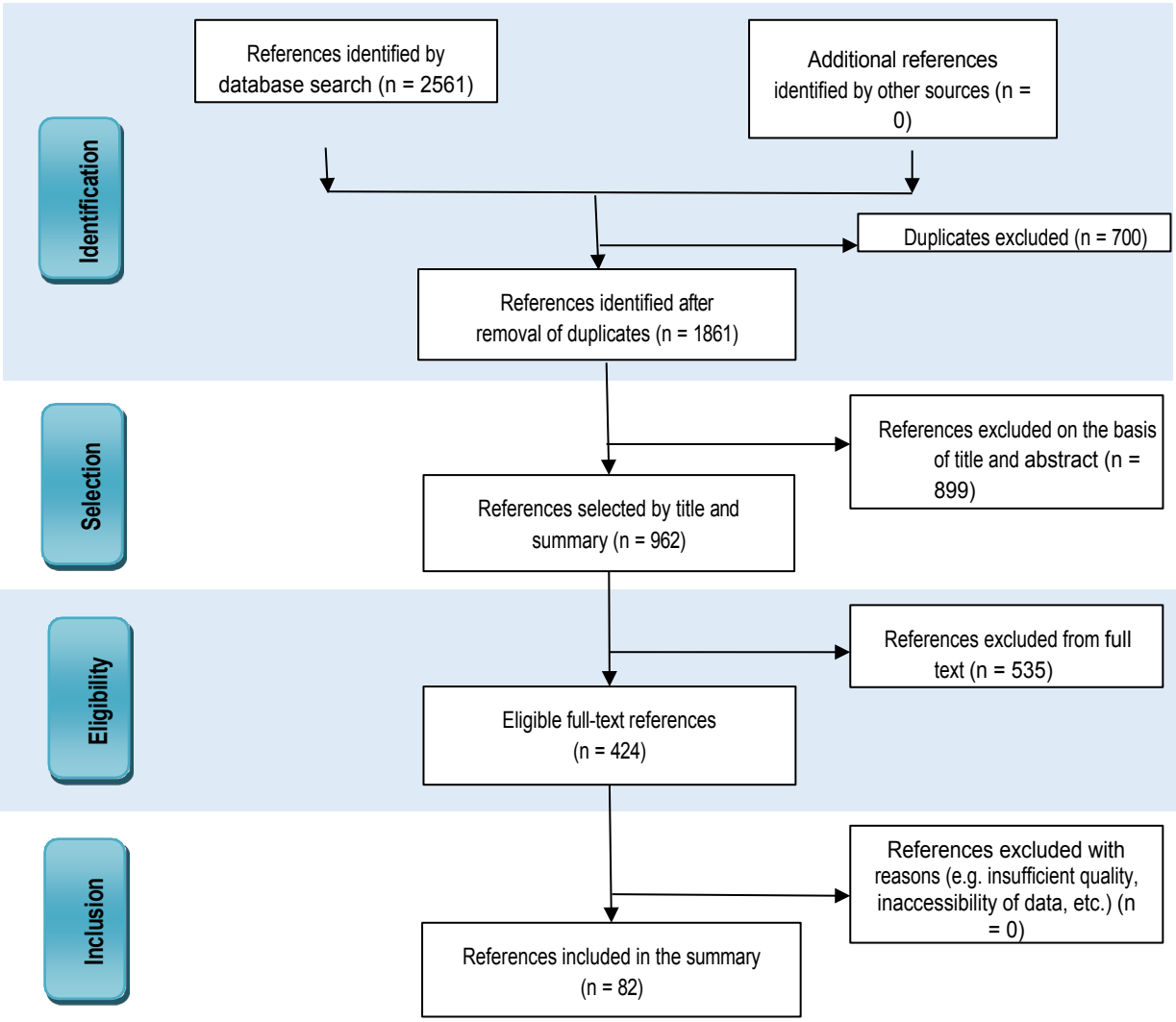
Themes	Keywords from thesaurus
Population (or subjects studied)	Plants
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Plants not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. Ex: mortality, health effects, psychosocial effects, perceptions, economic results)	Unintended effects on and off target
Temporality (Research periods)	∞ - 01/06/2023

2. BIBLIOGRAPHIC SEARCH STRATEGY

Base of data	Date	Request	Number of references
Scopus	01/06/2023	(plant OR plants OR crop OR crops OR tree OR trees OR rice OR "riz" OR "oryza sativa" OR tomato OR tomate OR "Solanum lycopersicum" OR maize OR "maïs" OR "zea mays" OR wheat OR "blé tendre" OR "triticum aestivum" OR medick OR burclover OR luzerne OR medicago OR camelina OR cameline OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "pomme de terre" OR "solanum tuberosum" OR cucumber OR cucumber OR "cucumis sativus" OR arabidopsis OR nicotiana) AND (CRISPR OR "genome editing" OR "genome-editing" OR "genome edition" OR "genome-edition" OR "gene editing" OR "gene-editing" OR "gene edition" OR "gene-edition" OR "site-directed mutagenesis" OR "directed mutagenesis" OR "NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*") AND ("off-target" OR "off target" OR undesired OR unwanted OR unintended OR "on target" OR "on-target") Keywords searched for in titles, summaries and keywords Articles in English or French	538

PubMed	01/06/2023	(plant OR plants OR crop OR crops OR tree OR trees OR rice OR "riz" OR "oryza sativa" OR tomato OR tomate OR "Solanum lycopersicum" OR maize OR "maïs" OR "zea mays" OR wheat OR "blé tendre" OR "triticum aestivum" OR medick OR burclover OR luzerne OR medicago OR camelina OR cameline OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "pomme de terre" OR "solanum tuberosum" OR cucumber OR cucumber OR "cucumis sativus" OR arabidopsis OR nicotiana) AND (CRISPR OR "genome editing" OR "genome-editing" OR "genome edition" OR "genome-edition" OR "gene editing" OR "gene-editing" OR "gene edition" OR "gene-edition" OR "site-directed mutagenesis" OR "directed mutagenesis" OR "NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*") AND ("off-target" OR "off target" OR undesired OR unwanted OR unintended OR "on target" OR "on-target") Keywords searched in all fields Articles in English or French	576
CAB Abstracts	01/06/2023	(plant OR plants OR crop OR crops OR tree OR trees OR rice OR "riz" OR "oryza sativa" OR tomato OR tomate OR "Solanum lycopersicum" OR maize OR "maïs" OR "zea mays" OR wheat OR "blé tendre" OR "triticum aestivum" OR medick OR burclover OR luzerne OR medicago OR camelina OR cameline OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "pomme de terre" OR "solanum tuberosum" OR cucumber OR cucumber OR "cucumis sativus" OR arabidopsis OR nicotiana) AND (CRISPR OR "genome editing" OR "genome-editing" OR "genome edition" OR "genome-edition" OR "gene editing" OR "gene-editing" OR "gene edition" OR "gene-edition" OR "site-directed mutagenesis" OR "directed mutagenesis" OR "NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*") AND ("off-target" OR "off target" OR undesired OR unwanted OR unintended OR "on target" OR "on-target") Keywords searched in all fields Articles in English or French	1447

3. FLOW CHART (PRISMA)



*As indicated in the text of the report, after analysing three systematic reviews of the literature, the analysis was finally limited to original articles published between 2021 and June 2023, whereas the search had initially been conducted on all types of references, with no date limits.

Appendix 6: AMSTAR-2 assessment reports of systematic reviews identified by the WG on the undesired effects of the CRISPR-Cas system on the plant genome

Modrzejewski et al. 2019 11/ 12

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☒ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)
- ☒ Timeframe for follow-up

☒ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☒ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☒ justification for any deviations from the protocol

☒ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☒ OR *Explanation for* including both RCTs and NRSI

☒ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☒ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☒ searched the reference lists / bibliographies of included studies
- ☒ searched trial/study registries
- ☒ included/consulted content experts in the field
- ☒ where relevant, searched for grey literature
- ☒ conducted search within 24 months of completion of the review

☒ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☒ Yes
☐ No

AMSTAR 2.' a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare inter entions, or both

6. Did the review authors perform data exti-action in duplicate'?

For Ycs, cithcr ONE of thc following:

O at least t" o reviewers achieved consensus on which data to extract from included studies OR two reviewers exkacted data from a sample of eligible studies and achieved good agreement (at least b0 percent), with the reinauider extracted by one reviewer.	Yes No

7. Did the review authors provide a list of excluded studies and justify the exclusions'?

For Partial Yes:	For Yes, must also have:	
provided a list of all potentially relevant studies that were read ui full-text form but excluded from the review	Justified the exclusion frotn the review of each potentially relevant study	Yes Partial Yes No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
O described populations described interventions U described coinparators Udescribed outcomes U described research designs	described population in detail described intervention in detail (including doses wh ereNo relevant) dcscribcd comparator in dctail (including doses whcrc relevant) described study's setting timeframe for follow-up	Yes Partial Yes

9. Did the review authors use a satisfactory technique for assessing the risl' of hias (RoB) in individual studies that were included in the review'?

RCTs

For Partial Yes, tnusf have assessed RoB	For Yes, must also have assessed RoB	
unconcealed allocation, *uuid* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objcctivc outcomcs such as all-causc mortality)	allocation sequence that was not truly random, on'f selection of the reported result from among multiple measurements or analyses of SI specified outcome	Ycs Partial Yes No Includes only aNR

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
from confounding, oii'f from selection bias	methods used to ascertaui exposures and outcomes, *uuid* selection of the reported result from among multiple measurements or analyses of s specified outcome	Yes Partial Yes No Includes only aRCT

I fl. Dirt the review authors report on the sources of fuiuling for the stuilies incluiletl in the rei4esv'?

for Yes

Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	O Yes *O* No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was **performed did** the review **authors** use **appropriate methods for statistical combination** of **results'?**

RCTs

For Yes:

Thc authors justificd combining thc data in a mcta-analysis
AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
AND investigated the causes of any heterogeneily

O Yes
O No
O No meta-analysis conducted

For NRSI

For Ycs:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
AND fliey statistically combuied effect estimates frotn NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates *were* not available
AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

O Yes
No
O No meta-analysis conducted

12. If met:i-iiniilysis wits performed, **did** the revieu iiuthors :issess the **potential impact of RoB in individu:i1** studies on the results of the metre-iiniilysis or other evidence sj nthesis?

For Yes:

Oincluded only low risk of bias RCTs
OOR , if thc poolcd cstimatc was bascd on RCTs and/or NRSI at variablc RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect

O Yes
No
O No meta-analysis conductcd

13. Did the review **authors account for RoB in individual studies** when interpreting/ discussing the results of the

For Yes:

Ouicluded only low risk of bias RCTs
OOR , if RCTs with moderate or high RoB, or NRSI were included the review pro"ided a discussion of the likely impact of RoB on the results

O Yes
O No

14. **Did** the review **authors** pro"ide **a satisfactory explanation for, and discussion of, aHy** heterogeneity oliserx ed in the results of the rex iew'?

For Yes:

O There was no significant heterogeneity in the results
OOR heterogeneity was present the authors performed an investigation of Yes sources of any heterogeneity in the results and discussed the impact of the results of the review

if
O
thisO
No on

13. lf they performed **quantitative** synthesis **did** the review **authors** carry **out an adequate investigation of' pulilication** liias **(small study** liias) **and discuss** its likely **impact on** the **results o1'** the review'?

For Yes:

Opcrformcd graphical or statistical tcsts for publication bias and discussed the likelihood and magnitude of impact of publication bias

O Yes
O No
O No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

16. Did the re'âe" **authors report any potential** sources **of conflict of interest, including** any **funding** they received for conducting the	
For Yes:	
☐ The authors reported no competing interests OR	Yes
☐ Thc authors dcscribcd thcir funding sourccs and how thcy nagcdNo potential conflicts of interest	ma

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☒ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☒ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☒ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☒ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☒ OR *Explanation for* including both RCTs and NRSI

☒ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☒ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☒ searched the reference lists / bibliographies of included studies
- ☒ searched trial/study registries
- ☒ included/consulted content experts in the field
- ☒ where relevant, searched for grey literature
- ☒ conducted search within 24 months of completion of the review

☒ Yes
☐ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☒ Yes
☐ No

AMSTAR 2: a critical appraisal tool for systematic re i e w s that include randomised or non-randomised studies of healthcare inteo*entions, or both

11. II' meta-analysis was perlomed **did** the review **authors** use **appropriate methods for statistical combination of results'?**

RCTs

For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study rcsults and adjustcd for hctcrogcncity if prcscnt.
AND investigated the causes of any heterogeneity

Yes
O No
O No meta-analysis conducted

For NRSI

For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study results, adjustuig for heterogeneity if present
AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

O Yes
O No
O No mcta-analysis conductcd

12. If meta-analysis was tierformed, **did the** review **authors** assess **the potential impact of RoB in individual studies on the results of** the **meta-analysis** or other es'idence synthesis'?

For Yes:

included only low risk of bias RCTs
OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

O Yes
O No
O No meta-analysis conducted

13. Did the res'iew iiuthors iiccount **for RoB in individuiil studies** when interpreting/ discussing the results ct' the review'?

For Yes:

includcd only low risk of bias RCTs
OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

O Ycs
O No

14. Did the review iiuthors **provide a satisfactory** expliination for, iind **discussion of,** iiny hctcrogcncity observed in the results of the rciâcw"

For Yes:

Thcrc was no significant hctcrogcncity in thc results
OR if heterogeneity was present the authors performed an investigation of YcS sources of any heterogeneity in the results and discussed the impact of

the results of the review

O thisO No on

IN. If they performed **quantitative synthesis did** the review **authors carry out** an **adequate investigation of publication bias (small study bias) and discuss its likely impact** on **the results of** the review'?

For Yes:

performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

O Yes
O No
O No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results'?

RCTs

For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
AND investigated the causes of any heterogeneity

O Yes
No
O No meta-analysis conducted

For NRSI

For Yes:

The authors justified combining the data iii a tneta-analysis
AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

O Yes
O No
O No meta-analysis conducted

12. If meta-analysis was performed. did the renew authors assess the potential impact of RoB in indiiñduiil studies on the results of the mctii-aniilysis or othcr ciâdcncc synthcsis?

For Yes:

included only low risk of bias RCTs
O OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summttry estimates of effect.

Yes
O No
O No meta-analysis conducted

13. Did the review authors account for RoB in indiiñdual studies when interpreting/ discussing the results of thc rcvicu '?

For Yes:

O included only low risk of bias RCTs
OOR , if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

O Yes
O No

14. Did the renew :iuthors provide ii s:itisfactory explain:ition for, and discussion of, tiny heterogeneity observed in the results of the review'?

For Yes:

O There was no significant heterogeneity ui the results
OR if heterogeneity was present the authors performed an uivestigation of Yes sources of any heterogeneity in the results and discussed the impact of the results of the review

O thisO No on

IS. If they performed quantitative synthesis did the renew authors carry out an adequate invcstigation of publiciition bias (smiill study biiis) and discuss its likely impiict on the rcsults of the review*'

For Yes:

performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

Yes
O No
to meta-ana1ysis conducled

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non randomised studies of healthcare interventions, or both

16. Did the res4e" authtirs **report** any }uitentia1 sources tif **conflict uf interest, including any funding** they received for conducting the review"?

For Ycs:

- ☐ Thc authors rcportcd no compcting intcrcsts OR
- ☐ The authors described their funding sources and how they *manage* *dO* potential conflicts of interest

O Ycs

No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☑ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☑ review question(s)
- ☑ a search strategy
- ☑ inclusion/exclusion criteria
- ☑ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☑ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☑ OR *Explanation for* including both RCTs and NRSI

☑ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☑ searched at least 2 databases (relevant to research question)
- ☑ provided key word and/or search strategy
- ☑ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☑ searched the reference lists / bibliographies of included studies
- ☑ searched trial/study registries
- ☑ included/consulted content experts in the field
- ☑ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☑ Yes
☑ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☑ Yes
☐ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

6. Did the renew authors perform data extraction in duplicate?

For Yes, either ONE of the following

- O at lcast two reviewers achicvcd conscnsus on which data to cxtract from included studies
- O OR two reviewers cxtractcd data from a samplc of cligiblc studies and achieved good agreement (at least 50 percent), with the remainder extracted by *one* reviewer.

0 **Ycs**
D **to**

7. Did the review **authors provide a list of** excluded **studies and justify** the exclusions'?

For Partial Yes:

- O provided a list of all potentially relevant studies that were read in frill-text form but excluded from the review

For Yes, must also have:

- O Justified the exclusion from the review of each potentially relevant sfiidy

0 Yes
0 Partial Yes
No

8. Did the review **authors** describe the included studies in adequate detail?

For Partial Yes (ALL the fol1o "4ng):

- O described populations
- U described interventions
  described comparators
  Udescribed
  outcomes
- O described research designs

For Yes, should also have ALL the follou'ing:

- O described population in detail
- O described intervention
  Yes detail (including doses
- O described comparator in detail (including doses where relevant)
- O described study's setting
- O timcframc for follow-up

O Yes
inO Partial
whereO
No relevant)

9. Did thc rciâc'v **authors** use ii **satisfactory tcchniquc** for iisscssing **thc risk of** bins (RoB) in **indix idual** studies **that** svere **included in** the review'?

RCTs

For Partial Yes, must have assessed RoB

unconcealed allocation, *ancl* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-causc mortality)

For Yes, must also have assessed RoB

- O allocation sequence that was not truly random, *and*
  selection of the reported result frotn atnong multipleO
  Includes only measurements or analyses of aNRSI specified outcome

O Yes
Partial Yes
No

NRSI

For Partia1 Yes, must have assessed RoB.

from confounding, a"'f
from selection bias

For Yes, must also have assessed RoB:

- O methods used to ascertain exposures and outcomes, an'f Ycs
- O selection of the reported result from among multipleO
  Includes only measurements or analyses of a specified outcome

O Yes
O Partial
O No
RCTS

1t1. Did the review authors report on the sources of funding for the studies included in the review'?

For Ycs

Must have reported on the sources of funding for individual studies included ui the review. Note: Reportuig that the reviewers looked for this uiformation but it was not reported by study authors also qualifies

O Yes
O No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If mets-analysis was performed did the re'âew **authors use appropriate methods for statistical combination of'** results'?

RCTs

For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneitv if present.
AND investigated the causes of any lieterogeneif y

O Yes
O No
No meta-ana1ysis conducted

For NRSI

For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adi "sted effect estimates were not available
AND thcy rcportcd scparatc summary cstimatcs for RCTs and NRSI separately when both were included ui the review

O Yes
O No
O No meta-analysis conducted

12. If meta-analysis was pcrformcd, iliil **thc** review **authors** assess **thc potential impact of RoB** in **iudii4dual studies** on the results of the meta-analysis or other evidence synthesis'?

For Yes:

uicluded only low risk of bias RCTs
O OR, if the pooled estimate was based on RCTs and 'or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

Yes
O No
O No meta-analysis conducted

13. **Did** the review **authors account** for RoB **in individual studies** when interpreting/ discussing the results of the review'?

For Ycs:

included only low risk of bias RCTs
OOR , if RCTs with modcratc or high RoB, or NRSI were includcd thc review provided a discussion of the likely impact of RoB on the results

Yes
O No

14. **Did** the review authors provide a **satisfactory** explanation for, and discussion o1; any heterogeneity observed in the results of the re'4ew'?

For Yes:

O There was no significant heterogeneity in the results
O OR if heterogeneity was present the authors performed an investigation ofO sources of any heterogeneity in the results and discussed the impact of

thisNo

on thc rcsults of the rcvicw

Yes

lS. II' they tierlormed quantitative synthesis did the re"iew authors carry out an adequate investigation of publication **bias** (small **study bins) and discuss its** likely impact on the results of the review'?

For Yes:

O performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

O Yes
No
O No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare inter entions, or both

1fi. Did the review authors retiort any potential sources of conflict of interest, including any funding they received for conducting the re'âeu '?	
For Yes:	
Thc authors rcportcd no compcting intcrcsts OR	O
Ycs The authors described their funding sources and how they	*managed*
O potential conflicts of intcrcst	No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☒ Population
- ☒ Intervention
- ☒ Comparator group
- ☒ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☒ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☒ review question(s)
- ☒ a search strategy
- ☒ inclusion/exclusion criteria
- ☒ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☒ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☒ OR *Explanation for* including both RCTs and NRSI

☒ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☒ searched at least 2 databases (relevant to research question)
- ☒ provided key word and/or search strategy
- ☒ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☒ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☐ Yes
☒ No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised reviews
randomised studies of healthcare interventions, or both

6. Did the res'iesv authtirs perftirm data **extractiun in duplicate'?**

For Yes, either ONE of the fol1ow'ing:
- O at least two reviewers achieved consensus on which data to extract from included skidics
- O OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 50 percent), with the remainder extracted by one reviewer.

O Yes
O No

7. Did the re"ieiv **authors** pro'4de **a list of excluded studies and justify the exclusions'?**

For Partial Yes:
- O provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- O Justified the exclusion from the review of each potentially relevant study

0 Yes
0 Partial Yes
0 No

8. Did thc rcs'iciv **iiuthors dcscribc the included studics in adequate dctail?**

for Partial Yes (ALL the following).
- described populations
- U described interventions
- U described comparators
- Udescribed outcomes
- U described research designs

For Yes, should also have ALL fire following:
- O described population in detail
- O described uitervention Yes dctail (including doscs
- O described comparator in detail (including doses where relevant)
- described study's setting
- O timeframe for follow-up

O Yes
uiO Partial whcrcO No relevant)

9. Did the review authors use a **satisfactory** technique **for** assessing the **risk** of bias (RoB) in **individual studies** that were **included in the** renew'?

RCTs

For Partial Yes, must have assessed RoB
- unconcealed allocation, *rind* lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB
- allocation sequence that was not kuly random,

Partial Yes Oselection resultO from among multiple measurements or analyses of SI specified outcome

O Yes
ordO of the reported No Includes only aNR

NRSI

For Partial Yes, must have assessed RoB:
- frotn confoundhig, 'i'"?

For Yes, must also have assessed RoB:
- methods used to ascertaui exposures and outcomes,

Partial Yes from sclcction of the reported result from among multiple measurements or analyses of s specified outcome

O Yes
andO biasOselection No Includes only aRCT

10. Did the review authors report on the sources of funding **for** the studies included in the review'? For Yes

Must have reported on the sources of funduig for individual studies uicluded in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

O Ycs
D No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

11. If meta-analysis was performed did the re'âeu authors use appropriate methods for statistical combination of results?

RCTs
For Yes:

The authors justified cornbinuig the data ui a meta-analysis
AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
AND investigated the causes of any heterogeneity

O Yes
O No
O No meta-analysis conducted

For NRSI
For Yes:

The authors justified combining the data in a meta-analysis
AND they used an appropriate " eighted technique to combine study results, adjusting for heterogeneity if present
AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates "ere not available
AND they reported separate summary estimates for RCTs and NRSI separately when both were uicluded in the review

O Yes
O No
O No meta-analysis conductcd

12. If meta-analysis was **performed, did** the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis"?

For Yes:

Oincluded only low risk of bias RCTs
OR if the pooled estimate was based on RCTs and 'or NRSI at variable RoB, the authors performed analyses to uivestigate possible impact of RoB on summary estimates of effect.

O Yes
O No
O No meta-analysis conducted

15. Did the review anthems account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

included only low rislc of bias RCTs
OOR if RCTs with moderate or high RoB, or NRSI were included

Yes

the

No review provided a discussion of the likely impact of RoB on the results

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the rcsults of thc rcvicu "?

For Yes:

There was no significant heterogeneity in the results
OOR
heterogeneity was present the authors performed an investigation of
Yes sources of any heterogeneity in the results and discussed the impact of

if
O
thisO
No on

the results of the review

lS. If they performed quantitative synthesis did the review authors carry out an adequate investigation **of publication bias (small** study bias) and discuss its likely impact on the results of the review?

For Yes:

Opcrformcd graphical or statistical tcsts for publication bias and
discussed the likelihood and magnitude of impact of publication bias

O Yes
O No
O No mcta-analysis conducted

AMSTAR 2.' a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare inter entions, or both

16. **Did** the review authors report any **potential** sources of **conflict of** interest, **including any funding** they received for conducting the review'?

For Ycs:

- ☐ The authors reported no competing interests ORO
- ☐ Yes
- The authors described their funding sources and how they managed potential condicts of interest No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 7: Table extracting the data contained in the articles selected for the systematic review of the literature on the undesired effects of the CRISPR-Cas system on the genome of all plants for which applications have been documented.

Annex 7 is available on the Anses website.

https://www.anses.fr/fr/system/files/BIORISK2021SA0019Ra-Anx2-4-7.xlsx

Appendix 8: Research methodology for the systematic literature review on the health and environmental risks associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system

1. PICO STRUCTURE

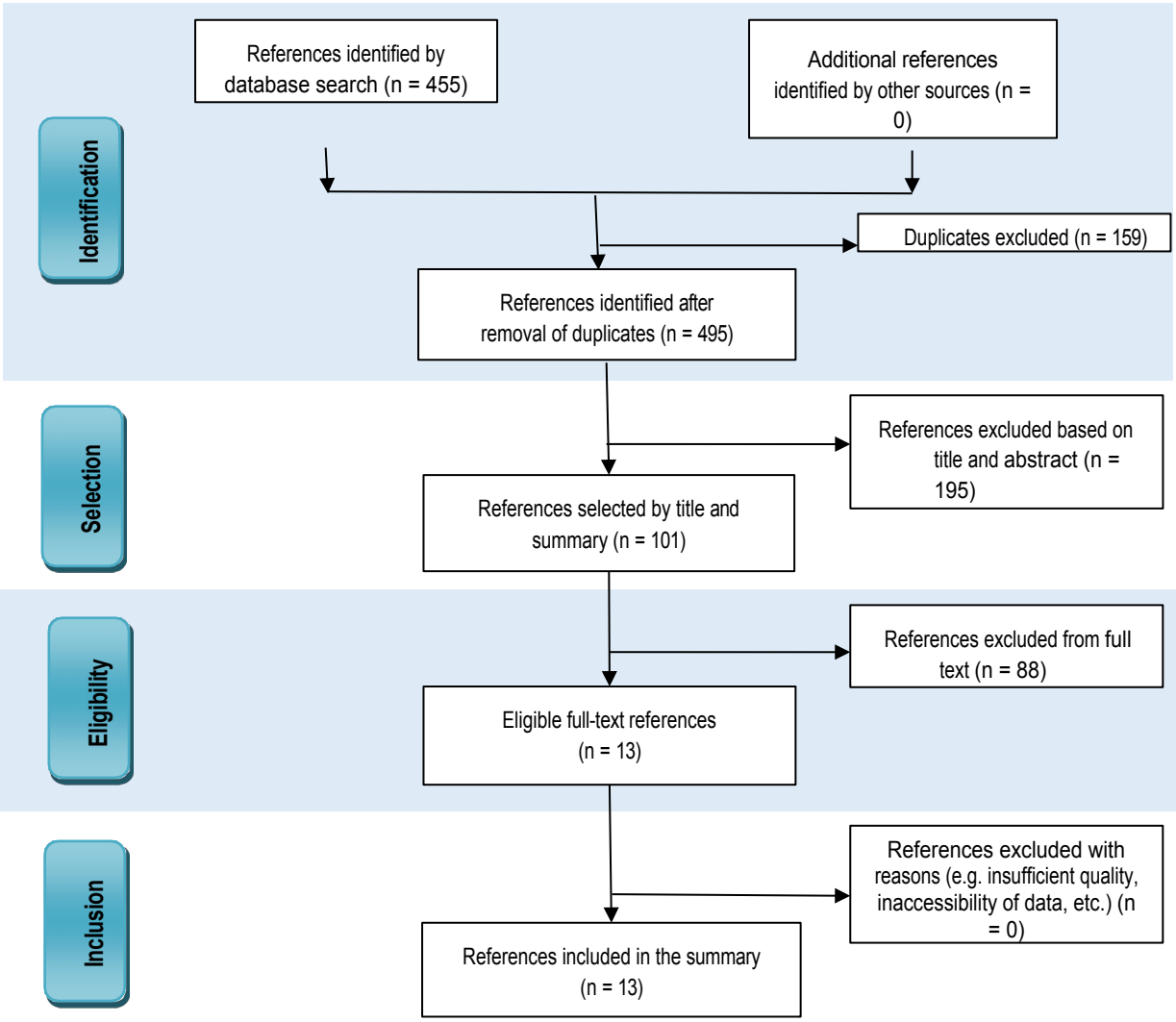
Themes	Keywords from thesaurus
Population (or subjects studied)	Plants
Targeted intervention (may refer to a technology, drug, intervention method or programme)	Site-directed mutagenesis using the CRISPR-Cas system
Comparator (reference scenario against which the exposed population is compared)	Plants not derived from site-directed mutagenesis using the CRISPR-Cas system
Outcome (result of interest, event measured, judgment criterion. Ex: mortality, health effects, psychosocial effects, perceptions, economic results)	Effects on health or the environment
Temporality (Research periods)	∞ - 01/06/2022

2. BIBLIOGRAPHIC SEARCH STRATEGY

Database	Date	Request	Number of references
Scopus	01/06/2023	(((plant OR plants OR crop OR crops OR tree OR trees) OR (rice OR "oryza sativa" OR tomato OR "Solanum lycopersicum" OR maize OR "zea mays" OR wheat OR "triticum aestivum" OR medick OR burclover OR medicago OR camelina OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "solanum tuberosum" OR cucumber OR "cucumis sativus") OR (arabidopsis OR nicotiana)) AND ((CRISPR) OR ("genome editing" OR "genome-editing" OR "genome edition" OR "gene editing" OR "gene-editing" OR "gene edition") OR ("site-directed mutagenesis" OR "directed mutagenesis") OR ("NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*")) AND ((risk OR risks) AND (environment* OR health OR sanitary))) Keywords searched for in titles, summaries and keywords Articles in English or French	198

PubMed	01/06/2023	(((plant OR plants OR crop OR crops OR tree OR trees) OR (rice OR "oryza sativa" OR tomato OR "Solanum lycopersicum" OR maize OR "zea mays" OR wheat OR "triticum aestivum" OR medick OR burclover OR medicago OR camelina OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "solanum tuberosum" OR cucumber OR "cucumis sativus") OR (arabidopsis OR nicotiana)) AND ((CRISPR) OR ("genome editing" OR "genome-editing" OR "genome edition" OR "gene editing" OR "gene-editing" OR "gene edition") OR ("site-directed mutagenesis" OR "directed mutagenesis") OR ("NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*")) AND ((risk OR risks) AND (environment* OR health OR sanitary))) Keywords searched in all fields Articles in English or French	152
CAB Abstracts	01/06/2023	(((plant OR plants OR crop OR crops OR tree OR trees) OR (rice OR "oryza sativa" OR tomato OR "Solanum lycopersicum" OR maize OR "zea mays" OR wheat OR "triticum aestivum" OR medick OR burclover OR medicago OR camelina OR soy OR soybean OR "glycine max" OR rapeseed OR canola OR colza OR "brassica napus" OR potato OR "solanum tuberosum" OR cucumber OR "cucumis sativus") OR (arabidopsis OR nicotiana)) AND ((CRISPR) OR ("genome editing" OR "genome-editing" OR "genome edition" OR "gene editing" OR "gene-editing" OR "gene edition") OR ("site-directed mutagenesis" OR "directed mutagenesis") OR ("NBT" OR "NGT" OR "new breeding techn*" OR "new genomic techn*")) AND ((risk OR risks) AND (environment* OR health OR sanitary))) Keywords searched in all fields Articles in English or French	105

3. FLOW CHART (PRISMA)



Appendix 9: Research methodology for the systematic literature review on the socio-economic issues associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system

1. PICO STRUCTURE

Themes	Keywords from thesaurus
Population/Subject: socio-economic issues associated with NGTs, in particular directed mutagenesis using CRISPR-Cas9 and techniques derived from it.	new genomic techniques, gene editing, targeted mutagenesis, genome editing, gene targeting, genome targeting, crispr
Intervention/field: plants	seeds, plants, agri-food, agriculture
Comparator: regulation of NGTs as OMGs Vs different regulation Vs current seed regulation	regulations, legislation
Outcome 1: NTG adoption dynamics and impacts upstream of value chains	market power, multinationals, seed production, intellectual property, patent, licence
Outcome 2: Trade, competition and international impact	safety security, sovereignty international trade, competitiveness
Outcome 3: Coexistence, segregation costs, contractual relations and market segmentation	traceability, control, detection, coexistence, value chain, productivity, cost-benefit, cost-effectiveness, savings, impact
Outcome 4: Consumers and NTGs	consumer, attitudes, acceptability, willingness to pay, perception, preference, behaviour
Outcome 5: Choice of regulation	regulation, market access, legislation, traceability, labelling
Outcome 6: NTG controversies	controversy, perception, opinion, acceptance, debate, conflict
Outcome 7: Governance of controversies and stakeholder positions	governance, politics, conflict management
Temporality (Research periods)	Not defined

2. BIBLIOGRAPHIC SEARCH STRATEGY

The bibliographic search queries will be based on 3 combined equations (see table below):

Equation 1 (EQ1): definition of the main subject

"NGT" OR "NBT" OR "new genomic techniques" OR "new breeding techniques" OR "gene edit" OR "gene-edit*" OR "targeted mutagenesis" OR "genome edit*" OR "gene targeting" OR "genome targeting" OR crispr OR crispr-cas9*

Equation 2 (EQ2): definition of scope *tree OR plant* OR*

*crop OR agri-food OR agricultur** Equation 3 (EQ3):

definition of desired results

a) *Outcome 1 : "market power" OR market OR "multinational companies" OR "farmer* rights" OR "farmer seeds" OR "property rights" OR patent* OR license*

b) *Outcome 2 : "food security" OR "food safety" OR sovereignty OR "competitiveness" OR productivity OR 'trade'.*

c) *Outcome 3: traceability OR detection OR coexistence OR "value chain" OR "supply chain" OR "cost benefit" OR "cost effectiveness OR economic*

d) *Outcome 4 : consumer AND (attitudes OR valuation OR accept* OR perception OR preference OR behavior OR willingness)*

e) *Outcome 5 : (regulation OR deregulation OR legislation) AND (label OR labelling OR traceability OR fraud)*

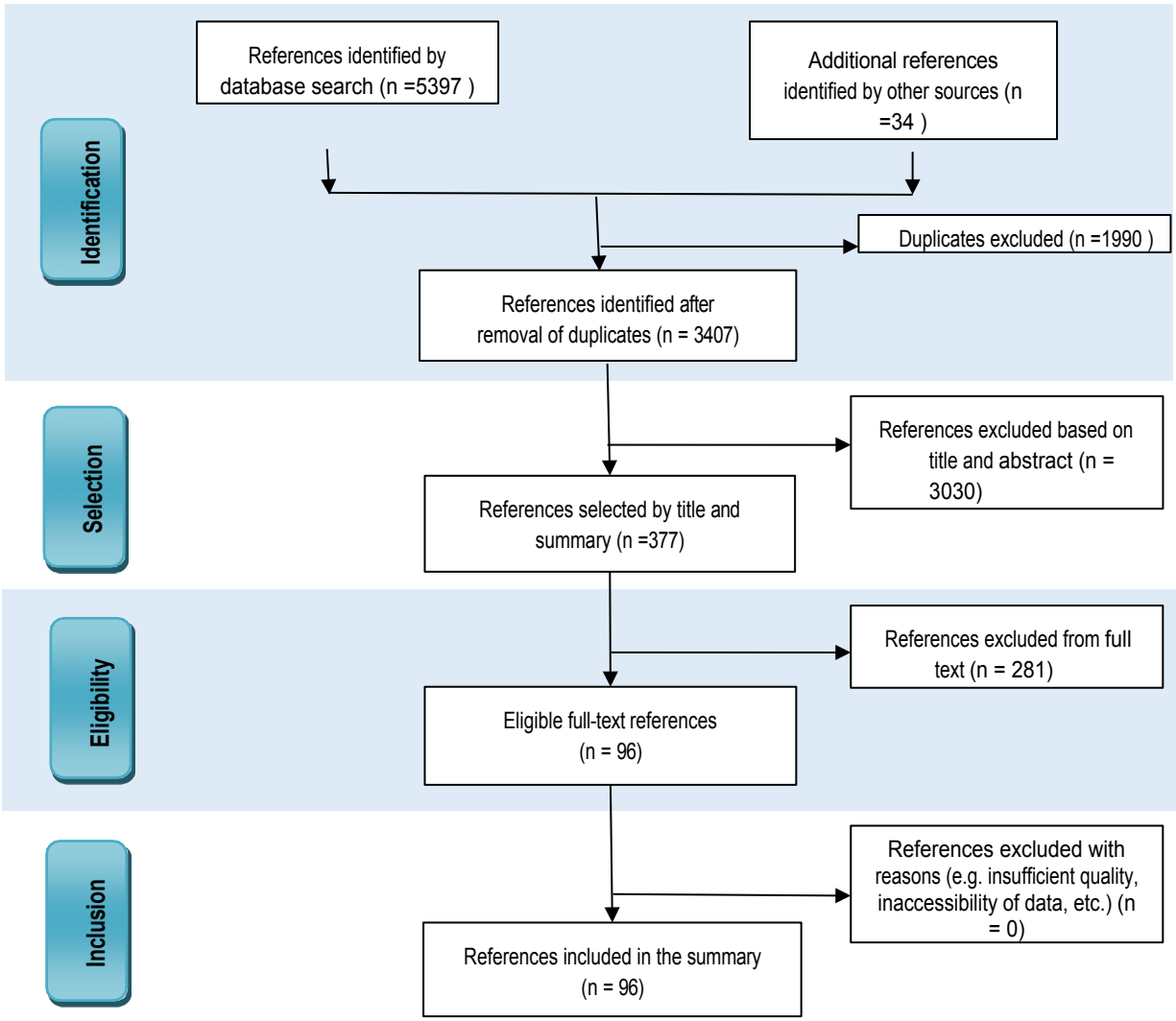
f) *Outcome 6 : (societal OR social OR public OR risk) AND (concern OR perception OR opinion OR accept* OR debate OR relevance OR conflict)*

g) *Outcome 7: governance OR "conflict management" OR "management of conflict" OR policy*

Database	Date	Request	Number of references
Scopus	20/10/2022	*EQ1 +EQ2+EQ3c*	1430
CAB ABSTRACTS	20/10/2022		899
Scopus	20/10/2022	*EQ1 +EQ2+EQ3a*	274
CAB ABSTRACTS	20/10/2022		215
Scopus	20/10/2022	*EQ1 +EQ2+EQ3b*	978
CAB ABSTRACTS	20/10/2022		684
Scopus	12/10/2022	*EQ1 +EQ2+EQ3d*	78
CAB ABSTRACTS	20/10/2022		84
Scopus	12/10/2022	*EQ1 +EQ2+EQ3e*	50

Database	Date	Request	Number of references
CAB ABSTRACTS	20/10/2022		17
Scopus	12/10/2022	*EQ1 +EQ2+EQ3f*	327
CAB ABSTRACTS	12/10/2022		203
Scopus	12/10/2022	*EQ1 +EQ2+EQ3g*	213
CAB ABSTRACTS			107

3. FLOW CHART (PRISMA)



Appendix 10: Questionnaires from the hearing on the supply of plants obtained using New Genomic Techniques (NGT) in relation to the legal aspects of intellectual property rights, patents and licensing

anses

Réflexion méthodologique sur l'évaluation des risques sanitaires et environnementaux liés à l'utilisation de plantes issues de mutagénèse dirigée ou de cisgénèse et enjeux socio-économiques associés

(Saisine n° 2021-SA-0019)

Audition de :

Stéphane Lemarié
Directeur de recherche INRAE, Laboratoire d'Economie Appliquée de Grenoble

Fabien Girard
Maître de conférences, droit privé - Université Grenoble Alpes, Centre de Recherches Juridiques

Date : 24 janvier 2022

Principales questions de l'audition

Cette audition est réalisée dans le cadre de la saisine de l'Anses « *Réflexion méthodologique sur l'évaluation des risques sanitaires et environnementaux liés à l'utilisation de plantes issues de mutagénèse dirigée ou de cisgénèse et enjeux socio-économiques associés* ». Sur les enjeux socio-économiques en particulier, la saisine demande le traitement des deux questions suivantes :

- Établir un descriptif de la filière ou des filières concernées par l'utilisation de plantes et produits issus des NBT (*new breeding techniques*) de l'amont vers l'aval de la chaîne de valeur, en particulier de la mutagénèse dirigée et de la cisgénèse.
- Sur cette base, documenter et analyser les enjeux socio-économiques associés, en premier lieu pour les entreprises et opérateurs économiques concernés, s'agissant notamment de la compétitivité et de la capacité d'innovation, et en second lieu et selon l'état des données disponibles, pour les consommateurs et les autorités de contrôle.

Un collectif d'experts (groupe de travail) a été constitué pour traiter cette saisine. En complément de ses propres recherches, le collectif a identifié un besoin particulier d'éclairage sur les enjeux socio-économiques liés à l'offre des plantes et produits issus des NBT. L'objectif de l'audition est donc d'appuyer le groupe de travail dans sa compréhension ces enjeux. A cette fin, ce document présente les questions que le groupe souhaite soumettre aux experts auditionnés. Des questions complémentaires pourront être posées pour précision et clarification lors de l'audition.

Question 1

Quels sont (et comment sont définis) les droits de propriété intellectuelle/industrielle et les modalités de brevetage autour des plantes et produits issus des NBT selon la réglementation en vigueur sur les OGM et sur les semences en général ?

1

What could be the legal and economic consequences/impficu öons for those involved in the Œièrœ concerned (seed/plant reproducibility, dependence on foiuziissenrs, efc.) of infe8ectoJe/industrial property rights as dè£inis ac hiellement for feathers and products derived from h&T?

What could be the impact of an OGkI regulatory framework specific to feathers derived from NRT on the research and development of plants and products derived from these techniques (in terms ofaction strategies, levers and brakes for innovation, etc.1 ?

As a mother of **law,** are the current European düertñ es on OGhW&T iæes coaiæe clear and precise, or, on the contrary, coanzie flones by the actors of t'u gricnlfure (agro-üidnstvie, researchers, public authorities...)?

Ozi could make the hypothesis that it is mainly taken actors who plnident for nn chung-eæenf concert nt £a régJemezitetion on your OGñf, namely to consider that the hTT deiveient not to enter within the framework of the direct m European coæme *?01clé I** ef 2018/û--0. Is this necessarily the case? Are we seeing anti'es players taking a stance in favour of a chung°eæenf?

Oses'bon 6

There have been debates and legal battles over seeds, with a great deal of tension between 'free' seeds and proprietary seeds. Does the debate on the rights of plants derived from .N8T. also concern the management of free licences and creative coœiæons? On, 1s question concern f mainly 'classic' rights and licences?

Question 7

Some obsern a their talk of 'ethical licences'-, when private players use bw ets on CRISPR techniques to prohibit certain practices, such as inteiGre the use of CRISPR to oiodify tobacco plantn **(e.g. Broad** Insfitofel. Is this a widespread problem?

Appendix 11: Hearing report on the supply of plants obtained using New Genomic Techniques (NGT) in relation to the legal aspects of intellectual property rights, patents and licensing

The hearing will be held on 24 January 2023 by videoconference. It was recorded to ensure that the minutes reflected the information provided by the experts. The experts are informed of the recording.

The following are connected by videoconference:

Experts interviewed:

- Fabien Girard: Senior Lecturer, Private Law - Grenoble Alpes University, Centre de Recherches Juridiques, junior member of the IUF
- Stéphane Lemarié: INRAE Research Director, Grenoble Applied Economics Laboratory

WG experts :

- Michel Gautier: Professor, Head of the food microbiology laboratory, Institut Agro Rennes-Angers, Rennes campus
- Valérie LE CORRE: Research Fellow, UMR1347 Agroécologie Dijon, INRAE
- Youenn LOHEAC: Lecturer and researcher, Rennes School of Business
- Morgan MEYER: CNRS Research Director in Sociology, NRS, CSI Centre for the Sociology of Innovation (CNRS-Ecole des Mines)
- Louis-Georges SOLER: Deputy Scientific Director, Food & Bioeconomy, INRAE
- Paul VASSEUR: Emeritus Professor of Toxicology, University of Lorraine

WG coordination :

- Youssef EL-OUADRHIRI: Head of Mission, Biotechnologies Mission (UMB), Anses
- Legrand SAINT-CYR: NBT WG Coordinator, Social Sciences, Economy and Society Department (DiSSES), Anses
- Karine FIORE: NBT WG Coordinator Social Sciences, Economy and Society Department (DiSSES), Anses

The experts at the hearings presented information on the NBT offer in response to the main questions put to them in advance of the hearings through the hearing questionnaire. These elements are organised around the following points.

I. Regulatory landscape for plants

As far as plants are concerned, there are two industrial property rights that apply in Europe:

a. Plant variety rights

The plant variety certificate (PVC) was created by the Paris Convention of 2 December 1961 (known as the UPOV Convention, the latest version of which dates from 9 March 1991).[144] incorporated into French law in 1970;
Regulation (EC) No 2100/94 of 27 July 1994[145] now makes it possible to obtain a varietal certificate valid throughout Europe.
In the European context, a plant variety can only be protected by a PVC (and not by a patent).[146]. This protection is based on a set of criteria that give the new plant variety its DUS characteristics (distinctness-homogeneity-stability).

Industrial property rights give the holder of a plant variety a monopoly on exploitation for a period of 25 to 30 years. Exclusive rights apply only to products, allowing breeders to reproduce processes to obtain other marketable varieties. Since the 1991 revision, the farmer's right to resow (farm-saved seed) has been an (optional) exception to the breeder's right. It is known as the "farmer's privilege" and is tightly controlled.
All breeders also benefit from the breeder's privilege, which allows them to use a protected variety as a source of variation. They do not need the consent of the breeder of the protected variety, either to develop their new variety or to market it. The consent of the breeder of the initial variety is only necessary if the production of the new variety requires the repeated use of the protected variety or if the new variety is an essentially derived variety (EDV) of the initial variety.[147]
In both cases, the breeder must negotiate a licence with the owner of the protected variety in order to exploit the new variety.

b. Patents

Patents are governed in Europe by the 1973 Munich Convention (European Patent Convention - revised in 2000). This framework has been adapted in the EU to the development of biotechnologies by Directive 98/44/EC.[148].

Only inventions that are new, involve an inventive step and are capable of industrial application are patentable. A patent confers a 20-year monopoly on exploitation and covers both manufacture and sale. However, a distinction must be made depending on whether the patent relates to a product or a process.

The farm-saved seed exception also exists for patents under Directive 98/44/EC. In some countries, such as France and Germany, there is an extended research exception that allows breeders to use biological material to develop other varieties without the agreement of the patent holder. However, a breeder cannot market varieties with patented elements without the prior agreement of the patentee.

[144] https://www.upov.int/edocs/pubdocs/fr/upov_pub_221.pdf
[145] https://cpvo.europa.eu/sites/default/files/documents/lex/394R2100/FR394R2100.pdf
[146] In the United States, a plant variety may be protected (including simultaneously) by a plant variety right and by a patent.
[147] See *below*.
[148] https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:31998L0044&from=EN

c. *The case of GMOs and NBT*

The deliberate release of GMOs/NBTs and their placing on the internal market in Europe is regulated by Directive 2001/18/EC of the European Parliament and of the Council.[149]. The scope of the directive covers a range of genetic mutation techniques, with the exception of certain exemptions such as mutagenesis and cell fusion, even though they are genetic modification techniques (Annex I B). The Ruling of 25 July 2018 (Confédération paysanne and others, C-528/16) of the Court of Justice of the European Union (CJEU)[150] however provided further clarification by restricting these exemptions to mutagenesis methods that appeared or were developed before the directive and for which safety has been proven. These exemptions therefore exclude directed mutagenesis techniques (genome editing) and random *in vitro* mutagenesis techniques that subject plant cells to chemical or physical mutagenic agents.[151]. For plants derived from these techniques and considered to be GMOs, there is an obligation to carry out a risk assessment, a specific authorisation and recommendations on labelling, traceability and post-market monitoring.

GMO/NBT regulations have no direct impact on the patentability of plants and products derived from these techniques. However, the supply of these plants and products may be indirectly affected by the regulatory situation. Changes in regulations can influence patenting decisions, depending on whether they are perceived as flexible or rigid by biotech companies.

II. Legal implications of patents on NBT

a. *Patentability of processes*

The analysis presented in this section focuses only on genome-editing techniques (Oligonucleotide-directed mutagenesis (ODM), Site-directed nucleases (SDN) - targeted mutagenesis) and in particular on the CRISPR-Cas technique, which is relatively cheaper than other techniques.[152]. According to the IPStudies database (2020), there are around 1,232 patent families relating to CRISPR techniques for plant improvement.[153]. A patent family is a set of patents that share the same technology and priority date. These patent families are mainly held by university research organisations. There has been a marked increase in patent applications relating to CRISPR-Cas9 techniques since 2014 (see Figure 1).

149 https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0007.02/DOC_1&format=PDF

150 https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:62016CA0528&qid=1675081531484&from=FR

151 A judgment of the Court in Case C-688/21 | Confédération paysanne and Others (Random in vitro mutagenesis) was published after the hearing on 03 February 2023. https://curia.europa.eu/jcms/upload/docs/application/pdf/2023- 02/cp230022en.pdf

152 Cécile Collonnier, Webinar: New breeding techniques & the challenges of their IP protection, , CPVO & European IP Helpdesk, 8 June 2021 : https://cpvo.europa.eu/en/news-and-events/webinars/webinar-new-breeding- techniques-challenges-their-ip-protection

153 https://www.ipstudies.ch/2020/10/2020-crispr-patent-landscape-where-do-we-stand/

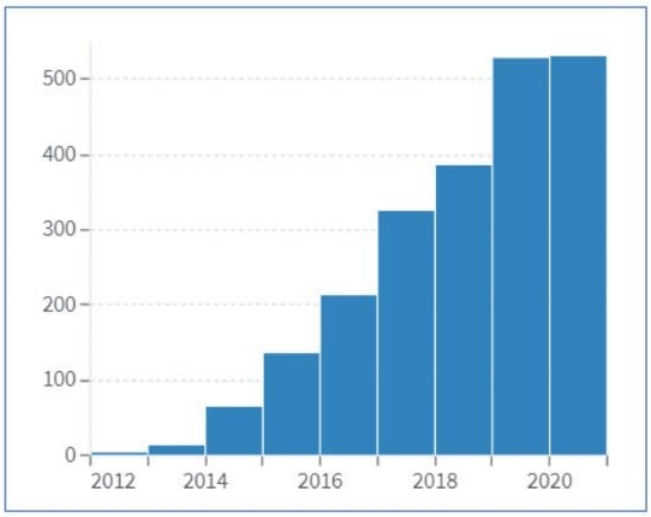


Figure A1: Number of patent applications (by year) relating to CRSIPR-Cas technologies of interest to plants. (from Kock, M.A.[154] (2021))

First and foremost, the patent protects the process itself. Any breeder wishing to use a process protected by a patent will have to negotiate a licence. It is important to note that, depending on the breeding objectives, several processes will be required. For example, the techniques needed to develop traits or plants using NBTs (e.g. techniques for the efficient generation of plants after editing; technologies for improving repair using HDR); ZFNs and Talens; and not forgetting the patents on the founding techniques (Crispr-cas9 for use in eukaryotes). Depending on the context, a single edition may sometimes require the negotiation of several licences. It should be noted that, given the ongoing litigation surrounding the founding techniques[155]It should be noted that, given the ongoing litigation surrounding the founding techniques, any licensing negotiations will have to take account of the uncertainty surrounding the ownership of intellectual property rights. They are likely to continue for several years and there may be differences depending on the patent system under consideration (e.g. EU or US).

A process patent normally also extends to the **product obtained** by the process. This is the case, for example, under the Agreement on a Unified Patent Jurisdiction 2013/C 175/01, Article 25 of which states that "A patent shall confer on its proprietor the right to prevent, in the absence of his consent, any third party: [...]

c) offer, place on the market, use or import or possess for these purposes a product obtained directly by a process which is the subject of the patent".

The scope of the rule varies from one legal system to another. This is an important question, since the scope of a process patent can extend to any product obtained by the said process. In this respect, the rules can be divided into three categories:

- in some cases, such as in the United Kingdom, the scope of the patent extends only to the
  "Directly obtained product", which means that it only covers the parental line, but not the seed, which is obtained after several generations of propagation.[156]

[154] Kock, M. A. (2021). Open Intellectual Property Models for Plant Innovations in the Context of New Breeding Technologies. *Agronomy*, *11*(6), 1218. https://doi.org/10.3390/agronomy11061218
[155] https://www.nature.com/articles/d41586-022-00629-y
[156] e.g., UK High Court of Justice, Monsanto Technology LLC v Cargill International SA (Case No: HC06C00585; decision of Oct. 10, 2007) HJ Pumfrey - no extension of the breeding process to descendants: "the phrase 'directly obtained by means of the process' means 'the immediate product of the process', (No. 35). Consequently, "all the RR soybean plants in Argentina... can be described as the ultimate product of the original

- in other cases, such as in the United States, the patent extends to any downstream product (35 USC 271(g)).
- Directive 98/44/EC takes an intermediate position. A claim to a method for producing biological material with "specific properties" as a result of the process extends to the offspring if it has the same properties (i.e. the properties must still be present).

A reasonable interpretation of this last rule is that, in the case of a patent extended to descendants, the properties determined must be clearly disclosed to avoid infringement in the use and exploitation of the NBT plant.

b. Product patentability

The European Patent Convention established by the EPO (European Patent Office) allows patents to be granted for products. However, in accordance with Article 53 of the Convention, the EPO has revised Rule 28(2) of the Implementing Regulations to specify that "*European patents shall not be granted for plants or animals obtained exclusively by means of an essentially biological process*", an exception that was already applied in certain countries such as France, Germany, Italy and the Netherlands through their respective national laws.[157]. As a result, the granting of a patent on a product that can be obtained by an essentially biological process requires the introduction of a "disclaimer", the purpose and effect of which is to limit the claim to products obtained solely by technical means. The situation is therefore different depending on the technique used to develop the plant (see Table 1).

Techniques	**Process (technical/essentially biological)**	**Product**	**Patentability (process) Art. 53(b)**	**Patentability (product) Art. 54**	Need for a disclaimer
Transgenesis	Technical process	Synthetic sequence	Yes	Yes	
Intragenesis	Technical process	Synthetic sequence	Yes	Yes	
Cisgenesis	**Technical process**	**Sequence "native**	**Yes**	**? (yes)**	**Yes**
SND3	Technical process	Synthetic sequence	Yes	Yes	

transformation of the parent plant. But I cannot see that it can be properly described as the direct product of that transformation, a phrase I would reserve for the original transformed plant. This aspect of the claim must fail. (No.37 of the ruling). https://www.casemine.com/judgement/uk/5a8ff75f60d03e7f57eabda1

[157] https://www.epo.org/law-practice/legal-texts/official-journal/2017/07/2017-07.pdf In Germany, Patentgesetz, PatG, section 2a (amended in 2013); in France CPI, art. 611-19, I 3° bis (amended by L. n° 2016-1087 of 8 August 2016 pour la reconquête de la biodiversité, de la nature et des paysages); in Italy, Codice della proprietà industriale, art. 81quater (1)e); in the Netherlands, Rijkswet van 15 december 1994, houdende regels met betrekking tot octrooien, art. 3(1)d).

SDN3	**Technical process**	**Sequence "native**	**Yes**	**? (yes)**	**Yes**
SDN2	Technical process	Desired mutation - non-native	Yes	Yes	
SND2	**Technical process**	**Desired native mutation**	**Yes**	**? (yes)**	**Yes**
ODM, SDN1	Technical process	Random mutation - not still identified "in the wild	Yes	Yes	Yes
ODM, SDN1	**Technical process**	**Random mutation - native**	**Yes**	**? (yes)**	**Yes**
Random mutagenesis	Technical process	Random mutation (not yet identified in nature)	Yes	Yes	Yes
Random mutagenesis	**Technical process**	**Random mutation (already identified in the nature)**	**Yes**	**? (yes)**	**Yes**

Table 1. Patentability of processes and products according to the genome-editing technique used (the question mark preceding certain entries expresses the legal uncertainty that characterises the patentability of certain products).[158]

III. Economic implications of patents on NBT

From an economic point of view, what is at stake for companies is the granting of licences. There are studies on the licences obtained for processes, but the analysis presented in this section refers only to patents for products. Given that very few NBT products are already on the market, the literature on GMOs is used here to analyse the NBT situation. However, the potential of NBTs to produce

[158] Adapted from Cécile Collonnier, Webinar: New breeding techniques & the challenges of their IP protection, , CPVO & European IP Helpdesk, 8 June 2021: https://cpvo.europa.eu/en/news-and-events/webinars/webinar-new-breeding-techniques-challenges-their-ip-protection

modified varieties more quickly than GMO technologies could have effects on the licensing process and therefore different economic implications.

a. Relationship between seed companies and patent holders

In the case of GMOs, business strategies are essentially based on the sharing of value between two companies that manage to market a variety combining existing characteristics (conventional seed) and a new characteristic (GMO seed) (see Figure 2).

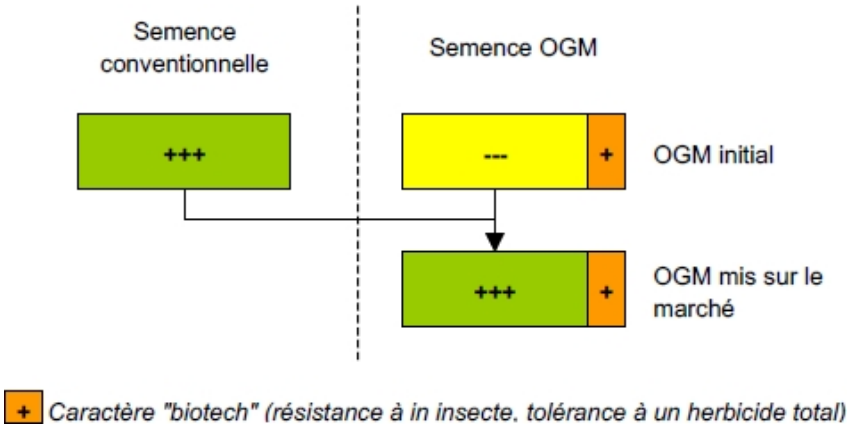


Figure A2. Illustration of the combination of a conventional variety and a GMO trait on the market

The strategy of companies with GMO production patents depends on the company's position in the market. A patent holder has less bargaining power if it is not present on the seed markets. As a result, the development of GMOs has led to seed companies being bought out by firms holding patents relating to GMO traits (vertical integration). If the company has its own seed production subsidiary, it can reserve the GMO for its own subsidiary only (foreclosure strategy). However, some companies may continue to sell licences to other companies (non-exclusive licensing strategy). This latter strategy has been used by certain biotech companies such as Monsanto (now Bayer), resulting in the widespread dissemination of these GMO traits. There has been an increase in the share of sales of GM seeds since their introduction in 1996. This trend has been accompanied by a sharp increase in concentration in the overall seeds market (see Figures 3 and 4). The level of market concentration varies, however, depending on the crop concerned and the country (see Figure 5).

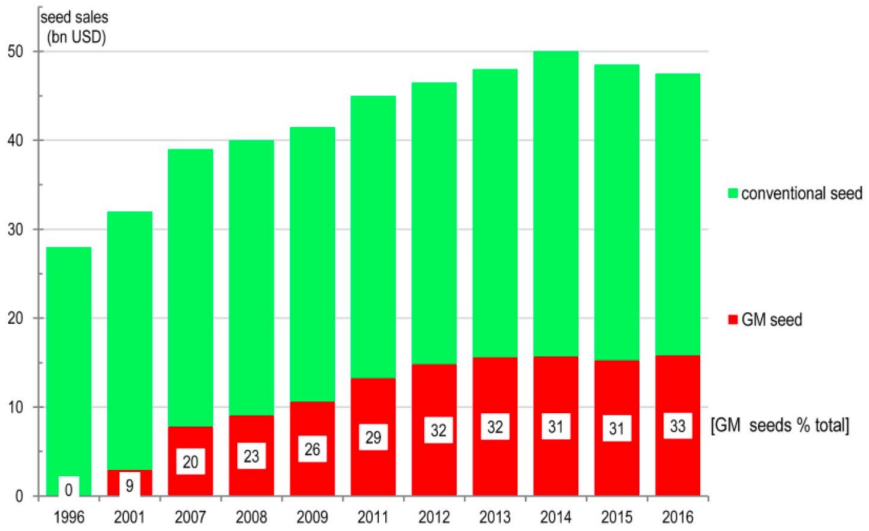


Figure A3. Trends in global seed industry sales and the breakdown between conventional and GMO seeds (taken from Bonny (2017)[159])

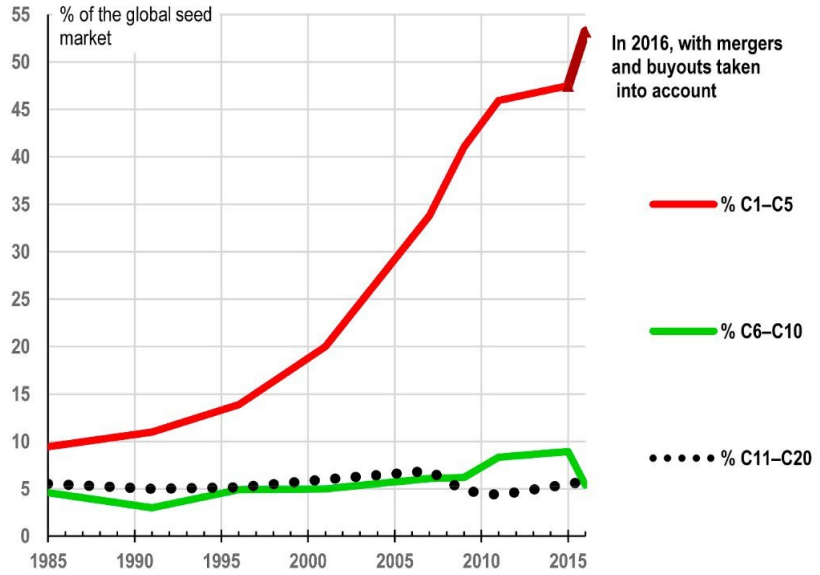
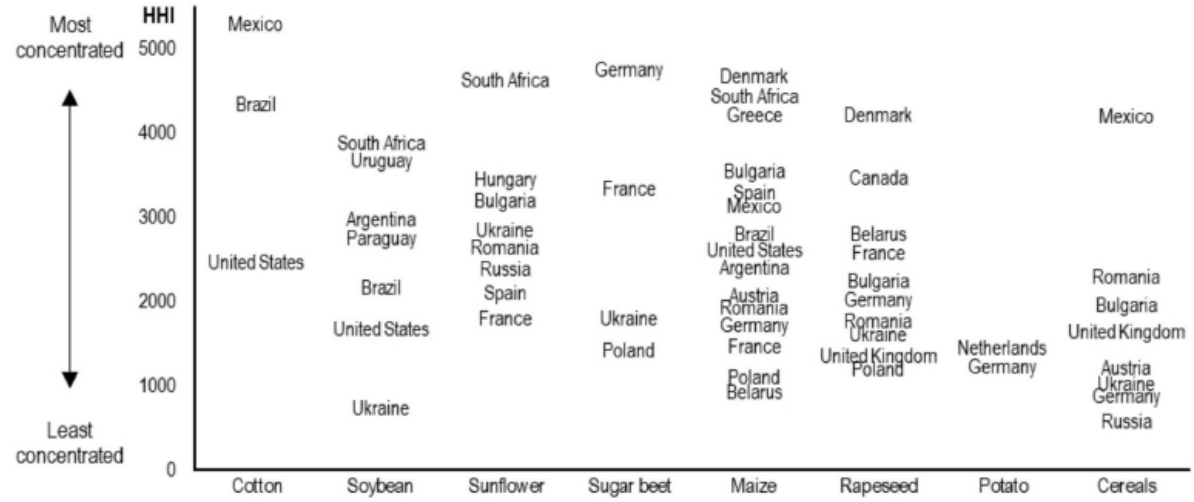


Figure A4. Concentration trends in the global seeds market (from Bonny (2017))

[159] Bonny, S. (2017). Corporate concentration and technological change in the global seed industry. *Sustainability*, *9*(9), 1632. https://doi.org/10.3390/su9091632



Note: HHI = sum of squared market shares (min = 0 / max=10000)

Figure A5. Seed market concentration by crop and country (from Deconinck (2019)[160])

b. Surveys of seed companies on NBT research efforts

In the literature, Jorasch (2020) [161] and Wesseler et al (2019)[162] present the results of two surveys of seed companies. The sample surveyed by Jorasch (2020) includes 62 seed companies that are members of Euroseeds or national seed associations. The survey covers companies of different sizes (53% small, 37% medium; 10% large).

The results of these surveys show that the proportion of these companies investing in NBTs differs according to size category (100% of large companies, 86% of medium-sized companies; 47% of small companies). Research efforts cover a wide range of plant species, regardless of company size (see Figure 6). There is also a very wide range of traits being worked on. However, it is important to qualify this point, as the same observation was made for GMOs in the early 2000s, when a very limited number of agronomic traits were ultimately disseminated. The market filter is therefore important. A large proportion of companies (67% of large companies, 4% of medium-sized companies and 36% of small companies) anticipate that NBT applications will be marketed in the next 10 years.

160Deconinck, K. (2019). New evidence on concentration in seed markets. *Global Food Security*, *23*, 135-138. https://doi.org/10.1016/j.gfs.2019.05.001

161 Jorasch, P. (2020). Potential, challenges, and threats for the application of new breeding techniques by the private plant breeding sector in the EU. *Frontiers in Plant Science*, *11*, 582011. https://doi.org/10.3389/fpls.2020.582011

162 Wesseler, J., Politiek, H., & Zilberman, D. (2019). The economics of regulating new plant breeding technologies- implications for the bioeconomy illustrated by a survey among Dutch plant breeders. *Frontiers in Plant Science*, *10*, 1597. https://doi.org/10.3389/fpls.2019.01597

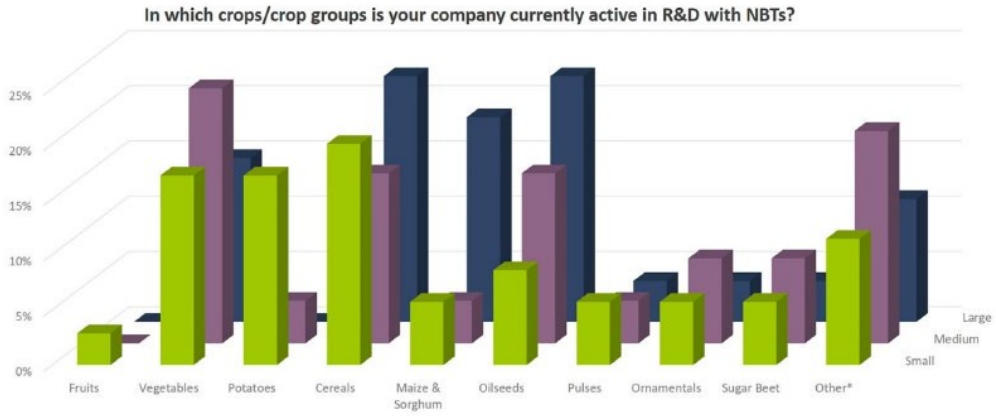


Figure A6. NBT research efforts by plant species (from Jorasch (2020))

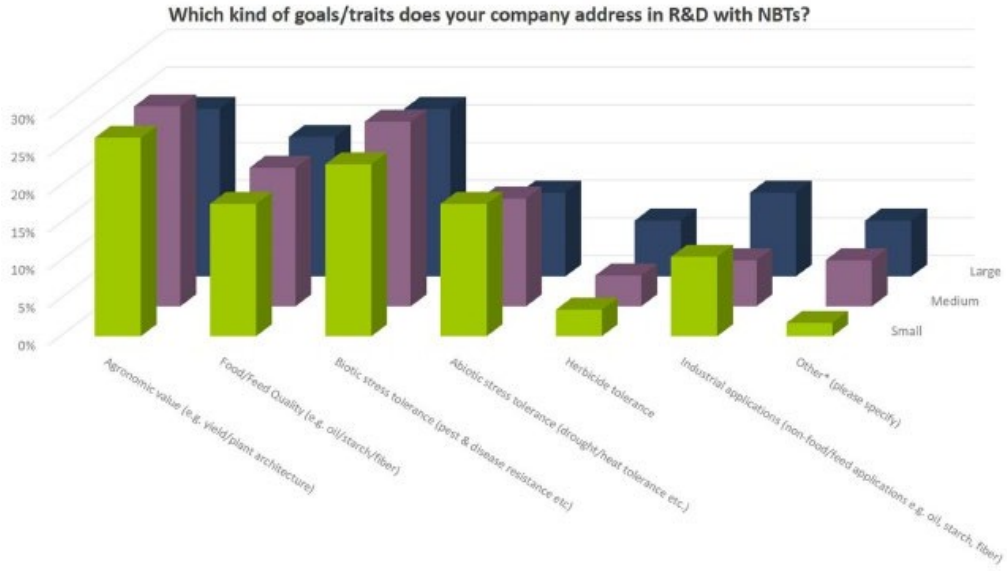


Figure A7. NBT research efforts by type of trait sought (from Jorasch (2020))

The survey results also show that issues related to NBT regulation (e.g. uncertainty and regulatory costs) are among the main factors that could influence investment in NBT. More specifically, the decision of the Court of Justice of the European Union (CJEU) on 25 July 2018 regarding NBT could impact companies' strategies. Indeed, a high percentage of companies (100% of large companies, 86% of medium companies, 68% of small companies) would choose to invest in NBTs if they were regulated like conventional seeds. What's more, large companies (100%) in particular admitted that they had changed their strategies to focus on products with outlets on markets outside the European Union following the CJEU ruling. Finally, companies anticipate a delay in the marketing of applications on an international scale as a result of the CJEU ruling.

Bullock et al (2021)[163] have shown that NBTs need a smaller market share to be profitable than GMOs (see Figure 8). In their estimates, this difference is linked to the fact that the R&D costs associated with NBTs are lower and the probability of success higher. Such an estimate might suggest that applications based on NBTs could be made on minor crops, unlike GMOs. These estimates have been made taking into account the North American regulatory context, which is less restrictive than the European context.

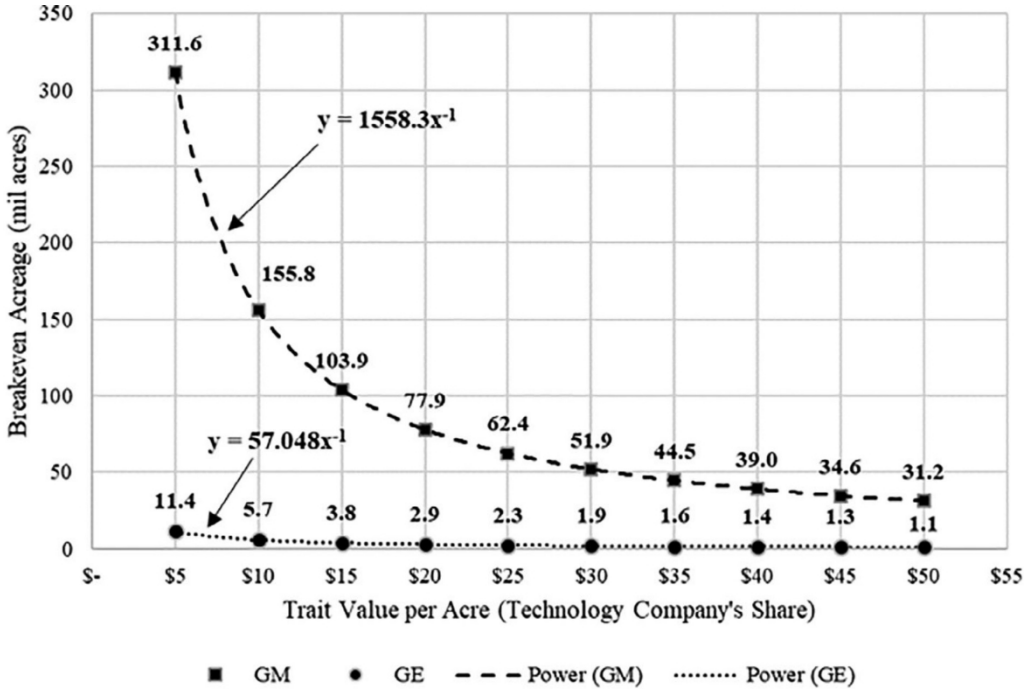


Figure A8. Estimate of the minimum market size to make a research effort on NBTs vs GMOs profitable (from Bullock et al. (2021))

IV. Essentially derived varieties (EDVs)

A VED is a variety that is clearly distinguishable from the initial variety except for the differences resulting from derivation[164]. It therefore conforms to the initial variety in the expression of the essential characteristics that result from the genotype or combination of genotypes of the initial variety. The VED can be protected but cannot be exploited without a licence granted by the breeder of the initial variety. In the case of NBTs, a potential difficulty lies in the fact that there is a high degree of **genetic conformity between** the VED and the initial variety, but **a clear distinction in the essential** (phenotypic) **characteristics** depending on the desired trait.

[163] Bullock, D. W., Wilson, W. W., & Neadeau, J. (2021). Gene editing versus genetic modification in the research and development of new crop traits: An economic comparison. *American Journal of Agricultural Economics*, *103*(5), 1700-1719. https://doi.org/10.1111/ajae.12201

[164] UPOV, EXPLANATORY NOTES ON ESSENTIALLY DERIVED VARIETIES ACCORDING TO THE ACT OF 1991 OF THE UPOV CONVENTION, Document adopted by the Council at its thirty-fourth extraordinary session on 6 April 2017, UPOV/EXN/EDV/2, 6 April 2017, https://www.upov.int/edocs/expndocs/fr/upov_exn_edv.pdf
UPOV, EXPLANATORY NOTES ON ESSENTIALLY DERIVATIVE VARIETIES UNDER THE 1991 ACT OF THE UPOV CONVENTION, DRAFT (Revision), 3 September 2021, UPOV/EXN/EDV/3 Draft 2, https://www.upov.int/edocs/mdocs/upov/fr/wg_edv_4/upov_exn_edv_3_draft_2_marked_version.pdf

The impact of the VED concept on plants obtained by NBT will depend on the interpretation given to VED (Girard and Noiville, 2014)[165] :

- The first approach, supported by the major NBT companies, is based on phenotype;
- The second approach, defended by breeders (small and medium-sized companies), is based on genotype.

From a legal point of view, it is difficult to decide, but we can consider that the
The term "essential characteristics" ("indispensable" or "fundamental" characteristics of an economic, agronomic or cultural nature) refers more to the phenotype.

However, in terms of jurisprudence (in practice), the genotypic approach is more generally used as it seems to be favoured by jurisprudence and international arbitration procedures. For example, in the ISF (International Seed Federation) guidelines, an analysis of genotypic components may be requested to justify the distinction between a VED and an initial variety.[166].

Taking these factors into account, the impact of the development of NBTs on the industry could be different depending on the regulations adopted for VEDs. In any case, NBT companies point out that a molecular approach would limit the use of the best germplasm in genome-editing selection programmes.

V. Types of patents for NBT: what solution(s) for the future?

A large number of patent applications have been filed for NBT traits in plants. At least 138 patent applications have been filed for biotechnologies developed using CRISPR-Cas (Kock, 2021). However, a limited number of varieties are covered by at least one patent (around 1.85% according to the catalogue of varieties authorised in Europe). The development of NBTs could therefore have an impact on the number of varieties covered by patents. Kock (2021) estimates that the number of patents on plant varieties could reach up to 30% in 2030, depending on the country, and more than 80% in 2040 in the United States, compared with almost 50% in Europe. Changes in the number of patents on plant varieties, particularly in Europe, will depend not only on changes in the regulatory landscape but also on a number of other factors, such as the acceptability of these technologies and certain technical obstacles to their development and adoption.

There is also a risk that the development of NBTs will speed up the pace of innovation and make it easier to stack up characteristics, which would contribute to the creation of "patent bushes" (see Figure 9). In this case, the development of a new variety from a patented variety would require the negotiation of several licences.

Several solutions have been proposed in the literature to regulate/framework the development of patents on NBT. These proposals range from certain forms of patent (patent pools, clearinghouses, licensing pledges, open source)[167] legislative reform of the system

[165] Girard, F. & Noiville, C. (2014). Industrial property and plant biotechnologies: the Nova Atlantis: A propos de la recommandation du Haut Conseil des Biotechnologies. International Review of Economic Law, XXVIII, 59-. 109. https://doi.org/10.3917/ride.281.0059 "

[166] https://worldseed.org/wp-content/uploads/2015/10/Guidelines_EDV_Ryegrass_Nov_2009.pdf

[167] See, among others, G. VAN OVERWALLE, *Gene patents and collaborative licensing models: patent pools, clearinghouses, open source models, and liability regimes*, Cambridge, Cambridge University Press, 2009 ; J. KLOPPENBURG, "Re-Purposing the Master's Tools: The Open Source Seed Initiative and the Struggle for Seed Sovereignty", *The Journal of Peasant Studies*, vol. 41, no. 6, 2 November 2014, pp. 1225-1246; C.H. LUBY, J.

with different possible options (abandonment of the patent, in-depth revision of patent law or adjustments). The interest in and use of these different types of patent (in the development phase) depend on the type of players/companies developing these technologies.

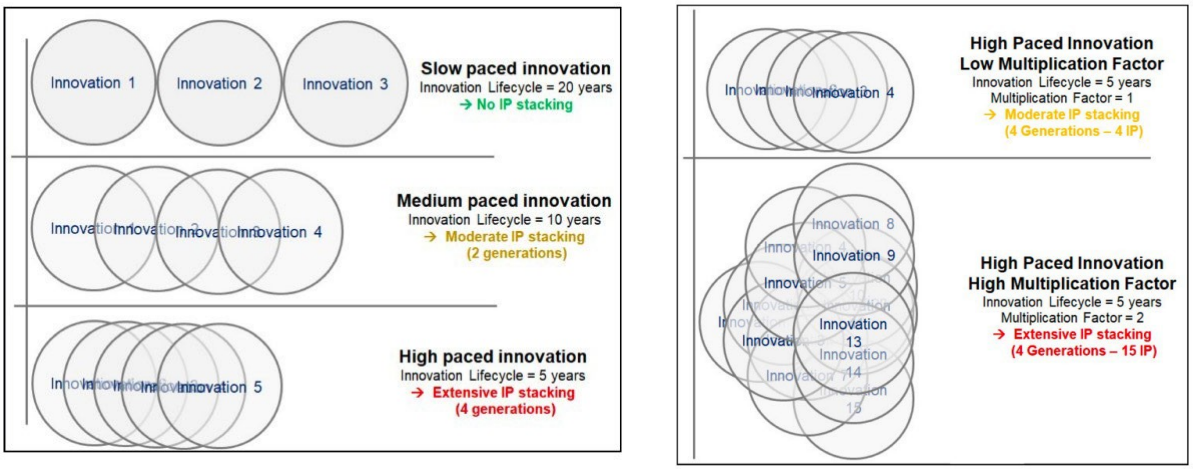


Figure A9. Innovation acceleration and "patent bushes" (from Kock et al. (2021))

Discussions

Foreclosure strategy :

L-G. Soler: *What are the trade-offs at company level when it comes to foreclosure strategy? Does the decision to foreclose depend on the company's characteristics (size, market positioning)?*

S. Lemarié : There are no studies in the literature to explain companies' strategies for opening up or not opening up the use of biotechnologies to other companies. However, taking into account the data available on the commercialisation of these technologies (in the case of GMOs), it is possible to identify the companies which use one or other strategy. The choice of strategy adopted would depend on the company's main objective or activity. The foreclosure strategy could be used in the case where the company's main activity is seed production. In this case, it would develop biotechnologies to increase its production range and market share. If the seed production activity is secondary, the company would be better advised to develop non-exclusive licences in order to profit primarily from the sale of the biotechnology.

Types of patents and patent holders:

L-G. Soler : *What is the effect on patenting procedures if the biotechnology is developed by public/university bodies?*

KLOPPENBURG, T.E. MICHAELS and I.L. GOLDMAN, "Enhancing Freedom to Operate for Plant Breeders and Farmers through Open Source Plant Breeding", *Crop Science*, vol. 55, no. 6, November 2015, pp. 2481-2488; J. KOTSCHI and
B. HORNEBURG, "The Open Source Seed Licence: A Novel Approach to Safeguarding Access to Plant Germplasm", *PLOS Biology*, vol. 16, no. 10, 23 October 2018, p. e3000023; M. MONTENEGRO DE WIT, "Beating the Bounds: How Does 'Open Source' Become a Seed Commons?", *The Journal of Peasant Studies*, vol. 46, no. 1, 2 January 2019, pp. 44-79; M.A. KOCK and F. TEN HAVE, "'The 'International Licensing Platform-Vegetables': A Prototype of a Patent Clearing House in the Life Science Industry", *Journal of Intellectual Property Law & Practice*, vol. 11, n° 7, July 2016, pp. 496-515 ; M.A. KOCK, " Open Intellectual Property Models for Plant Innovations in the Context of New Breeding Technologies ", *Agronomy*, vol. 11, n° 6, 15 June 2021, p. 1218.

F. Girard: When it comes to patent management, the university should behave like a company under the law (filing patents, managing patent portfolios, creating subsidiaries, etc.),
...). However, there may be more "ethical licensing" in universities than in the private sector. Some academic institutions (Wageningen University, Broad Institute) make their licences freely available to promote access by not-for-profit institutions, NGOs and developing countries.

L-G. Soler : *In the case of traits that would enable us to meet future challenges (adaptation to climate change, for example) for which there is no economic interest for producers or consumers, couldn't we imagine types of patent to encourage the development of these types of NBT that would be supported by research players?*

S. Lemarié: The problem that could arise with these types of NBT is the complexity of bringing them to market. It is therefore important to carry out a prospective analysis, taking into account the constraints on marketing (including problems of detection, traceability and acceptability) of the products resulting from these NBTs. It is also interesting to compare these technologies with possible alternatives that could respond to the same problem using different technologies.

Mr Meyer: *Is the "disclaimer" a legal innovation?*

The disclaimer is not a legal novelty. It is an old patent law mechanism proposed by the European Patent Office to force applicants to limit the scope of patents on characteristics that already exist in nature.

On patent bushes :

L-G. Soler: *Given that piling up patents can involve complications in the procedure for patenting and using these technologies, what incentive is there for companies to pile up patents?*

F. Girard & S. Lemarié: Genetic improvement is often defined as a process of stacking favourable genes (agronomic characteristics) within a single plant. The use of new technologies would therefore make it possible to obtain the desired characteristics in a shorter timeframe. Unlike the variety certificate, these characteristics will be patented, which may make stacking more complicated.

M. Meyer: *Can we expect NBTs to be democratised? Or could the same situation of concentration observed for GMOs be repeated for NBTs?*

F. Girard & S. Lemarié: Large companies have more resources (financial resources, legal expertise, etc.) to launch into the development of NBT. There have also been a lot of start-ups. Start-ups are likely to be taken over by multinationals because their financial resources are limited. What's more, the patent thickets could make the patented traits less valuable, because start-ups generally only hold a fragment of the technology in the case of NBTs.

Directives on intellectual property rights :

L. Saint-Cyr: *When it comes to intellectual property rights and patenting procedures, are the directives clear for the players involved?*

F. Girard: Understanding and using the laws on intellectual property and patenting is extremely complex. Companies use

usually legal specialists (law firms) to support them with appropriate tools[168]. In this sense, large companies have a strategic advantage when it comes to accessing patents. It should also be remembered that these companies (from the pharmaceutical and biochemical sectors) already have a patent culture, which gives them another advantage over medium-sized European seed companies/breeders. The latter prefer the plant variety certificate, which they are more familiar with, as well as the fact that it allows them to maintain access to germplasm, which they value.

On the positioning of players with regard to the regulation/deregulation of NBTs

Mr Meyer: *What is the position of civil society and NGOs on the regulation of NBTs?*

F. Girard & S. Lemarié: The positions of civil society and NGOs are fairly clear and the debates show that these players are rather against the development of NBTs, which they consider to be GMOs. However, the arguments have changed somewhat following the withdrawal of biotech companies from the European market (for lack of a request for deliberate release). The debate is now focusing on economic aspects, in particular the question of concentration in terms of its impact on innovation trajectories, seed availability, and so on. There are very few studies in France on the analysis of NBT controversies. However, we can refer to the work that has been done on GMOs.

Mr Meyer: *How should we interpret the fact that the debate is focusing on economic aspects? Does this impoverish or enrich the debate?*

F. Girard : The emergence of the economic theme to the detriment of the purely ethical aspects bears witness to the understanding of the issues at stake behind the development of these technologies. In this sense, the focus of the debate on economic aspects can be seen as an enrichment, with a better understanding of the impact of GMOs on breeding, innovation and agriculture.

P. Vasseur: *How will consumers be informed if NBTs are deregulated?*

F. Girard & S. Lemarié: The risk of not being able to identify and control plants and products derived from NBTs is one of the arguments put forward by those opposed to deregulation. However, unlike GMOs, which concern a limited number of desired traits and for which detection is possible, the situation seems more complex for NBTs, which concern more traits and for which detection seems more difficult.

[168] For example, information on the link between plant varieties and patents does not exist on any document. However, the link can be traced using databases such as PINTO (https://euroseeds.eu/pinto-patent- information-and-transparency-on-line/pinto-database/login). In general, legal monitoring requires the employment of several people on a full-time basis.

Appendix 12: Questionnaire from stakeholder hearings on the socio-economic issues associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system

RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

anses

Réflexion méthodologique sur l'évaluation des risques sanitaires et environnementaux liés à l'utilisation de plantes issues de mutagénèse dirigée ou de cisgénèse et enjeux socio-économiques associés

(Saisine n° 2021-SA-0019)

Audition de :

Date :

Principales questions de l'audition

Cette audition est réalisée dans le cadre de la saisine de l'Anses « *Réflexion méthodologique sur l'évaluation des risques sanitaires et environnementaux liés à l'utilisation de plantes issues de mutagénèse dirigée ou de cisgénèse et enjeux socio-économiques associés* ». Sur les enjeux socio-économiques en particulier, la saisine demande de :

- Établir un descriptif de la filière ou des filières concernées par l'utilisation de plantes et produits issus des NBT (*new breeding techniques*) de l'amont vers l'aval de la chaîne de valeur, en particulier de la mutagénèse dirigée et de la cisgénèse.
- Sur cette base, documenter et analyser les enjeux socio-économiques associés, en premier lieu pour les entreprises et opérateurs économiques concernés, s'agissant notamment de la compétitivité et de la capacité d'innovation, et en second lieu et selon l'état des données disponibles, pour les consommateurs et les autorités de contrôle.

Un collectif d'experts (groupe de travail) a été constitué pour traiter cette saisine. En complément de ses propres recherches, le collectif a identifié un besoin particulier d'éclairage sur les enjeux socio-économiques associés aux plantes et produits issus des NBT. L'objectif de l'audition est donc d'appuyer le groupe de travail dans sa compréhension de ces enjeux. A cette fin, ce document présente les questions que le groupe souhaite soumettre aux experts auditionnés. Des questions complémentaires pourront être posées pour précision et clarification lors de l'audition.

A. Questions générales (pour les diverses parties prenantes auditionnées)

- **Certaines publications soutiennent que les effets du développement des plantes et produits issus des NBT pourraient être différents en fonction de la réglementation (plus ou moins contraignante) qui pourrait être adoptée concernant ces technologies. *Quelles seraient selon vous les conséquences potentielles sur votre secteur d'activités de l'une ou l'autre situation réglementaire (dans le cas ses scénarios présentés par la DGPR dans le document en annexe) ?***

- **Certaines publications soulèvent la nécessité d'avoir des informations disponibles sur le développement et l'adoption des plantes et produits issus des NBT au niveau européen et mondial à travers des bases de données accessibles au grand public.**

1

issus des NBT ? Faut-il les intégrer dans les dispositifs actuels ?

- literature **scientifique** identifies the issue of detection and traceability as one of products from **NBT** the major rnissues. vint rœ ir relori un s fr
  système de traçabilité/d'étiquetage adapté pour les plantes et produits issus des NBT (en l'état actuel des connaissances) si ces plantes et produits obtiennent des autorisations de mise sur le marché ?

▪ *Les acteurs que vous représentez sont-ils suffisamment informés sur les bénéfices et les risques liés aux plantes et produits issus des NBT ?*

• Fn res uns i ne dQœ
cer *po mmm* d obrrnii
i act Uni ft' *iwei cpared* *short palindromic repeats ļ RfSPRI,, oligonucleotide-directed* ni urogro rrir *lODùI), Transcription activator-like effector nuclease (TALEN), Zinc-finger nuclease (ZFN)…) ? Si oui, envisagez-vous des conséquences économiques et*

▪ *Observez-vous des divergences sur ce sujet parmi les acteurs que vous représentez ? Si oui, quels sont les sujets débattus ?*

B. Çhses "bosses spécifîgztes Ï } i a t'tîe pzeaaate}

B.1. The qoætioss su "aafes s'adzesseot aos **seæeaciem**: Groztp+œeaf aaôoaaJ ùiteijirofessionnel des semences et plants (Semuel

– *Envisagez-vous de créer des variétés par mutagénèse dirigée ? Si oui,*

CRISPR-Cas9 ou de techniques dérivées de CRISPR-Cas9 ?

– *Prévoyez-vous de réaliser des essais au champ en France, dans l'Union européenne ou*

- Quelles iiifa' niafion s suivi-tzii s ëirposës * /oiiïnii, tous *i'one ñassiei 4s ñrninadr*

votre (vos) variété(s) issue(s) de mutagénèse dirigée ? Sous quelles conditions de confidentialité ?

– *Comment le développement des plantes et produits issus des NBT pourrait-il impacter la diversité des espèces et des variétés disponibles dans le catalogue officiel français ou*

-Ein!nir -van i qiir fri *plaiites ei pt 'amin* tie iii des .fiB F sei ritm r sus r ribfes dc rrno *iform* o In d1'nniiiiqiie dii serteu i des senienres * *Sî* cii i, coninieni *

B.2. des quesöons suivant s'adrmsent aux nodJcats agricoles : Fédération nationale de ymdicats d'exploilunts agtfioles (FNSEA) rt Confédération pujuanne

- ***Comment les plantes et produits issus des NBT sont-ils perçus par les agriculteurs***

- ***Le développement des plantes et produits issus des NBT présente-t-il un enjeu particulier pour la réutilisation des semences (« privilège de l'agriculteur ») par rapport aux méthodes conventionnelles ?***

- ***Question pour la Confédération Paysanne : Vous critiquez régulièrement le terme NBT***

- ***Question pour la Confédération Paysanne : Selon votre article (https://www.confederationpaysanne.fr/sites/1/mots_cles/documents/Livret_OGM_V3_web.pdf), les petites et moyennes entreprises (PME) qui développent des plantes et produits issus des NBT risquent à terme de disparaître et/ou être absorbées par les multinationales***

B..3. The following suggestions are addressed to those involved in organic farming: Fédération Nationale d'.Ç-ricaltore Biologique {FN. fil

- ***Le développement des cultures de plantes issues de NBT est-il compatible avec le cahier***

B.4 Quesöons spécifiques aux acteurs de lu disnUution : Fèdêra öon du Commerce et de **Distribution (FCD)**

- ***Souhaitez-vous un système de surveillance/contrôle des lots produits issus de NBT provenant des fournisseurs non européens ?***

- ***Les produits issus des NBT présenteraient-ils un intérêt particulier pour le secteur/les*** nrrru i s de fr diam button?

B.n. Outgoing questions are addressed to players in the lrensformnäoo/agro-industry .lssoeiztion neäonete des industries alimentaires.)and SjudJcat des entreprises bio agroalimentaires (Sjmbio)

- What could be the *impact* of *the* &hufo j'eniraf fss pfnnfzs *erprodiiits* issus '-BT sur ***la transformation et la conservation des aliments ?***

B.6. Les quesôoaz ~~zw aates~~ s*aéresseat aax assoc-îatîoas 4e üéfease des coasoœatears : **Conseil** National des .Associations FaudliaJes Laïques (CN.YE.ML)

– ***Existe-t-il une demande des consommateurs pour certaines caractéristiques ou propriétés des plantes et produits pouvant être obtenus par les NBT ?***

- Some ui-iæii s ni+rttrnf rn aiunf fa kristen et tu i'epfdiÑ der prorersus dr la G$D, *prodiictiNtê gains,* fss cui arJistïques *rendering* fus rœsoniniatæiis rr fr *durabdn-é Jean,* sii-lirress", riim nt, rè furñoii les *ioh nts...),* rfr. Qrisprnsrr-vous *

– ***A en juger des articles que vous avez publié sur votre site internet, vous utilisez surtout le terme NBT, mais pas celui d'édition génomique ou génétique ou CRISPR. Pourquoi ce***

B.7. Qnesäozis specific to associations for the protection of ezrriro zie -ut ~~. France~~ **Nature** Environnement {FNE)

– ***Quels sont les enjeux du développement des NBT concernant la protection de***

– ***Certains acteurs mettent en avant la précision et la rapidité des processus de recherche et développement (R&D), des gains de productivité, des caractéristiques répondant à des demandes des consommateurs et de durabilité (eau, sécheresse, climat, réduction des intrants…), etc. Que pensez-vous ?***

– ***Quelle devrait être la place des ONGs dans la gouvernance des risques liés aux NBT ?***

– ***Certaines ONGs estiment que le débat autour des NBT est trop centré sur la technologie et le risque, et qu'il ne prend pas assez en compte les aspects sociaux, politiques, écologiques, éthiques etc. Partagez-vous cet avis ?***

4

Annex: Possible solutions to the megleinentation r oiicernaiit 'la utes and n'oiliiits from NBTs (soørre: prese mation tie la DGPR)

Part 1: Risk assessment and management,

Scénario pour 2030-2035	Risk assessment	Détection
:0 : Pòliiieu Ü rćgle ieixă "dön. inchangées	Ćo "mrn era ujou "rá,k\"u'i e "yaluaÌžon des risques selon les exigences actuelles de la législation sur les 9C-M	Comme aujourd'hui : détection requise avec différenciation du produit conventionnel
AI : Autori3ation av'c Üoluoãon p ouonÏlioHnclÏc des ri soue' ot eaigen'ec en matière .ïe mü·iur <— cle d*teçtion adapter	I?rupou.ionńe a "u croft de r üuc or prosuit is su.d e CGI	'wlćth sde de detectic n re qtJis ' Lais la d enciation du "proãü c iäsu c NGT n u era 1u r Con'a' nticnr gi n'tst [illegible] nossible
A2: "Âe-nütificaôon of products q uź p-cuvont ńgolnnen "Ł:et "re ·oăLenuc naturalm ęn -.ou per el'ection 'onveńtzónnelle	.Num n éœs£aiie si le 'pro duit issu dč NGO peut úe˚element "źtre. obrenu naMr+ II+menu ou par' s "élection œnvenüon relle	Not necessary if the product from 'N GT put ègaJčme nt et "re ôôŕ¢ n u --naturellerrient- or *by's é e c t Ì a r i* .conventionnëlle .

Assessment by EFSA

Checked by I!EF3A

Section 2 - Traceability and labelling

Slario for J03U -JO4S	Étžguet&ge efligences C ïÌi es.euk UGfihi	"'"-* ' '*"*-' *;;*, -**"Ìi***ì** *"
0 : Politique et réglementation inchangées	Comme aujourd'hui : l'étiquetage en tant qu'OGM est toujours requis	Comme aujourd'hui : la traçabilité de l'OGM est toujours exigée
B1 i Efiquccte de dun bilitc supglêmenca're	Cornme euro'u d Łui. ma ir sre c la Isozśhi litń d'ur iat-cl suaplcmertzi"< œur es a:IL-.'srior* a e ¢iumb' i:i , ïa sanr rż "i-c nc,e the i:ni rISu hon à ü n:i an.'iié n u ra c inrro3\i'	cc z'me aujcw rö'n ui, mars ax'ec a traçabilité supolémentaire pour les of.ú cn čc durability
"Bż! Pač ó'éüquątâge SiDurable"	dâ nS "i·è.reğistre""p "+iüi"c o "1+"ccociuÌT Ì "s "Su "óe "N "GW	c mé auisucò""h "ú r
eJ. - Ps s rl' éciqu'etage et be ,rsçan IIIté ü u°° î rcrluir p˚-u1 *snl<n ont Um obtcńu nature llc-ń cnt or poč sck-ction "conventional	uon néces aire sl le pro duitr su c e uû1 eut 4eel en *n1 ie.r< bÛn'i nnt"rc'ic *n i ou ver sócctÌcn con nntùnncll c scul cm cnt l'inc.usicn ğans le red iÏre ouhJic	Non ú" n e ,ł +- oiod ulr issus d e u roT a cml ć-eolr "mñnl în.re uktcnu noturcličmcn- ou *päi scienticri* cońven-ior ne'l e

Part 3: Taking sustainability criteria into account

-"-.""-.-.. gonr ü"" """	Autorisation
0: P.'oJ itiqLrc. ¢t rcglerncritation inr.ãaneées	Co mmc -cu iou rdoday: .z"-cxio< i.m-.'dč:durabilitż/inc1tafiòn to i!autorisaiÌon""
: Incitations au développement durable pour l'autorisation	I ncitations lêm en "aire ú paüťwes, fi'our l',utcrisation - Le ú pm "d.'i "s véeéraux in+-"die NG7 W "i les raître ¢ont uent aU- oD "jecïir5 cl+ uu!"a uiiiié Dčriéncieni d'inüiacioi\ s rčgie'\\enLaï e, iodtive s pa *ur* l'au ztrîsaticn. Ex :"'conaeiïr reg "eÏenŁaires et ieMücuesaan:ćpenJan.apœ'miœdagpoodion; me:use, †:ačtàMcilit*rleçroœ:zu:oäucon:atón-.foan:iere: ou adminsu-ciives)
C2 : Exigence de durabilite : pas rl'aiicnńsarim Ih'ń.i!i"I*'le å la .uu'anlilć	ten prodni's ucğitavx prú:ań'an"dt c "c¥ra<ttres oiúiuJkiabi n a- ob<cJs ar "durth "i˚- ne sum eas avtcri't'-

Que III vúMfi cation des critÈres **da durabilitú ?**

PILisieurS optianú >emÙlent etre sur la ta6le: au .niveau national (autoritó> compôtentos) ou au nivea i européen Eh5A)

Appendix 13: Verbatim report from stakeholder hearings on the socio-economic issues associated with plants derived from site-directed mutagenesis using the CRISPR-Cas system

Annex 13 is available on the Anses website.

https://www.anses.fr/fr/system/files/BIORISK2021SA0019Ra-Anx-13.pdf

Appendix 14: History of transgenic plants on the market: results of existing meta-analyses

I. Economic impact of GMOs on producers

Box 4: Production and marketing of transgenic plants

Crops based on GMO seeds began to be marketed around twenty years ago. Since then, they have become increasingly important, and are expected to grow at an annual rate of 9.4% worldwide over the period 2022-2030 (Marone et al. 2023). They will cover 190 million ha in 2022 (compared with 1.7 million ha in 1996), spread across 29 countries, 24 of them developing and 5 industrialised. The main producing countries are the United States, Brazil, Argentina, Canada and India. In Europe, GM crops are underdeveloped, and are mainly grown in Spain and Portugal.

The vast majority of GM crops are grown on four crops: soya, maize, cotton and oilseed rape, most of which is used for animal feed or industrial purposes. The largest number of approved GM traits is in maize, followed by cotton, potato, soya and oilseed rape. The main traits are herbicide tolerance and insect resistance.

An abundance of literature has been published on the economic impact of GMOs since their launch on the seed market. The available meta-analyses and reviews focus mainly on the economic impacts at the level of agricultural production, often considering certain crops or specific traits, and attempt to identify general results regarding the effects on yields, seed costs, quantities and costs of pesticides used, and producers' earnings. Carpenter (2010) evaluates 168 studies on the yield performance of GM seeds and notes yield increases in 124 studies, no effects in 32 studies and yield decreases in 13 studies. Carpenter (2013) summarises around twenty economic studies published in the late 1990s and early 2000s. The author draws out the following ideas: producers who adopt GMO crops have higher earnings; small producers in developing countries benefit from GMO technology in terms of income; in terms of labour, the results are more ambiguous, with some studies showing an increase in labour requirements, while others point to a reduction.

Klümper and Qaim (2014) focus on GM soya, examining the results of 147 studies worldwide. From these, it emerges that the use of GM seeds leads to a reduction in pesticide use (-37%), an increase in yields (22%) and gains for producers. Yield gains and pesticide reductions are higher for crops with insect resistance than for those with herbicide tolerance. They are also higher in developing countries than in developed countries. The meta-analysis by Pellegrino et al (2018) looks at the agronomic and toxicological impacts of GM maize. The authors highlight yield gains (5 to 25%) and a reduction in contamination levels (e.g. -28% in mycotoxins). Finger et al (2011) applied a statistical treatment to 721 studies from 203 publications to assess the effects of GMOs on producers' costs and profits. Essentially, they note an increase in yields, a reduction in the quantities and expenditure on pesticides used, and an increase in expenditure on seeds, due to the higher prices of GMO seeds compared with non-GMO seeds. Overall, the effects of higher yields and lower pesticide use outweighed the increase in seed costs, resulting in improved economic performance for seed-using producers.

GMO. However, the authors note a high degree of variability between countries and production regions, due to the heterogeneity of pathogen pressures and cultivation practices. Areal et al (2012) propose a meta-analysis of the agronomic and economic impacts of GMOs, focusing on the two main characteristics of GM crops (herbicide tolerance (HT) and insect resistance (Bt)) and three of the main GM crops produced worldwide (Bt cotton, HT soya and Bt maize). The analysis covers developing and developed countries, six world regions and all countries combined. The results of the statistical analyses indicate that genetically modified crops outperform their conventional equivalents in agronomic and economic (gross margin) terms. In terms of countries' level of development, GM crops tend to perform better in developing countries than in developed countries, with Bt cotton being the most profitable crop.

Overall, the results of the reviews and meta-analyses tend to point to positive effects for producers who have adopted GMOs worldwide, thanks to the impact on yields and the reduction in certain expenditure items (pesticides), despite an increase in the cost of GMO seeds. **However, these studies should be viewed with caution, both because of certain methodological limitations (most of the meta-analyses published do not follow the procedures recommended today, particularly in terms of transparency in the selection of articles retained; the studies summarised are generally based on very heterogeneous approaches and data, etc.), and because most of these studies are based on data collected in the early 2000s, and therefore do not allow us to know whether these conclusions will be confirmed in the long term.** In particular, certain results concerning glyphosate resistance induced by GMOs tolerant to this herbicide are now well established, including in the United States (Livingston et al. 2016, Mortensen and Smith, 2020, Van Deynze et al. 2021). This tends to increase the use of herbicides, thereby reducing producers' profits, as shown by reports from Anses[169].

In addition, certain issues remain relatively undocumented, in particular the social dimensions. In this respect, the review by Fischer et al (2015) stresses the variability of economic impacts depending on the type of producer, the political and regulatory context, and the existence or absence of institutional support (advice, access to credit, public support, etc.). The authors also note the ambiguities in the results of available studies on work and activities on small farms, the small number of studies looking at gender-related effects (women's work) and the lack of studies on agriculture in northern countries. This critical view of the available literature also emerges from the systematic review by Catagora-Vargas et al. (2017) based on 410 publications. The main findings are as follows: the majority of published research focuses on a narrow set of monetary economic parameters; there are very few empirical studies on social and non-monetary aspects; varying local contexts and conditions are generally ignored in the methodology; conventional agriculture is the commonly used comparator, with minimal consideration of other substantially different farming systems. These findings highlight the lack of comprehensive empirical research on the socio-economic impacts of GM crops for developing countries.

[169] See the report of anses on the varieties made tolerant to herbicides. https://www.anses.fr/fr/system/files/UPO2015SA0063Ra.pdf

It should also be noted that the available studies tend to focus on microeconomic effects, but few of them provide an overview of the consequences for the dynamics of agriculture. For example, it is likely that GMOs (along with seed coatings) have contributed to two movements in the agricultural sector in the United States: the concentration of land in very large arable farms and the maintenance of a large number of small farms managed on a part-time basis (Hurley 2016). Insect resistance eliminates treatments. Crop tolerance to glyphosate makes it possible to exploit, at least in the medium term, the extraordinary effectiveness of this herbicide to switch to semi-direct. As a result, a lot of work can be saved, enabling farms to be expanded or to work only part-time.

II. Concentration, pricing and value sharing

The biotechnology and seed industry has undergone significant concentration over the last 20/30 years. This trend, which coincides with the development of GMOs, can be seen at different levels. Worldwide, 4 companies controlled 21% of the seeds market in 1994, 32% in 2000 and 54% in 2009. In 2008, 3 companies held 85% of GMO maize patents, and 70% of GMO patents excluding maize. The economic impact of this concentration has been studied in a number of publications. To our knowledge, there are no rigorous meta-analyses, but some studies have attempted to summarise the available results.

A first general result concerns the price of GMO seeds, which is consistently assessed as being higher than that of non-GMO seeds (Shi et al. 2009). This higher price can be explained primarily by the R&D investment made by the biotechnology and GMO seed industries. This higher price also reflects the fact that part of the value derived by the producer from the use of a GMO seed (compared with a conventional seed) is passed on to the seed company.

As far as producers are concerned, the results summarised above suggest that, if we accept that their profits are, on average, higher with GM than non-GMO seeds, they are recovering a fraction of the value associated with the development of GMOs. The review by Smythe et al (2015) deals precisely with this issue and is based on some fifteen publications analysing the distribution of gains between seed companies, agricultural producers and consumers in 5 countries (United States, Canada, Argentina, Spain, India and China) and for 4 crops (rapeseed, soya, maize and cotton). The results are highly variable, partly because of the different methodologies used in the studies under consideration, and partly because of the different institutional and regulatory contexts in the various countries (property rights, in particular). Nevertheless, the authors conclude that the gains associated with GM crops are distributed between the various types of player, with producers and consumers capturing, on average, a non-zero fraction of these gains.

Here again, the results must be treated with caution given the heterogeneity of the approaches used in the studies taken into account. Here too, the data dates from the early 2000s and does not guarantee that the conclusions are valid over the long term. Furthermore, while producers' gains are not zero despite a highly concentrated seed industry, there is no analysis to establish whether these gains would be higher in the presence of a more competitive seed market.

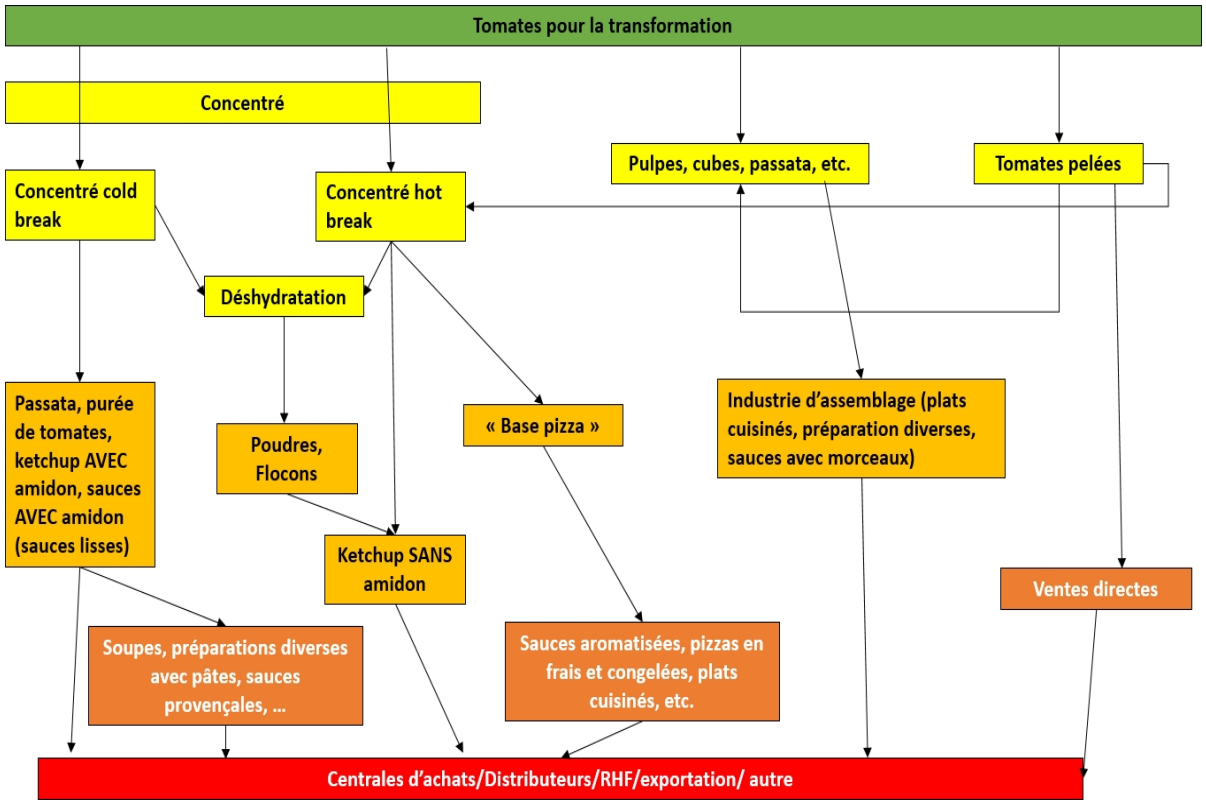
It is through the price of seeds that the division of value between the seed industry and producers is regulated. In a monopoly position, the seed industry could set this price in such a way as to capture all the gains, and therefore position producers' profits at almost zero. If we accept the existence of gains for GMO producers, this suggests that the seed industry is not in a position, despite the high level of concentration, to increase seed prices to such a level. There are two possible reasons for this (Demont et al. 2007). The first is that growers' agronomic and technical performance is highly heterogeneous. The second is that the seed industry is in competition with the chemical crop treatment industry: if the price of GM seeds is too high, then growers may prefer, in situations where they have a choice, to use conventional seeds and respond to phytosanitary risks with chemical treatments.

As far as consumers are concerned, the question of whether they benefit from a share of the value associated with the development of GMOs must be addressed through the question of final prices. In this respect, it should first be noted that, generally speaking, consumers penalise GMO products, even in countries where they have a strong presence, by being less willing to pay for GMO products than for non-GMO products. The meta-analysis by Lusk et al (2004) shows that in the EU, the willingness to pay for GMO products, which varies according to the type of product, is on average 30% lower than for non-GMO products (26% in the United States). This means that GMO products (in the absence of specific characteristics valued by consumers) can only enter the market at a lower price than non-GMO products. Under these conditions, in order to obtain sufficient market share, upstream companies must return some of the value to consumers through lower price levels. This lower level of prices for GMO products compared to non-GMO products is clearly established in countries in which both types of products (GMO and non-GMO) are present (see Kalaitzandonakes et al. (2018) for an in-depth econometric study using data from the United States).

The question of value sharing is ultimately conditioned by the regulatory methods put in place (competition policy, coexistence rules, etc.). **There are no systematic reviews or meta-analyses providing an overview of this issue. But it is a major issue that needs to be taken into account in public policy discussions.**

Appendix 15: Description of tomato processing

The following diagram is adapted from one drawn by François-Xavier BRANTHÔME of SONITO:



Yellow represents the first transformation, light orange the second and dark orange the third.

NATIONAL HEALTH SAFETY AGENCY
of Food, Environment and Labour

14 rue Pierre et Marie Curie 94701 Maisons-Alfort Cedex

www.anses.fr - @Anses_fr

979-10-286-0489-9 - Legal Deposit: January 2024 - Anses Éditions 2024 - CC BY-NC-ND - Photo credit: *123 RF*